SFBTM

Bienvenue aux 26èmes JFBTM

20-22 MAI 2026 | LE MESNIL-AMELOT

Message de bienvenue

Chères participantes, chers participants,

C'est avec un grand plaisir que nous vous accueillons à Paris (...enfin tout près), du 20 au 22 mai 2026, pour la **26ème édition des JFBTM**.

En effet, nous laisserons la Tour Eiffel aux touristes et les croisières sur la Seine aux amoureux : le lieu incontournable pour les experts des tissus minéralisés sera **l'Hôtel Jangle** ! Ce site moderne et chaleureux, associé à une formule résidentielle sans transport ni stress, offrira un environnement idéal pour favoriser les échanges, les discussions passionnantes et les collaborations impromptues qui font la richesse de nos rencontres. Et pour éviter la surchauffe neuronale, vous pourrez profiter de l'espace aquatique Plaine Oxygène pour vous dépenser ou vous détendre et on vous garde quelques surprises en soirée ! Si nous vous éloignons un peu de la frénésie touristique parisienne, c'est donc pour mieux nous rapprocher scientifiquement et humainement.

Nous vous souhaitons de très belles découvertes scientifiques et des discussion passionnantes!

Le comité local d'organisation


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Jérôme BOUCHET


Emilie DAMBROISE


Eric HAY


Xavier HOUARD


Delphine LOGEART


Krisztina NIKOVICS


Esther POTIER

Bureau des Jeunes Chercheurs


Mathilde PALMIER
Présidente


Abdelkader TEIBI
Adjoint


Laura ENTZ


Maria MATEROZZI


Léa THORAVAL

Grâce à toute l'équipe : les coulisses sont solides, le spectacle peut commencer !

- **William BAKARI**
- **Reem EL MONLA**
- **Adriana FIGUEROA GARCIA**
- **Stéphane HILLIQUIN**
- **Vanessa KABBOUCCHY**
- **Guilhem LIGNON**
- **Shengyi LU**
- **Nicolas OBTEL**
- **Célia ORENGO**
- **Julien PO**
- **Marie SEVIN**

Nous remercions également tous les partenaires qui nous soutiennent pour ces 26èmes JFBTM.

Star

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OSCAR du public

Scannez le QR code et votez pour votre présentation « Jeunes Chercheurs (*) » préférée.

Tentations à éviter :
- l'auto-admiration,
- le favoritisme de laboratoire,
- la multiplication exponentielle des votes,
- la création de faux comptes,
- la diffusion clandestine du QR code à l'extérieur du congrès,
- l'intelligence artificielle au service du mal.

Les noms seront vérifiés. Nous avons des moyens.... ;)

Prix poster

Candidats aux prix du meilleur poster,

Merci d'être présents aux horaires indiqués pour accueillir le Conseil Scientifique ET le jury post-doc :

- Posters pairs (Post-docs) : jeudi 21.05 - 13:30-14:00
- Posters pairs (PhDs et étudiants) : jeudi 21.05 – 10:35–11:30
- Posters impairs (Post-docs) : mercredi 20.05 - 15:45-16:15
- Posters impairs (PhDs et étudiants) : jeudi 21.05 – 15:50–16:45

3 minutes pour convaincre que votre poster est génial.
2 minutes pour vérifier si c'est vraiment le cas.

Bonne chance à tous!

Programme - Mercredi 20 Mai

26èmes JFBTM

13:00	Accueil des participants
13:45	Ouverture des 26èmes JFBTM

SESSION 1
MODERATEURS : Xavier LERAY, Marthe ROUSSEAU

14:00	**KEYNOTE : Alexandra HOUSSAYE (K1)** MUSÉUM NATIONAL D'HISTOIRE NATURELLE, PARIS Studying bone from an adaptive perspective in functional morphology
14:45	**14:45 Sabaa SAHI (O1*)** Mineralization abnormalities underlying eruption defects in enamel renal syndrome **15:00 Amélie CIFUENTES (O2*)** The Fibroblast Growth Factor 23 regulates phosphate and iron in animals and patients with arthritis **15:15 Julien PO (O3*)** Altération de la croissance dans l'hypophosphatémie liée à l'X : étude de l'axe GH/IGF-1 dans le modèle murin Hyp **15:30 Mathilde PALMIER (O4*)** Myeloid Zinc Finger 1 distinguishes permissive and inhibitory glucocorticoid effects during osteoblast differentiation
15:45	**Pause café** Visite des posters (impairs) et des exposants

SESSION 2
MODERATEURS : Romain GUIHO, Juliane ISAAC

16:15	**16:15 Elodie ZOCOLA (O5*)** Oral administration of Setanaxib reduces cartilage catabolism in DMM murine model **16:30 Manel BEN ABDELATIF (O6*)** Optimized cFGF23 variants enable low-dose gene therapy for X-linked hypophosphatemia **16:45 Julia HALPER (O7*)** Tryptophan catabolism shapes the immune landscape offering a therapeutic opportunity in rheumatoid arthritis **17:00 Pierre-Henri HELOU (O8*)** Role of MAPK pathway modulation in skeletal cell fate decision during bone regeneration **17:15 Sans prise de thèse**
17:20	Assemblée générale de la SFBTM
19:30	Apéritif de bienvenue
20:00	Dîner et animation surprise du bureau des jeunes chercheurs

Programme - Jeudi 21 Mai

07:30	Petit-déjeuner thématique : “Décryptons ensemble les postes de CR, MCU, IgR”

SESSION 3
MODERATEURS : Hervé KEMPF, Stéphanie LUCAS

08:45	**KEYNOTE : Marc D. McKEE (K2)** MC GILL UNIVERSITY, MONTREAL Patterning in the biomineralization morphospace: the structural biology of symmetry breaking in extracellular matrices of mineralized tissues
09:30	**09:30 Dalia GERARDIN (O9*)** Not yet exhausted, TNAP also dephosphorylates NMN to contribute to NAD metabolism **09:45 Alix CALOT (O10*)** La mutation d’EXTL3 favorise l’ossification pathologique dans un contexte d’inflammation chronique au cours de la spondylarthrite ankylosante **10:00 Kenza BOUMAD (O11*)** Impact des microplastiques sur les processus cellulaires de calcification valvulaire **10:15 Nicolas OBTEL (O12*)** Amelogenesis imperfecta in patients with hypercalcemia due to GNA11 mutations **10:30 Sans prise de thèse**
10:35	**Pause café** Visite des posters (pairs) et des exposants

SESSION 4
MODERATEURS : Jérôme LAFONT, Delphine MAUREL

11:30	**11:30 Marie SEVIN (O13*)** Impact de l’invalidation de claudine-19 sur le phénotype osseux **11:45 Rosa Nicole FREIBERGER (O14*)** Impact of SARS-CoV-2 infection on bone integrity: insights into cellular and molecular mechanisms **12:00 Camille GIROLET (O15*)** Integrated transcriptomic and functional analysis revealed sexual dimorphism in mature osteoclasts **12:15 Giada DE PONTI (O16*)** Decisive interactions between skeletal stem/progenitor cells and endothelial cells in early stages of fracture repair **12:30 Sans prise de thèse**
12:35	Déjeuner
13:30	Visite des posters (pairs) et des exposants

Programme - Jeudi 21 Mai

SESSION 5
MODERATEURS : Céline COLNOT, Guillaume COURBON

14:00

KEYNOTE : Antoine ZALC (K3)
INSTITUT COCHIN, PARIS
Investigating an epigenetic mechanism safeguarding cranial neural crest cells development and plasticity

14:45

14:45 Franceska KOVACI (O17*)
Deficieny in GNA11 impairs enamel mineralization by delaying ameloblast transition to the maturation stage
15:00 Laurine HAMON (O18*)
Déséquilibre de l'homéostasie osseuse et engagement adipocytaire : nouvelles données dans la maladie osseuse liée a la mucoviscidose
15:15 Mel GAVENS (O19*)
Rôle de RANKL dans le contrôle systémique exercé par le squelette sur la croissance et la dissémination du cancer du sein
15:30 Maria ETHEL (O20*)
Human and mouse musculoskeletal stromal cell atlases define skeletal stem/progenitor cell identities and spatial origins
15:45 Présentation Sponsor (BIOTECHNE)

15:50

Pause café
Visite des posters (impairs) et des exposants

SESSION 6
MODERATEURS : Emeline PERRIER-GROULT, Arnaud METAIS

16:45

KEYNOTE : Ivan MARTIN (K4)
BASEL UNIVERSITY, BASEL
Bone and bone marrow engineering

17:30

17:30 Cassandre GOACHET (O21*)
Distinct epigenetic profiles of skeletal stem/progenitor cells dictate their fate during bone regeneration
17:45 Claire DUMORTIER (O22*)
L'augmentation d'Interleukine 1-b dans la cystinose a un impact sur les populations cellulaires de la niche stromale : du modèle murin à l'humain
18:00 Hassane TOIWIYA (O23*)
Immobilisation passive de vésicules extracellulaires sur implants en titane texturés par laser femtoseconde pour la régénération tissulaire
18:15 Malorie COSSEZ GUIGNE (O24*)
Impact de l'activité de la COMT sur l'homéostasie osseuse

18:30

Temps libre

20:00

Cérémonie de l'OSCAR - Repas de Gala

Programme - Vendredi 22 Mai

SESSION 7
MODERATEURS : Claudine BLIN, Jérôme GUICHEUX

09:15	**09:15 Stéphanie LUCAS (O25)** L'administration au long terme de Dapagliflozine (SGLT2i) améliore la quantité d'os trabéculaire des souris ovariectomisées **09:30 Dominique MODROWSKI (O26)** CAPN6+ cancer stem cells drive metabolic reprogramming and immune deactivation in osteosarcoma **09:45 Hervé KEMPF (O27)** Airway calcification: an overlooked phenomenon with major respiratory impact? **10:00 Marie ALBERIC (O28)** Biomineral pigmentation in sea urchins **10:15 Sans prise de thèse**
10:20	**Pause café** Visite des exposants
10:45	**KEYNOTE : Marian HU (K5)** KIEL UNIVERSITY, KIEL Why pH matters- the cell physiology of marine calcifiers
11:30	Remise des prix
12:00	Clôture des 26èmes JFBTM

K1 STUDYING BONE FROM AN ADAPTIVE PERSPECTIVE IN FUNCTIONAL MORPHOLOGY

Alexandra Houssaye 1

(1) UMR 7179, Mécanismes Adaptatifs et Evolution, Muséum National d'Histoire Naturelle, Centre National de la Recherche Scientifique, CP 55, 57 rue Cuvier, 75005 Paris, France

The skeleton adapts to the mechanical constraints it is subjected to, both in terms of bone shape and internal structure. If bone adapts over the course of an organism's lifetime, changes can naturally be far more extensive on an evolutionary scale. Our research focuses on highlighting form-function relationships in the vertebrate skeleton in order to understand how bone adapts, which in turn enables us to improve paleoecological inferences on extinct forms and thus to better reconstruct the steps in the evolutionary history of various lineages. We have particularly focused on the conquest of the aquatic environment by mammals and reptiles (e.g., cetaceans, sirenians, mosasaurs, ichthyosaurs) and on the adaptation to massive body weight in heavy terrestrial mammals and reptiles (e.g., rhinoceroses, elephants, sauropod and theropod dinosaurs). Our approaches combine 3D analyses of the shape and internal structure (via X-ray tomography) of bones from a wide variety of organisms, with methodological developments in 3D bone microanatomy, as well as biomechanical analyses. Working on these form-function relationships also enables us to develop our research in (paleo)bioinspiration.

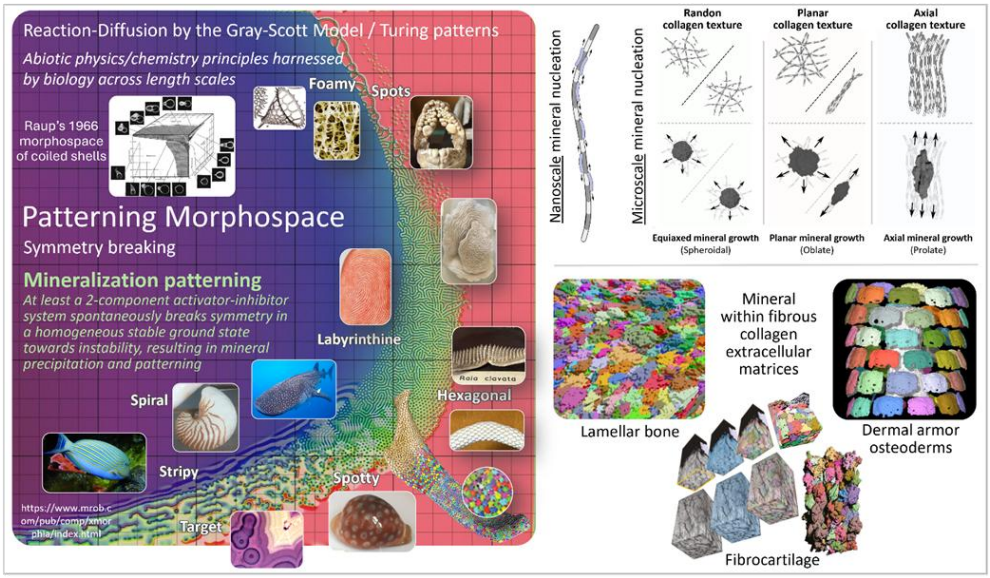
K2 PATTERNING IN THE BIOMINERALIZATION MORPHOSPACE: THE STRUCTURAL BIOLOGY OF SYMMETRY BREAKING IN EXTRACELLULAR MATRICES OF MINERALIZED TISSUES

Marc D. McKee 1

(1) McGill University, Montreal, Quebec, Canada

Biomineralization lies at an intriguing intersect between biology and geology/mineralogy. Mineralization of various structures, including exoskeletons and endoskeletons, began in the Cambrian explosion and propelled life along many trajectories from which a dazzling array of mineralized structures and tissues emerged. Functions ranged from optical sensing in trilobite calcium-carbonate eyes to the many roles of vertebrate calcium-phosphate endoskeletons. Central to the latter were complex arrays of fibrillar collagen forming extracellular matrices that constrained and guided potentially catastrophic growth of faceted mineral crystals in an organism. Such control resulted in macroscopically rounded mineralized structures rather than faceted, angulated surfaces (even sharp-tipped spines have rounded shafts). All skeletal bones and teeth have curved surfaces, as do avian eggshells, most marine seashells, and many other biomineralized structures. Molecular regulation generates biomineral curvature and patterning, and nano- and macroscale architecting of both amorphous and crystalline mineral is a central theme in the biomineralization field, regardless of organism, tissue, structure or mineral type.

For vertebrate mineralized tissues, we have incorporated first principles of atomic/nanoscale mineral initiation and growth to develop a symmetry-breaking notion called the Stenciling Principle. The notion describes that in all tissues, starting in the embryo, mineralization is initially and subsequently prevented by inhibitors as the default condition, followed by cell/tissue-specific expression of enzymes that degrade the inhibitors at skeletal sites (inhibiting the inhibitors), allowing mineralization to proceed in collagenous matrices. Known and well-characterized inhibitor-enzyme pairs include pyrophosphate-TNAP and osteopontin-PHEX. We refer to the outcome of these paired enzyme-inhibitor degradative actions in tissues as 'biological stenciling' of mineralization. Mineralization initiated at the atomic/nanoscale then expands towards the microscale, additionally aligned by the fibrous collagen matrix. Such parallelism between local collagen fibril texture and preferential directional mineral growth often patterns as a 3D Voronoi-type tessellation/tiling. Using 2D and tomographic 3D X-ray and electron microscopy techniques, I will describe some tissue/structure examples of patterning in the biomineralization morphospace arising at the nanoscale and extending to the microscale, in bone, cartilage, osteoderms and avian eggshell.



K3

INVESTIGATING AN EPIGENETIC MECHANISM SAFEGUARDING CRANIAL NEURAL CREST CELLS DEVELOPMENT AND PLASTICITY

Antoine Zalc 1

(1) Université Paris Cité, CNRS, Inserm, Institut Cochin, Paris, France

Craniofacial disorders represent a third of birth defects worldwide. They predominantly originate from defects in cranial neural crest cells (CNCC) development. CNCC are a transient cell population that arises in the anterior neuroepithelium during embryogenesis. First induced as an epithelial cell type, they undergo an epithelial-to-mesenchymal transition, delaminate from the neuroepithelium and migrate through the embryo to populate the craniofacial regions where they differentiate into various derivatives. While pre-migratory CNCC are patterned along the antero-posterior axis, expressing either Otx2 (anterior) or Gbx2 (posterior), this positional identity is erased upon migration. The functional relevance of CNCC initial axial patterning remains unknown.

To study the function of CNCC axial patterning, we developed an in vitro CNCC differentiation system recapitulating anterior-posterior identity establishment and erasure. We showed modulating diverse signaling pathways alters the proportion of $OTX2^{+}$ and $GBX2^{+}$ cells but never disrupts their boundary, revealing intrinsic developmental robustness. Modification of proteins by Small Ubiquitin-like Modifiers (SUMO) has been described as a key regulator of cell identity and cell fate transition. Furthermore, SUMO1 haploinsufficiency is associated with cleft lip and palate in humans and SUMOylation inhibition in pregnant mice induces severe craniofacial defects in the resulting embryos. Yet, how SUMOylation regulates early CNCC development remains undetermined. We showed SUMOylation inhibition disrupts CNCC axial patterning, reduces migration, and impairs differentiation, both in vitro and in vivo.

These results identify SUMOylation as a key epigenetic mechanism safeguarding CNCC development. We are now combining in vivo and in vitro phenotypic studies with molecular analyses to uncover how this mechanism ensures CNCC development robustness.

K4 BONE AND BONE MARROW ENGINEERING

Ivan Martin 1

(1) Department of Biomedicine, University of Basel, Switzerland

The lecture will present the development and translational trajectory to robustly generate bone tissue through the recapitulation of endochondral ossification. The strategy, which implies the chondrogenic differentiation of mesenchymal stromal cells derived from human bone marrow or adipose tissue, has offered the opportunity not only to generate osteoinductive grafts, but also to address fundamental questions related to the process of limb development in a fully human system. In particular, insights have been generated on the onset and function of 'skeletal stem cells' in an environment mimicking the growth plate in developing bones.

The lecture will also present a recently engineered iPS cells-derived 3D culture system capable to model the osteoblastic, endothelial and neural cellular elements of the bone marrow niche. The platform has been used to investigate how specific elements of the bone marrow niche regulate engraftment and lineage specification of hematopoietic stem/progenitor cells. The engineered model is currently being extended to investigate niche-mediated processes in specific malignancies, including chemoresistance.

K5 WHY PH MATTERS- THE CELL PHYSIOLOGY OF MARINE CALCIFIERS

Marian Hu 1

(1) Institute of Physiology, Christian-Albrechts-University, Hermann-Rodewald-Strasse 5, 24114 Kiel, Germany

Calcium carbonate minerals are used by all five kingdoms of life to serve a great diversity of functions ranging from mechanical support in shells and skeletons to gravity perception in the vertebrate inner ear. In the calcification process protons are liberated that need to be removed from the calcification front to promote mineralization and to defend cellular acid-base balance. Thus, biological calcification and pH regulation are intrinsically linked processes that remain relatively unexplored.

Using the sea urchin larva as a model system that generates an elaborate calcitic endoskeleton we studied the cellular pH regulatory machinery of the calcifying primary mesenchyme cells (PMCs). We identified proton transporting mechanisms in these mineralizing cells including the proton channel, spOtop2l that is critically involved in modulating cellular as well as vesicular pH. Vesicular pH is of particular interest since the first step of mineral formation happens within sub-cellular compartments where amorphous calcium carbonate (ACC) is formed. Furthermore, regulation of pH in mineralizing cells and mineralization vesicles is a master regulator of the carbonate system dictating the equilibrium between CO2 and CO3- in concert with carbonic anhydrases. Here we characterized a cellular carbon concentration mechanism involving a membrane associated carbonic anhydrase that utilized the natural pH gradients between different cellular compartments to help accumulate inorganic carbon.

Using the sea urchin larva we are able to resolve fundamental principles of mineral formation in a marine calcifying organism. A deep mechanistic understanding will help to identify unifying principles that organisms used to generate calcium carbonate minerals and may explain different sensitivities of marine calcifiers in past present and future marine systems.

O1* MINERALIZATION ABNORMALITIES UNDERLYING ERUPTION DEFECTS IN ENAMEL RENAL SYNDROME

Sabaa Sahi 1, Kemelly Resend 3, Ana-Carolina Acevedo 3, Valérie Cormier Daire 1, Ariane Berdal 1,2, Nunthawan Nowwarote 1

1. INSERM UMR1163, Institut Imagine, Inserm, Université Paris-Cité, Paris, France
2. Reference Centre for Rare Oral and Dental Diseases, Rothschild Hospital, Assistance Publique Hôpitaux de Paris, Paris, France
3. Faculty of health science, University of Brasília. Brasilia, Brazil

Introduction: Enamel Renal syndrome (ERS) (OMIM# 204690) is a rare genetic disorder caused by pathogenic variants in the FAM20A gene. Loss of function of this gene leads to an altered oral phenotype characterized by imbalance in mineralization, with deficiency in hard tissues and excess in soft tissues.

Objective: This study focuses on mineralization in ERS, progressing from cohort characterization and genotype phenotype correlation to mineralization dynamics, followed by tissue alterations related to tooth eruption, cellular behavior, and clinical eruption outcomes.

Methods: Our study is based on a cohort of 29 ERS patients. Among them, 24 are followed at the Rare Disease Reference Center of Rothschild Hospital and 5 patients were recruited from the Oral Care Center for Inherited Diseases in Brasília. Nineteen patients have already undergone genetic sequencing and a genotyping study is currently underway to explore possible correlations between the ERS oral phenotype and the causative variants. Primary cultures obtained from these samples, including dental pulp, apical papilla and alveolar bone, were established to investigate the biological behavior with particular emphasis on mineralization capacity of dental tissues affected by ERS. Then, an eruption score was developed to complement the molecular analysis with a clinical assessment.

Results: Analysis of the 29-patient ERS cohort enabled combined an integrated clinical, genetic, histological and cellular investigation across a range of ages and treatment histories. Genetic testing showed most causative variants were deletions, predominantly located in exon 11 and six previously unreported FAM20A variants were identified. Across tissue, histological and cellular levels, the findings consistently pointed to a dysregulation of mineralization. This imbalance was characterized by ectopic mineral deposits in soft tissues particularly the gingival connective tissue and follicular sac together with reduced mineralization potential in hard tissues such as alveolar bone. These soft-tissue mineralization appeared epithelial in origin (CK14-positive) and expressed enamel proteins including amelogenin and ODAM (Odontogenic ameloblast-associated protein). Supporting this pattern cellular studies demonstated increased mineralization capacity in fibroblasts derived from gingiva, follicular sac and dental pulp, contrasted by decreased mineralization in alveolar bone derived cells. Clinically, the ERS eruption score reinforced these biological findings by confirmed consistent diagnostic features, especially delayed tooth eruption and ectopic calcifications, while highlighting substantial inter-individual variability in disease expression.

Conclusion: The demonstrated imbalance between soft-tissue mineralization and hard-tissue deficiency represents a key pathogenic feature of Enamel Renal Syndrome and may guide future diagnostic assessment and therapeutic strategies targeting mineralized tissues.

Mots clés : Enamel Renal Syndrome, Ectopic mineralization, Mineralization defect

Thème de recherche : Génétique et Physiologie

O2* THE FIBROBLAST GROWTH FACTOR 23 REGULATES PHOSPHATE AND IRON IN ANIMALS AND PATIENTS WITH ARTHRITIS

Amélie Cifuentes 1, Stéphanie Mundweiler 1, Nina Meynard 1, Mireille Thomas 1, Elisa Dalix 1, Nadia Boutahar 2, Hubert Marotte 1,3, Guillaume Courbon 1

1. INSERM U1059 LBTO St Etienne, France
2. University hospital of St Etienne, Department of Biochemistry St Etienne France
3. University hospital of St Etienne, Department of Rheumatology St Etienne France

The bone-derived hormone Fibroblast growth factor 23 (FGF23) regulates phosphate metabolism and is involved in inflammation, iron deficiency, and cardiovascular disease (CVD). Proteolytic cleavage of FGF23 produces circulating peptides; while intact FGF23 regulates Pi, the cleavage mechanism appears directly linked to inflammation and iron-regulating hormone hepcidin. Rheumatoid arthritis (RA), a prevalent chronic inflammatory condition is characterized by osteoarticular damage and is associated with iron deficiency and CVD. We characterized FGF23 production, cleavage, and roles in arthritis.

Arthritis was mimicked in rats using the adjuvant-induced model (AIA). We also investigated a monocentric cohort of 95 patients with RA: 27 with active disease and 68 considered in remission (based on disease activity score DAS28). In rats and in patients, we measured blood levels of intact FGF23 and total FGF23 (intact+peptides), phosphate, iron, and hepcidin. In rats, we performed histology and qPCR in ankle, heart, gut, and kidney.

Compared to control rats, AIA rats showed early increase in Fgf23 mRNA levels at the ankle joint, which parallels early osteoblast dysfunction and precedes clinical onset of synovitis ($p<0.001$). Circulating levels of intact and total FGF23 were increased following similar kinetics ($p<0.05$). The ratio of intact-over-total FGF23 showed a greater cleavage rate and generation of FGF23 peptides. FGF23 mRNA and blood levels remained elevated throughout the chronic phase of arthritis ($p<0.001$). AIA rats presented alterations in Pi absorption and reabsorption (decreased expression of Napi2b in gut and Napi2a in kidneys, $p<0.05$ both) and functional iron deficiency (low serum iron and high hepcidin levels, $p<0.05$ both). Moreover, hepcidin levels strongly correlated with cFGF23 ($r=0.93$, $p=8.10\text{-}7$). Additionally, we found that AIA rats developed CVD, characterized by cardiac hypertrophy and overexpression of hypertrophic factor Bnp that correlated with Fgf23 mRNA expression. In aggregate, these data demonstrate that FGF23 is elevated in AIA rats, and that this model is relevant for further exploration of FGF23-dependent iron dysfunction and CVD.

Similar to AIA, we detected elevated levels of intact and total FGF23 in patients with RA ($p<0.01$ both). Compared to patients with active RA, patients in remission showed a partial correction in total FGF23 levels. Functional iron deficiency was detected in 59% of patients with active RA and 28% of patients in remission. Levels of total FGF23 but not intact FGF23 levels correlated with the degree of iron deficiency in those patients ($r=0.69$, $p<0.05$).

Taken together, we evidence the excess of FGF23 in animals and patients with arthritis, that is linked to the handling of both phosphate and iron, and correlates with CVD in rats. In patients, FGF23 is a marker of iron deficiency, even in patients considered in remission for arthritis. Further studies to understand the molecular mechanisms are ongoing.

Mots clés : Fibroblast Growth Factor 23 (FGF23), Inflammatory arthritis, Cardiovascular–Mineral Disorders

Thème de recherche : Biologie cellulaire et moléculaire

O3* ALTERATION DE LA CROISSANCE DANS L'HYPOPHOSPHATEMIE LIEE A L'X : ETUDE DE L'AXE GH/IGF-1 DANS LE MODELE MURIN HYP

Julien Po 1, Laurène Delacourt 1,2, Reem Al Monla 1, Nathan Vellutini 1, Volha V. Zhukouskaya 1, Catherine Chaussain 1,3, Agnès Linglart 2 et Claire Bardet 1

1. Université Paris Cité, and Sorbonne Paris Nord, Inserm U1333, Santé Orale, F-92120 Montrouge, France
2. Paris-Saclay University, INSERM U1185, AP-HP, DMU SEA, Endocrinology and Diabetes for Children, Reference Center for Rare Diseases of the Calcium and Phosphate Metabolism, OSCAR filiere, EndoRare, and BOND ERN, Bicêtre Hospital, Le Kremlin-Bicêtre, France
3. AP-HP, Reference Center for Rare Disorders of the Calcium and Phosphate Metabolism, Dental Medicine Department, Bretonneau Hospital, GHN-Université Paris Cité, Paris, France

L'hypophosphatémie liée à l'X (XLH) est causée par des mutations du gène PHEX (Phosphate regulating endopeptidase X-linked), conduisant à une augmentation de la forme active du facteur FGF23 et une hypophosphatémie chronique entrainant des manifestations squelettiques dont une altération de la croissance squelettique. Les patients présentent un retard statural pouvant atteindre un score de -4 à -5DS. Le traitement par supplémentation en phosphate et vitamine D activée (PO4/VitD) améliore la minéralisation mais ne corrige pas complètement le retard statural. Un traitement par hormone de croissance rhGH (recombinant human Growth Hormone) est proposée en complément, montrant une efficacité uniquement chez les patients traités par PO4/VitD. Ces observations suggèrent une altération de la voie des effecteurs de la croissance jusqu'à présent jamais étudiée que ce soit chez le modèle murin de l'XLH, la souris Hyp, comme chez les patients.

L'obectif de ce travail vise donc à caractériser l'axe de la croissance dans l'XLH en étudiant l'impact du traitement par rhGH chez la souris Hyp en association ou non au traitement par PO4/VitD.

Des souris Hyp ont été traitées par PO4/VitD, rhGH, et PO4/VitD+rhGH en comparaison à des souris Hyp et sauvages (WT) non traitées. Les traitements ont été administrés de J21 à J51. Le suivi des paramètres de croissance a été effectué une fois par semaine. Les paramètres osseux ont été étudiés par analyse micro-CT à J21 et J51. Les effecteurs de croissance ont été étudiés par analyse qPCR et des analyses histologiques ont été effectuées sur le fémur, le rein et le foie.

Nos résultats montrent que les souris Hyp traitées par PO4/VitD+rhGH présente un gain de longueur naso-caudale et du fémur augmenté comparés aux souris Hyp non traitées et traitées par PO4/VitD ou rhGH seul. Les souris Hyp traitées par PO4/VitD+rhGH restent significativement plus petites que les WT et ne présentent pas d'amélioration de la microarchitecture osseuse par rapport aux souris Hyp traitées par PO4/VitD seule. L'analyse histologique du fémur montre que le traitement par rhGH associé au traitement par PO4/VitD améliore l'organisation de la plaque de croissance et de l'os trabéculaire sous-jacent, ainsi que les activités ostéoblastiques et ostéoclastiques. Les résultats préliminaires par immunomarquage montrent que l'expression de GHR et d'IGF1R dans le rein est diminué chez les souris Hyp non traitées par rapport aux WT, et restauré par le traitement PO4/VitD, associé ou non à la rhGH.

En conclusion, le traitement par rhGH associé au traitement par PO4/VitD permettrait d'optimiser la croissance staturale, d'améliorer la structure de la plaque de croissance et de l'os trabéculaire sous-jacent, mais semble inssuffisant pour permettre un rattrapage staturale complet. L'analyse des effecteurs de croissance dans les différents tissus permettra une meilleure compréhension de l'interaction entre la déficience en PHEX et les voies de signalisation de la croissance.

Mots clés : -

Thème de recherche : Génétique et Physiologie

O4* MYELOID ZINC FINGER 1 DISTINGUISHES PERMISSIVE AND INHIBITORY GLUCOCORTICOID EFFECTS DURING OSTEOBLAST DIFFERENTIATION

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Based on empirical knowledge, glucocorticoids (GC) are indispensable for in vitro differentiation towards human osteoblasts and adipocytes, yet their therapeutical use is a leading cause of secondary osteoporosis. GC-induced osteoporosis is characterized by reduced bone formation and impaired osteoblast differentiation from bone marrow stromal cells and is frequently accompanied by increased marrow adiposity. While these clinical observations suggest that GC exert dose- and context-dependent effects on stromal cell fate, the molecular mechanisms underlying these opposing actions remain unresolved.

We studied telomerase-immortalized human bone marrow derived stromal cells (hBMSC-TERT4-cells) capable of osteogenic and adipogenic differentiation. We combined GR (Glucocorticoid Receptor), MED1 (Mediator complex subunit 1) and H3K27ac (Histone H3 Lysine 27 acetylation) ChIP-seq, DNase-seq, and RNA-seq with motif-activity modeling (IMAGE) to determine lineage-selective chromatin actions of GR and transcription factors that linked glucocorticoid response to osteoblast-selective genes. Candidates were prioritized through integrating genomic coordinates of motifs with estimated Bone Mineral Density (eBMD) Single Nucleotide Polymorphisms (SNPs) and connected to GC-induced inhibition of osteoblast differentiation by loss of function studies in vitro (ALP activity, alizarin red staining, gene expression) and ectopic transplantation assays. Senescence was evaluated through gene expression (CDKN2A encoding p16, CDKN1A encoding p21) and b-galactosidase activity.

GR binding licensed lineage-selective and glucocorticoid-dependent acetylation of H3K27 driving transcriptional programs for both osteoblast and adipocyte differentiation. It indicated a binary chromatin "on-off switch" in response to GC rather than a graded dose sensor at day 1 of differentiation. Motif-activity and GWAS enrichment ($p = 0.104$) nominated Myeloid Zinc Finger 1 (MZF1) as a GC-dependent regulator of osteoblast-selective genes and a member of a senescence signature during late stage of high-dose glucocorticoid exposure. Genetic depletion of MZF1 upregulated osteogenic genes like BGLAP ($p=0.027$) and SPARC ($p=0.028$) and increased bone formation in vivo ($p=0.035$) under normal GC exposure, identifying MZF1 as an endogenous inhibitor of osteoblast differentiation. Under high-dose GC exposure, genetic depletion of MZF1 attenuated senescence-associated b-galactosidase activity, down regulated CDKN1A ($p=0.013$) and CDKN2A ($p=9x10-4$), and restored osteoblast differentiation.

Our data identify GR as a chromatin licensing factor for early human stromal cell specification and uncover MZF1 as a glucocorticoid-responsive, senescence-linked brake on osteoblast differentiation. This chromatin-anchored pathway provides a mechanistic framework and potential intervention point for glucocorticoid-induced osteoporosis in humans.

Mots clés : dexamethasone, osteogenesis, epigenomic

Thème de recherche : Biologie cellulaire et moléculaire

O5* ORAL ADMINISTRATION OF SETANAXIB REDUCES CARTILAGE CATABOLISM IN DMM MURINE MODEL

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Introduction: Osteoarthritis (OA) is a degenerative disease characterized by cartilage degradation, subchondral bone remodeling, and synovial inflammation. Low-grade inflammation plays a key role in OA progression through oxidative stress and excessive reactive oxygen species (ROS) production. We previously demonstrated that global deletion of NADPH oxidase 4 (NOX4), a major H_2O_2-producing enzyme, protected against cartilage degradation and synovial inflammation in a murine OA model. As no selective NOX4 inhibitor is currently available, we evaluated the efficacy of Setanaxib, an H_2O_2 scavenger, in experimental OA.

Methods: Human cartilage and subchondral bone explants (4 mm punches) were obtained during total knee arthroplasty (n=4). Samples were cultured for 6 days with PBS or IL-1β to induce ex vivo OA and treated with or without Setanaxib. Proteoglycan content was assessed by Safranin-O staining and sulfated glycosaminoglycan (sGAG) release quantified by Dimethylmethylene blue colorimetric assay. OA was induced in WT mice by destabilization of the medial meniscus (DMM). Three weeks post-surgery, mice received Setanaxib or vehicle by oral gavage (5 days/week for 5 weeks). Joints were collected 8 weeks after DMM for histological and immunohistochemical analyses (n=12/group).

Results: In human explants, IL-1β induced proteoglycan loss and increased sGAG release, both attenuated by Setanaxib. Treatment also prevented IL-1β–induced upregulation of 8-OHdG, an oxidative stress marker, and MMP13.

In vivo, DMM induced significant OA lesions (OARSI 4.1 ± 0.9/12). Setanaxib showed a trend toward reduced femoral OARSI score (1.8 ± 0.5 vs 1.3 ± 0.8/6; p=0.09) and decreased OA prevalence (OARSI ≥2) at the femur (75% vs 33%) and tibia (92% vs 67%). A similar trend was observed in treated sham mice. DMM significantly increased 8-OHdG and MMP13 expression and reduced type II collagen; Setanaxib significantly inhibited oxidative stress and MMP13 expression, and prevented significant collagen II loss. While DMM alone did not increase synovitis, Setanaxib was associated with significant increased medial synovitis at the surgical site. DMM increased osteophyte formation, which was not modified by treatment.

Conclusion: Setanaxib demonstrates antioxidant and anti-catabolic effects in human cartilage explants and attenuates cartilage structural damage in the murine DMM model. By inhibiting oxidative stress and MMP13 expression and preserving type II collagen, Setanaxib protects against cartilage matrix degradation. Although its effects appear compartment-specific, these findings support Setanaxib as a potential treatment for OA.

Mots clés : Osteoarthritis, oxidative stress

Thème de recherche : Biologie cellulaire et moléculaire

O6* OPTIMIZED cFGF23 VARIANTS ENABLE LOW-DOSE GENE THERAPY FOR X-LINKED HYPOPHOSPHATEMIA

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X-linked hypophosphatemia (XLH) is a rare genetic bone disorder caused by inactivating pathogenic variants in the PHEX gene. Elevated levels of FGF23 lead to renal phosphate wasting, resulting in hypophosphatemia and severe skeletal defects. We previously established proof of concept for gene therapy using adeno-associated virus (AAV) vectors, which rescued the bone phenotype in the Hyp-Duk mouse model of XLH. This innovative strategy bypasses direct bone targeting by using the liver as a biofactory to secrete a human C-terminal fragment of FGF23 (cFGF23) fused to human serum albumin (HSA), thereby inhibiting FGF23 signaling after a single injection. However, a major limitation for clinical translation is the high vector dose required (1×10^{14} vg/kg), which is associated with hepatotoxicity in humans. In a translational perspective, we aimed at developing an optimized product with enhanced therapeutic efficacy, particularly by improving bioavailability and/or receptor-binding affinity, thereby reducing the minimal efficacy dose.

To address this need, we engineered a murine version of cFGF23-HSA to improve its interaction with the endogenous α-Klotho receptor and explored alternative fusion variants. We generated murine cFGF23 fusion variants incorporating either an IgG Fc fragment or a 288–amino acid XTEN polypeptide. These variants were administered to wild-type and Hyp-Duk mice at a low dose (1×10^{13} vg/kg), and benchmarked against the human cFGF23-HSA which was injected at a ten-fold higher dose (1×10^{14} vg/kg).

We demonstrated that the murine cFGF23-HSA variant exhibited approximately ten-fold higher in vivo activity than the human cFGF23-HSA variant. Preliminary data showed that the murine cFGF23-FcIgG fusion significantly improved bone microarchitecture in Hyp-Duk mice. One month after vector injection, microCT analysis of trabecular bone revealed complete restoration of bone microarchitecture. In particular, treatment with murine cFGF23-FcIgG in Hyp-Duk mice restored Bone Volume/Total Volume (BV/TV), Trabecular Number (Tb.N), and Trabecular Separation (Tb.Sp) to levels comparable to those observed in WT mice, achieving similar effects to those obtained with the reference human cFGF23-HSA injected at a high dose.

We are currently performing histological analyses to confirm these findings and are further evaluating whether this effect is sustained three months post-injection.

Our results highlight the therapeutic potential of optimized cFGF23 variants for XLH, paving the way for clinical translation as a single-administration gene therapy for patients with XLH.

Mots clés : X linked hypophosphatemia, FGF23 pathway, liver gene therapy, AAV8, PHEX, bone mineralization, phosphate metabolism

Thème de recherche : -

O7* TRYPTOPHAN CATABOLISM SHAPES THE IMMUNE LANDSCAPE OFFERING A THERAPEUTIC OPPORTUNITY IN RHEUMATOID ARTHRITIS

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The essential amino acid tryptophan is mainly catabolized via the kynurenine pathway, thereby generating multiple different metabolites with reported anti- or pro-inflammatory properties. In clinical cohorts of auto-inflammatory diseases (Inflammatory bowel disease and Rheumatoid arthritis (RA)), pro-inflammatory metabolites are increased in the serum of patients compared to controls. AADAT, an enzyme producing anti-inflammatory metabolites, was found decreased in serum and synovial liquid of RA patients. In mouse, i.p. supplementation of murine recombinant enzyme has shown to ameliorate preclinical collagen-antibody-induced arthritis (CAIA). Based on these data, exploring kynurenine metabolism and understanding how this metabolic route is implicated in development and resolution of (auto-) inflammation during RA represents a promising target to investigate new therapeutic avenues.

Therefore, inducible, ubiquitous AADAT knockout mice were generated and subjected to CAIA. As hypothesized, paw oedema and clinical score are increased in the KO mice compared to controls ($p \leq 0.05$). Moreover, histological assessment of the knees confirmed changes in synovial hyperplasia, lymphocyte influx and cartilage destruction ($p=0.054$). Similarly, administration of recombinant human AADAT during CAIA in wild-type mice improved clinical scores and slightly reversed inflammation and tissue reorganization.

Moreover, to understand the observed impact of lack of AADAT on RA development, we performed exhaustive immunophenotyping. Ex vivo cell preparations of bone marrow, spleen and lymph nodes mice were analyzed by multiparametric (15 color) flow cytometry panels. In AADAT KO mice, changes in BM transitional B cell subsets were accompanied by significant splenomegaly, but only minor tendencies were observed in mature B cell populations in spleen or lymph nodes. Ex vivo differentiation of B cells towards plasma cells as mediators of RA development was decreased in KO animals compared to control ($p<0.05$), leaving us to speculate about changes in B cell development in between these stages.

Based on our histological results, bone morphometric measurements are ongoing to confirm a generalized bone phenotype in these mice. Moreover, marrow B cell impact with a strong potential to induce changes in bone metabolism are under examination; currently, investigations are ongoing to decipher the possible effect on marrow B cells on osteoclast and osteoblast differentiation between the 2 genotypes. Ultimately, we hope to link AADAT activity to inflammatory joint and bone destructive phenotypes during RA, which will confirming the modulation of Tryptophan catabolism as novel therapeutic opportunity.

Mots clés : Rheumatoid arthritis, tryptophan metabolism, osteoimmunology

Thème de recherche : Ostéoimmunologie

O8* ROLE OF MAPK PATHWAY MODULATION IN SKELETAL CELL FATE DECISION DURING BONE REGENERATION

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Bone regeneration is an efficient and scarless process driven by skeletal stem/progenitor cells (SSPCs), which are activated at the fracture site to generate cartilage and bone. SSPCs form heterogeneous populations residing in the periosteum, bone marrow, and adjacent skeletal muscle. In response to fracture, SSPCs transition via an activated state, or fibrogenic state, prior to osteogenic or chondrogenic differentiation (Perrin et al., 2024, doi: 10.7554/eLife.92519.). SSPC lineage commitment depends on interactions with the fracture microenvironment and on tightly regulated intracellular signaling pathways. This project investigates how modulation of the RAS/MAPK pathway regulates skeletal cell fate during bone repair. Previous work from the laboratory demonstrated that dysregulation of the MAPK pathway leads to severe defects in bone repair, including congenital pseudarthrosis of the tibia (CPT), a condition frequently associated with Neurofibromatosis type 1 (NF1). NF1 is a rare autosomal dominant disorder (prevalence 1/3000) caused by loss-of-function mutations in the Nf1 tumor suppressor gene, a negative regulator of RAS-MAPK signaling. Using a relevant NF1 mouse model, the laboratory showed that CPT results from altered SSPC fate, leading to fibrotic accumulation and fracture non-union (Perrin et al., 2024, doi: 10.1126/scitranslmed.adj1597). We therefore hypothesize that precise regulation of MAPK signaling is essential for proper skeletal cell fate decisions during bone repair.

To investigate the consequences of RAS/MAPK overactivation on SSPCs during repair, Nf1 was conditionally deleted using PdgfraCreERT2;R26tdTom;Nf1fl/fl mice. Tamoxifen was administered prior to tibial fracture to target SSPCs. Histological, microCT, and lineage-tracing analyses at days 7, 14, and 28 post-fracture revealed increased fibrotic tissue that persisted until later stages of healing, resulting in bone nonunion. Single-cell RNA-seq analyses showed elevated MAPK activity during the SSPC-to-fibrogenic transition (prior to day 7) and decreased activity during fibrogenic-to-chondrogenic differentiation (after day 5). We validated these observations by inhibiting the pathway with the MEK inhibitor selumetinib. Preliminary data indicate that inhibition during days 0-7 decreased cells in the fibrogenic state, whereas inhibition during days 5-10 increased cartilage, confirming early MAPK pathway modulation. Further bioinformatic analyses revealed abnormal activation not only of MAPK but also of additional RAS-dependent pathways in NF1-associated CPT. Together, these findings underscore the necessity of tightly regulated MAPK signaling and balanced RAS pathway activity for effective bone repair. Ongoing studies aim to further elucidate how MAPK modulation and related pathways regulate early SSPC fate decisions and how dysregulation of the MAPK pathway causes persistent fibrosis in NF1-related bone nonunion.

Mots clés : Bone repair, RAS/MAPK signaling, Neurofibromatosis type 1 (NF1)

Thème de recherche : Biologie cellulaire et moléculaire

O9* NOT YET EXHAUSTED, TNAP ALSO DEPHOSPHORYLATES NMN TO CONTRIBUTE TO NAD METABOLISM

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Tissue-nonspecific alkaline phosphatase (TNAP) is an extracellular enzyme essential for physiological mineralization through hydrolysis of inorganic pyrophosphate (PPi), a potent mineralization inhibitor. TNAP has also been implicated in pathological calcification, prompting the development of pharmacological inhibitors currently under clinical evaluation. However, TNAP dephosphorylates multiple substrates and is involved in diverse biological functions. For example, it hydrolyzes pyridoxal phosphate, enabling cellular uptake of pyridoxal and supporting vitamin B6–dependent processes, including GABA synthesis.

In a recent metabolomics study in ApoE-deficient mice treated with the TNAP inhibitor SBI-425 to prevent atherosclerotic plaque calcification, we observed a significant reduction in hepatic nicotinamide adenine dinucleotide (NAD^+) levels. Given recent evidence that TNAP contributes to FAD metabolism by dephosphorylating flavin mononucleotide (FMN) to facilitate riboflavin uptake, we hypothesized that TNAP may also hydrolyze nicotinamide mononucleotide (NMN) into nicotinamide riboside (NR), thereby influencing NAD^+ metabolism.

We show that TNAP inhibition in ApoE-KO mice leads to reduced hepatic NAD^+ levels, significantly associated with increased cholesterol accumulation and elevated inflammatory and fibrotic markers. Using NMR spectroscopy, we investigated NMN hydrolysis in human serum from four adult donors. NMN degradation was partially inhibited by either TNAP inhibition (SBI-425) or CD73 inhibition (AOPCP) alone, and fully suppressed when both enzymes were inhibited simultaneously.

We further examined cell-specific contributions using two osteosarcoma cell lines: MG63 cells (low TNAP expression) and Saos-2 cells (high TNAP expression). In MG63 cells, NMN hydrolysis was entirely dependent on CD73, whereas in Saos-2 cells it relied exclusively on TNAP. These findings indicate that TNAP and CD73 are the two major enzymes responsible for NMN hydrolysis at the cell surface and in circulation, with their relative contribution determined by expression levels.

Recombinant human TNAP efficiently hydrolyzed NMN in vitro, with activity comparable to or exceeding that observed for PPi and without substrate inhibition. Molecular docking identified interactions between NMN and key amino acid residues within the TNAP active site, some of which are different from those interacting with PPi and are mutated in patients with TNAP deficiency.

In conclusion, NMN is a newly identified TNAP substrate, establishing a direct link between TNAP activity and NAD^+ metabolism, and further expanding the functional scope of this enzyme.

Mots clés : alkaline phosphatase, osteoblasts, NAD metabolism

Thème de recherche : Biologie cellulaire et moléculaire

O10* LA MUTATION D'EXTL3 FAVORISE L'OSSIFICATION PATHOLOGIQUE DANS UN CONTEXTE D'INFLAMMATION CHRONIQUE AU COURS DE LA SPONDYLARTHRITE ANKYLOSANTE

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La spondyloarthrite est un rhumatisme inflammatoire chronique caractérisée dans ses formes sévères par une ankylose du rachis. Cette ossification pathologique, liée à une augmentation de l'ossification endochondrale, pourrait correspondre à une réponse réparatrice secondaire à l'inflammation chronique, comme le suggèrent plusieurs travaux (Sieper et al., Arthritis & Rheumatology, 2008). Le mécanisme conduisant à la néo-ossification reste cependant encore mal compris.

L'étude génomique d'une famille présentant une forme familiale de spondylarthrite ankylosante sévère a permis d'identifier un variant rare du gène EXTL3. Ce gène intervient dans l'initiation de biosynthèse des héparanes sulfates. Cette découverte a soulevé l'hypothèse d'un rôle d'EXTL3 dans les mécanismes d'ossification observés au cours de la spondyloarthrite. Le modèle murin porteur de cette mutation présente des caractéristiques évocatrices de spondylarthrite, sans augmentation significative de l'ossification chez la souris Extl3mut/+. Ces résultats suggèrent que la mutation d'Extl3, à elle seule, n'est pas suffisante pour induire une néo-ossification marquée.

Nous formulons l'hypothèse selon laquelle l'ossification pathologique caractéristique de la spondylarthrite résulterait de l'interaction entre cette prédisposition génétique et un environnement pro-inflammatoire.

Afin de tester cette hypothèse, nous avons généré un modèle murin combinant la mutation Extl3mut/+ et transgénique pour TNF transmembranaire (TNFtm TgA86). Une caractérisation phénotypique longitudinale a été réalisée à 1, 2 et 3 mois par imagerie par résonance magnétique (IRM) et micro-tomodensitométrie (micro-CT) du rachis, des articulations sacro-iliaques et des enthèses. Des analyses histologiques et immunohistochimiques des articulations sacro-iliaques, du rachis et des articulations coxo-fémorales ont également été menées.

Les souris Extl3–TNFtm développent dès l'âge de quatre semaines un phénotype sévère, associant déformation de la queue et boiterie précoce. L'IRM du rachis et des articulations sacro-iliaques révèle des anomalies de signaux inflammatoires dès 1 mois sur les séquences MGE et MSME. L'analyse par micro-CT montre des érosions précoces des sacro-iliaques, une altération des paramètres osseux trabéculaires incluant une diminution du volume osseux, de l'épaisseur et du nombre de trabécule, associé à un phénomène de néossification confirmé par histologie. L'immunohistochimie met en évidence une augmentation significative de l'infiltrat inflammatoire, avec un marquage accru du TNF et du CD45.

Nos résultats suggèrent, pour la première fois, qu'une interaction entre une prédisposition génétique liée à EXTL3 et un contexte inflammatoire chronique favorise le développement d'une ossification pathologique dans la spondyloarthrite ankylosante. Un aspect particulièrement novateur de notre travail réside dans la caractérisation phénotypique approfondie réalisée par imagerie multimodale. L'association de l'IRM et du micro-CT a permis une analyse structurelle détaillée du phénotype. À notre connaissance, une telle approche combinée n'avait jamais été appliquée dans ce contexte. Cette approche multimodale permet une meilleure compréhension des mécanismes conduisant à l'ossification pathologique et ouvre de nouvelles perspectives thérapeutiques.

Mots clés : Spondyloarthrite ankylosante, ossification endochondrale, EXTL3

Thème de recherche : Ostéoimmunologie

O11* IMPACT DES MICROPLASTIQUES SUR LES PROCESSUS CELLULAIRES DE CALCIFICATION VALVULAIRE

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Introduction – Les microplastiques (MPs) sont omniprésents dans l'environnement, absorbés et identifiés récemment dans différents tissus dont les tissus cardiovasculaires où ils ont été associés à une augmentation du risque et de la mortalité cardiovasculaires. La calcification valvulaire, processus actif impliquant les cellules interstitielles de valves (VICs), constitue un déterminant majeur de la progression de ce risque. A ce jour, l'impact direct des MPs sur les mécanismes cellulaires de la calcification valvulaire, n'a pas encore été étudié.

Objectif – Évaluer les effets de l'exposition aux MPs sur la physiologie des VICs : viabilité, apoptose, minéralisation en conditions pro-calcifiantes.

Méthodes – Des VICs primaires ont été isolées à partir de résections chirurgicales de valves aortiques humaines. Les VICs ont été exposées à des concentrations croissantes de MPs (5 à 500 µg/mL ; polystyrène, diamètre 0,5 µm) avec ou sans milieu pro-calcifiant (2,2mM Ca2+ x 2,2mM Pi). La viabilité et la prolifération cellulaires ont été évaluées par des tests de WST-1 et BrdU, et l'apoptose par marquage Annexin V/7-AAD. La minéralisation a été analysée par coloration au rouge alizarine et dosage du calcium. Enfin, l'expression des marqueurs ostéogéniques et pro-inflammatoires a été quantifiée par RT-qPCR.

Résultats – L'ajout de MPs est associé à une diminution significative de la viabilité des VICs à partir de 50 µg/mL dès 48h d'exposition conjointement à une augmentation de l'apoptose. En conditions pro-calcifiantes, les MPs favorisent la minéralisation des VICs dès la concentration de 10µg/mL. Cette réponse s'accompagne d'une modulation des marqueurs : ostéogéniques (BMP2), pro-inflammatoires (IL1β, TNFα), et de dé-différenciation (Coll1) des VICs.

Conclusion – Nos résultats montrent une altération importante de la physiologie des VICs en présence des MPs qui potentialisent leur minéralisation en conditions pro-calcifiantes. Ces premiers résultats suggèrent un rôle potentiel des MPs dans la progression de la calcification valvulaire et justifient la poursuite des travaux afin de mieux comprendre les mécanismes cellulaires et moléculaires impliqués.

Mots clés : Microplastiques, calcification, cellules valvulaires

Thème de recherche : Biologie cellulaire et moléculaire

O12* AMELOGENESIS IMPERFECTA IN PATIENTS WITH HYPERCALCEMIA DUE TO GNA11 MUTATIONS

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Introduction & objectives: Amelogenesis Imperfecta (AI) is a diverse group of rare inherited disorders that impact the enamel structure of both primary and permanent teeth. Although AI has been linked to normocalcemic and hypocalcemic conditions, no association has yet been identified with hypercalcemia. In this study, we aimed to determine whether Familial Hypercalcemia Hypocalciuria 2 (FHH2) is a cause of Amelogenesis Imperfecta.

Methods: We diagnosed hypomineralized amelogenesis imperfecta in the affected individuals of two unrelated families with FHH2. This manifested by high susceptibility to caries and enamel wear. We performed on deciduous teeth from 2 FHH2 patients several techniques to study the microanatomy of the dental tissues (SEM, Synchrotron ID19, EDS, Raman micro-spectroscopy, TOF-SIMS). We analyzed the expression of GNA11/ Gna11 in the human and mouse tooth germ via scRNAseq atlas, and investigated more in depth the expression of Gna11/Gα11 in the mouse tooth germ (RT-qPCR, RNA Scope, Western blot, immunohistochemistry).

Results: SEM analysis showed slightly more “tapered” enamel prisms in FHH2 teeth and abnormal dentin. EDS showed a significant difference in mineralization of both enamel and dentin (lower Ca/P ratio for both tissues in the FHH2 teeth). Synchrotron acquisitions at 3 um revealed punctual patches of demineralization, confimed by Raman microscopy. Further analysis by TOF-SIMS confirmed that the defect area had a lower Ca, and therefore mineral, content compared to a defect-free enamel area of the same tooth. Single-cell transcriptome atlas analysis of human and murine tooth germ revealed that GNA11/ Gna11 was expressed at all stages of amelogenesis. We performed RT-qPCR and western blot analyses on germs from WT mice, showing robust Gna11/Gα11 expression. We next performed RNA Scope and immunofluorescence on postnatal tooth germs and found Gna11/Gα11 expression in both ameloblasts and odontoblasts.

Conclusions: This study shows that GNA11 variants responsible for hypercalcemia, are a novel cause of amelogenesis imperfecta. Abnormal mineralization of enamel and dentin were showed and the expression of Gna11/Gα11 in the murine tooth germ was confirmed. This study introduces AI as a new phenotype of FHH2, therefore turning FHH2 not only as an anomaly of calcium metabolism but also as a syndrome.

Mots clés : Enamel, genetic disorders, calcium metabolism

Thème de recherche : Génétique et Physiologie

O13* IMPACT DE L'INVALIDATION DE CLAUDINE-19 SUR LE PHENOTYPE OSSEUX

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Les claudines (CLDN) sont des protéines des jonctions serrées. Au niveau rénal, CLDN19 s'associe à CLDN16 pour former des pores sélectifs aux cations divalents. Des variants pathogènes homozygotes des gènes CLDN16 et CLDN19 entraînent une pathologie rénale sévère, l'Hypomagnésémie Familiale avec Hypercalciurie et Néphrocalcinose (FHHNC), associée à une amélogénèse imparfaite. Des atteintes osseuses tels que des rachitismes ou des défauts de croissance sont aussi rapportés chez les patients. De plus, l'expression de Cldn16 et 19 a été montrée dans l'os de rat. Afin d'explorer le rôle de CLDN19 dans les manifestations rénales et en particulier extra-rénales, nous avons étudié un modèle murin invalidé pour Cldn19 (knockout, KO). L'objectif est d'évaluer l'impact de l'invalidation de CLDN19 sur le phénotype osseux.

Les os longs (fémur) et alvéolaires de souris mâles et femelles Cldn19 KO et sauvages (Wild-type, WT) âgées de 3 et 6 mois (n = 6-10 par groupe) ont été étudiés par micro-tomographie à rayons X (micro-CT) complétées par des analyses histologiques.

Les analyses microCT n'ont pas révélé d'altération du volume osseux ni de la densité minérale de l'os alvéolaire chez les mâles et femelles Cldn19 KO par rapport aux souris WT. Concernant le fémur, les paramètres de l'os trabéculaire ne sont pas significativement modifiés. En revanche, une altération du rapport volume osseux/volume total (BV/TV) de l'os cortical est observée chez les souris mâles Cldn19 KO comparés aux mâles WT, cette différence n'étant pas retrouvée chez les femelles. De façon intéressante, alors qu'une hypercalciurie est retrouvée chez les mâles et femelles Cldn19 KO comparés aux souris WT, l'augmentation de l'excrétion de magnésium dans les urines n'est observée que chez les mâles Cldn19 KO comparés aux mâles WT. Des analyses complémentaires sont en cours afin de déterminer l'expression des Cldn16 et 19 dans les tissus osseux WT de la mandibule et du fémur.

L'invalidation de Cldn19 induit un phénotype osseux sexuellement dimorphique affectant préférentiellement l'os cortical des os longs des mâles. La caractérisation de l'expression des Cldn16 et 19 dans l'os reste à confirmer. L'ensemble de ces données suggère un rôle de CLDN19, possiblement direct ou indirect, dans la régulation de la minéralisation et de l'homéostasie osseuse de manière dépendante du sexe, ouvrant de nouvelles perspectives quant à l'implication des claudines dans les manifestations extra-rénales de l'FHHNC.

Mots clés : jonction serrée, Hypomagnésémie Familiale avec Hypercalciurie et Néphrocalcinose (FHHNC), os long, os alvéolaire, micro-CT, dimorphisme sexuel

Thème de recherche : Biominéralisation

O14* IMPACT OF SARSCOV2 INFECTION ON BONE INTEGRITY: INSIGHTS INTO CELLULAR AND MOLECULAR MECHANISMS

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Bone is a highly dynamic organ system that is constantly renewed through the coordinated action of osteoclasts and osteoblasts. Osteoclasts mediate bone resorption, while osteoblasts ensure bone deposition and mineralization, two processes essential for skeletal strength and integrity. Proper osteoblast function relies on the synthesis of type I collagen and alkaline phosphatase activity, two crucial elements for matrix mineralization. Disruption of these finely regulated mechanisms compromises bone quality and increases fracture risk. Since the emergence of Coronavirus Disease 2019 (COVID-19), growing attention has focused on the long-term consequences of SARS-CoV-2 infection. Beyond its pulmonary manifestations, COVID-19 frequently evolves into long COVID, characterized by persistent multisystemic alterations. Although extrapulmonary complications are increasingly identified, the impact on skeletal health remains poorly defined. Experimental studies suggest that SARS-CoV-2 may affect bone remodeling indirectly, through inflammation-driven osteoclast activation, and directly via interactions with bone. In this regard, we previously demonstrated that ancestral and Omicron variants promote osteoclastogenesis and excessive bone resorption (1). However, the direct impact of SARS-CoV-2 on bone formation by human osteoblasts remained unexplored.

Here, we investigated the direct impact of SARS-CoV-2 on osteoblastogenesis using human umbilical cord–derived mesenchymal stem cells as osteoblast precursors. We show that differentiated osteoblasts express ACE2 and support productive infection, whereas precursor cells undergo abortive infection. Importantly, exposure to both ancestral and Omicron variants significantly impaired osteoblast differentiation, as evidenced by reduced alkaline phosphatase activity, collagen deposition, and matrix mineralization. These defects occurred independently of viral replication and were reproduced by UV-inactivated virus, indicating that viral structural components, particularly the Spike glycoprotein, are sufficient to disrupt osteogenesis.

Mechanistically, SARS-CoV-2 exposure exacerbated oxidative stress, transiently suppressed RUNX2 transcription during early differentiation, increased IL-6 secretion, and induced RANKL expression. Thus, viral exposure not only inhibits bone formation but also promotes a microenvironment favorable to osteoclastogenesis. Overall, these results uncover a dual mechanism by which SARS-CoV-2 disrupts bone homeostasis by acting on both osteoblasts and osteoclasts, providing a cellular basis for bone fragility and long-term skeletal complications following COVID-19.

1. Sviercz, F.; Jarmoluk, P.; Godoy Coto, J.; Cevallos, C.; Freiberger, R.N.; Lopez, C.A.M.; Ennis, I.L.; Delpino, M.V.; Quarleri, J. The abortive SARS-CoV-2 infection of osteoclast precursors promotes their differentiation into osteoclasts. J. Med. Virol. 2024, 96, e29597.

Mots clés : Osteoblast differentiation, Bone remodeling, SARS-CoV-2

Thème de recherche : Ostéoimmunologie

O15* INTEGRATED TRANSCRIPTOMIC AND FUNCTIONAL ANALYSIS REVEALED SEXUAL DIMORPHISM IN MATURE OSTEOCLASTS

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Sexual dimorphism in bone mass and osteoporosis susceptibility is well established and involves multiple factors that influence bone-cell differentiation and function. Among these cells, bone-resorbing osteoclasts (OCLs) are key regulators of bone homeostasis and belong to the myeloid lineage, which is well known for its diversity and sexual dimorphism. As such, OCLs are heterogeneous, comprising subsets with distinct roles in bone resorption, and immune and metabolic processes.

Studies of OCL sexual dimorphism have mainly focused on bone resorption, whereas potential differences in their immune function remain unexplored. Our aim was therefore to characterize murine OCLs from both sexes using complementary approaches to better define this dimorphism with a specific interest on immune processes.

OCLs were differentiated from bone marrow cells of 8-week-old male and female mice with RANK-L and M-CSF and characterized at the phenotypic and functional level.

Comparative scRNA-seq data on purified mature OCLs from males and females revealed great differences in pathways related to immune processes and osteoclastogenesis. It also uncovered sex-specific differences in the representation of previously defined OCL clusters. Cluster C0, strongly associated with bone resorption (Acp5, Ctsk) was 40% more abundant in males. In contrast cluster C1, characterized by an inflammatory gene signature (Fcgr2b, Fcgr3) and C2, combining high resorption and inflammatory features, were 13% and 100% more abundant in females, respectively. In vitro assays showed higher differentiation and resorption in OCLs from males than females. In contrast, in vivo analysis (µCT) revealed higher bone density in males. Functional assays showed that inflammatory OCLs from females exhibit higher antigen-processing capacity. They were also more efficient than male OCLs in stimulating CD4+ and CD8+ T-cell proliferation.

In conclusion, by revealing major sex-dependent differences in OCL composition, resorptive function and immune properties, our findings provide new insights into OCL sexual dimorphism and suggest that sex-specific therapeutic strategies may be beneficial in pathologies involving OCL dysfunction.

Mots clés : osteoclasts, osteo-immunology, sexual dimorphism

Thème de recherche : Ostéoimmunologie

O16* DECISIVE INTERACTIONS BETWEEN SKELETAL STEM/PROGENITOR CELLS AND ENDOTHELIAL CELLS IN EARLY STAGES OF FRACTURE REPAIR

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Efficient bone regeneration relies on skeletal stem/progenitor cells (SSPCs) from the periosteum that transit through a fibrogenic stage early after fracture before committing to chondrogenic or osteogenic differentiation (Perrin et al. 2024, DOI: 10.7554/eLife.92519). In pathological conditions, such as musculoskeletal traumatic injury (MTI), these differentiation processes can be disrupted, leading to persistent fibrosis and impaired healing (Hachemi et al. 2024, DOI: 10.1038/s41413-024-00347-3). Although adequate vascularization is crucial to promote osteogenesis during bone regeneration, little is known about the vessel-SSPC crosstalk during the early phases of healing and its impact on SSPC fate or fibrosis. The aim of the study was to further understand the crosstalk between endothelial cells (ECs) and SSPCs during early cell fate decisions after fracture.

First, we established a single-cell transcriptomic atlas of ECs from different musculoskeletal compartments at steady state, revealing similar EC clusters within bone marrow, periosteum and limb muscles. We analysed EC dynamics post-fracture using single-nucleus RNA sequencing (snRNA-seq). We found a decrease in capillary, arterial, venous, and lymphatic ECs after fracture, followed by an increase from day 5 post-fracture, and proliferative ECs from day 3. Although cartilage formation is usually associated with vascular regression, we observed colocalization of ECs and skeletal progenitors differentiating into SOX9+ chondrocytes on day 5 post-fracture calluses by immunostaining. Local genetic depletion of ECs during this early phase using Cdh5CreERT2;RosatdTom/DTA mice increased fibrosis, suggesting that close interactions with ECs are required for SSPC chondrogenic differentiation after fracture. Analyses of EC-SSPC interactions in our snRNA-seq datasets revealed that proliferative and capillary ECs promote angiogenesis and stimulate the transient fibrogenic response of SSPCs at day 5. Alongside, skeletal progenitors showed activation of proangiogenic signaling pathways. ANGPT1 was identified as one of the main factors released by skeletal progenitors to interact with ECs during the fibrogenic stage. We performed functional validation by inactivating Angpt1 in SSPCs in PdgfraCreERT2; Angpt1fl/fl mice, which resulted in impaired cartilage and fibrocartilage composition in the callus 7 days post-fracture, followed by incomplete healing. In the context of MTI, we observed an impaired angiogenic response by snRNA-seq, with reduced EC frequency and expression of proangiogenic ligands in SSPCs, including Angpt1. Administration of rec-ANGPT1 early after MTI improved the healing score. Overall, we characterized the decisive early crosstalk between ECs and SSPCs, and identified ANGPT1 as a mediator of this EC-SSPC crosstalk, suggesting new therapeutic strategies to stimulate healing after trauma.

Mots clés : Fracture repair, skeletal stem/progenitor cells, endothelial cells

Thème de recherche : Biologie cellulaire et moléculaire

O17* DEFICIENY IN Gna11 IMPAIRS ENAMEL MINERALIZATION BY DELAYING AMELOBLAST TRANSITION TO THE MATURATION STAGE

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Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal genetic disease with an estimated prevalence of 1 in 10,000-100,000 individuals. FHH is caused by heterozygous inactivating mutations in CASR (FHH1), GNA11 (FHH2), or AP2S1 (FHH3), all of which play critical roles in the extracellular calcium-sensing pathway. Clinically, FHH is characterized by elevated serum calcium levels, reduced urinary calcium excretion, and normal circulating parathyroid hormone (PTH) levels. In addition, FHH patients may exhibit mild skeletal abnormalities but also dental enamel defects, especially marked in FHH2 patients. However, the cellular origin and molecular mechanisms by which chronic hypercalcemia and GNA11 deficiency may influence enamel formation remain poorly understood.

To address these questions, we are analyzing the Gna11-Tm1b mouse model representing FHH2. We hypothesize that this model recapitulates the dental enamel phenotype observed in patients. Our aims are to (i) characterize the dental enamel phenotype, and (ii) elucidate the cellular and molecular mechanisms by which this mutation alter enamel formation.

To describe the dental phenotype, we performed Micro-CT analysis of incisors and molars in Gna11-Tm1b mice beginning at 2 months of age. Heterozygous Gna11-Tm1b+/- mutant mice showed significantly reduced enamel volume and density in both incisors and molars compared to Gna11-Tm1b+/+ control mice. Histological analyses revealed more retention of enamel matrix proteins during the maturation stage of ameloblasts in mutant mice compared to control mice. Consistently, immunofluorescence demonstrated persistent amelogenin protein accumulation during maturation stage in mutant mice. Furthermore, while ameloblastin expression was restricted to the transition stage of ameloblasts in control mice, it persisted into early maturation in mutant mice. In addition, tight junction and polarity markers, including Claudin-10 and ZO-1, were detected into early maturation in mutant ameloblasts, whereas in control mice their expression was downregulated at the transition stage. All together, these preliminary results suggest that mutant ameloblasts exhibit a delayed or incomplete transition from the secretory to the maturation stage, resulting in impaired enamel matrix clearance and defective mineralization.

We will further perform single-cell RNA sequencing of ameloblasts from control and mutant mice to identify stage-specific transcriptional changes and dysregulated pathways underlying enamel defects. We will also assess whether cinacalcet, an FDA-approved calcimimetic that lowers serum calcium, can prevent or rescue the enamel phenotype. Finally, we will analyze Casr (FHH1) and Ap2s1 mutant (FHH3) mouse lines to determine whether enamel abnormalities arise through shared mechanisms across FHH subtypes.

Mots clés : Familial hypocalciuric hypercalcemia, Ameloblasts, Dental phenotype

Thème de recherche : Biologie cellulaire et moléculaire

O18* DESEQUILIBRE DE L'HOMEOSTASIE OSSEUSE ET ENGAGEMENT ADIPOCYTAIRE : NOUVELLES DONNEES DANS LA MALADIE OSSEUSE LIEE A LA MUCOVISCIDOSE

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La maladie osseuse liée à la mucoviscidose (CFBD) concerne 50% des patients adultes atteints de mucoviscidose (CF). Dans de nombreuses pathologies érosives osseuses, une corrélation inverse entre densité minérale osseuse et adiposité médullaire est observée (Rozman, 1989 ; Verma, 2002 ; Zhou, 2008 ; Piccinin, 2014). Nous posons l'hypothèse que les mutations du gène CFTR orienteraient préférentiellement les cellules souches squelettiques (CSS) de la moelle osseuse vers un profil adipocytaire. A ce jour, la contribution de l'adiposité médullaire dans le déséquilibre de l'homéostasie osseuse associée à la ménopause chez les patientes CF n'a jamais été étudiée.

Les CSS de patients non-CF (n=7) ont été cultivées en milieu prolifératif, ostéoblastique ou adipocytaire, pendant 21 jours, avec ou sans Inh172 ou BPO-27 (inhibiteurs pharmacologiques de CFTR). Au sein des cultures, la présence d'adipocytes a été évaluée par colorations Oil Red'O et BodipyTM, et immunomarquages (PPARG, FABP4). En parallèle, des modèles d'ostéoporose liée au vieillissement allant jusqu'à 1 an, et induite par ovariectomie bilatérale (OVX) chez les souris F508delCFTR (CF) et sauvages (WT) à 8 et 16 semaines post-OVX, ont permis d'analyser l'évolution temporelle de la microarchitecture osseuse et de renseigner sur l'adiposité médullaire osseuse par microtomographie à rayons X.

Au sein des cultures ostéoblastiques et des CSS non différenciées, les inhibiteurs de CFTR mènent à une accumulation spontanée de lipides. Le nombre et la taille des adipocytes formés sont augmentés dans les cultures adipocytaires. In vivo, les souris WT OVX par rapport aux WT, ainsi que les souris CF OVX par rapport aux souris CF, présentent une altération des paramètres microarchitecturaux osseux : diminution du nombre et de l'épaisseur des travées, et de la quantité d'os. L'espace entre les travées et la résorption osseuse sont, eux, augmentés. Dans le modèle de vieillissement, les souris CF mâles meurent précocement (6 mois en moyenne), tandis que les souris CF femelles présentent un déclin accéléré de leurs paramètres osseux. Une hausse de l'adiposité médullaire a été notée dans le génotype CF sur un faible effectif, nécessitant des études complémentaires.

Ces résultats indiquent un lien, entre la perte de fonction de CFTR et l'adipogenèse, fournissant de nouvelles pistes de compréhension du développement de la CFBD. In vivo, l'OVX, mimant le phénomène de ménopause, aggrave le phénotype déjà décrit de la CFBD. Chez les souris femelles à phénotype CF, le vieillissement contribue à l'accélération de l'altération des paramètres osseux. Comprendre la formation du tissu adipeux médullaire et le rôle du métabolisme lipidique dans ce contexte permettrait de développer de nouvelles pistes thérapeutiques pour une meilleure santé osseuse chez les patients CF.

Mots clés : adipogenèse, mucoviscidose, ovariectomie

Thème de recherche : Développement et différenciation

O19* ROLE DE RANKL DANS LE CONTROLE SYSTEMIQUE EXERCE PAR LE SQUELETTE SUR LA CROISSANCE ET LA DISSEMINATION DU CANCER DU SEIN

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Une masse osseuse élevée est associée à un risque accru de cancer du sein, suggérant que des signaux dérivés de l'os peuvent influencer la progression tumorale au-delà du simple microenvironnement local. À l'aide de modèles murins présentant une hyperactivation des ostéoblastes, nous avons précédemment identifié plusieurs facteurs circulants dérivés des ostéoblastes capables de favoriser la croissance tumorale primaire ainsi que la dissémination métastatique, suggérant l'existence d'un dialogue systémique entre le squelette et la tumeur. Parmi ces facteurs, RANKL est apparu comme un régulateur potentiel des interactions immunitaires et inflammatoires à distance. Si RANKL produit par les cellules épithéliales mammaires est bien connu pour stimuler la prolifération et la progression tumorales du cancer du sein, sa contribution spécifique à ces processus lorsqu'il est sécrété par les ostéoblastes demeure largement inexplorée.

Afin d'étudier ce rôle, nous avons généré un modèle murin d'invalidation conditionnelle de RANKL spécifiquement dans les ostéoblastes (cKO). De manière inattendue, ces souris ont développé des tumeurs mammaires significativement plus volumineuses et à croissance plus rapide, associées à une altération marquée du paysage immunitaire tumoral, caractérisée par une diminution de l'infiltration des lymphocytes T et B et des cellules myéloïdes effectrices. Le profilage protéomique plasmatique a révélé une réduction de la chimiokine CCL3/MIP-1α, connue pour favoriser le recrutement des cellules immunitaires et l'activation des réponses inflammatoires, chez les souris cKO, en présence ou en absence de tumeur, suggérant un défaut immunitaire systémique préexistant.

De façon intéressante, le blocage pharmacologique de la signalisation via IL-10R a permis de restaurer les niveaux de CCL3 et de ralentir la croissance tumorale chez les souris cKO, jusqu'à des niveaux comparables à ceux observés chez les souris témoins WT. Ces résultats indiquent que le RANKL dérivé des ostéoblastes module l'immunité systémique en amont de l'initiation tumorale, via une régulation de l'axe IL-10.

Dans l'ensemble, nos travaux mettent en évidence un rôle antitumoral indirect et inattendu du RANKL d'origine ostéoblastique et soulignent le rôle du squelette comme régulateur endocrine de l'immunité antitumorale. Dans un contexte clinique où les thérapies anti-RANKL telles que le dénosumab présentent des bénéfices variables chez les patientes atteintes de cancer du sein, nos données suggèrent qu'une inhibition isolée de RANKL pourrait altérer certaines fonctions immunitaires protectrices. L'association d'un blocage de la voie IL-10 pourrait ainsi constituer une stratégie thérapeutique combinée visant à préserver l'immunité antitumorale tout en limitant la prolifération des cellules cancéreuses.

Mots clés : Cancer, Os, Immunité

Thème de recherche : Ostéoimmunologie

O20* HUMAN AND MOUSE MUSCULOSKELETAL STROMAL CELL ATLASES DEFINE SKELETAL STEM/PROGENITOR CELL IDENTITIES AND SPATIAL ORIGINS

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Bone regeneration relies on the activation and recruitment of skeletal stem/progenitor cells (SSPCs) that generate bone and cartilage after injury. Diverse SSPC populations have been described across skeletal regions, bone compartments, and adjacent skeletal muscles. These SSPCs have been defined using various markers in each anatomical context, and their differentiation capacities vary according to their tissue of origin. Whether these SSPCs overlap or are distinct populations with specific functions remains unknown, as we lack a unified view of the diverse SSPC populations. To establish an overview of SSPC identity across tissues and species, we constructed comprehensive mouse and human musculoskeletal stromal cell atlases by integrating 31 murine single-cell/nuclei RNAseq datasets and 49 human single-cell/nuclei RNAseq datasets from whole bone, isolated bone compartments, and skeletal muscle at steady state. These atlases encompass all stromal cells or sorted populations based on Cre-driven reporter expression or cell surface markers of long bones and limb skeletal muscles. We show that all SSPC populations correspond with two main populations with distinct transcriptomic profiles and spatial distributions: Cxcl12-abundant reticular (CAR) cells, found in the bone marrow, and PDGFRα+ Sca1+ (PαS) cells, found predominantly in periosteum and skeletal muscle. We found CAR and PαS cells encompass all previously defined SSPC populations. To assess the functional contributions of SSPCs from distinct tissue origins during bone repair, we used 3 genetic lineage tracing strategies: (i) systemic tamoxifen induction in PdgfraCreERT2;R26tdTom mice to label all SSPCs, (ii) systemic tamoxifen induction in AdipoqCreERT2;R26tdTom mice to specifically label bone marrow CAR cells, and (iii) a local tamoxifen delivery approach in PdgfraCreERT2;R26tdTom mice to selectively target PαS cells in periosteum and muscle. Lineage tracing analyses show that, contrary to bone marrow CAR cells that contribute minimally to intramembranous ossification in the medullary cavity, periosteum and muscle PαS cells serve as the primary source of SSPCs for both endochondral and intramembranous ossification during bone healing. Local genetic depletion of PαS cells in PdgfraCreERT2;R26tdTom/DTA mice further supports that these periosteum- and muscle-derived PαS cells are required for bone healing. Overall, this study proposes a unified SSPC framework that provides an unbiased cross-species overview of SSPC populations in long bones and reconciles earlier mouse and human SSPC definitions into CAR and PαS cells.

Mots clés : Skeletal stem/progenitor cells (SSPCs), Long bones, Bone regeneration

Thème de recherche : Biologie cellulaire et moléculaire

O21* DISTINCT EPIGENETIC PROFILES OF SKELETAL STEM/PROGENITOR CELLS DICTATE THEIR FATE DURING BONE REGENERATION

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Bone regeneration is an efficient and scarless process driven by skeletal stem/progenitor cells (SSPCs) that are recruited to the fracture site and rebuild bone through intramembranous and endochondral ossification. SSPCs are found in the bone marrow, periosteum, and nearby skeletal muscle, but fracture healing is primarily driven by periosteal and muscle SSPCs. While bone marrow SSPCs differentiate into osteoblasts and muscle SSPCs initially differentiate into chondrocytes, periosteal SSPCs are bipotent, contributing to both chondrogenesis and osteogenesis during bone regeneration. In this study, we aimed to understand how intrinsic programs control tissue-specific cell fate decisions during bone regeneration.

We compared the epigenetic profiles of SSPC found in the bone marrow, periosteum and skeletal muscle by analyzing newly generated single-nucleus multiomic datasets (i.e., combined single-nucleus RNAseq and ATACseq) of periosteum and skeletal muscle Prrx1-derived cells at steady state with that of previously generated datasets of bone marrow Prrx1-derived cells (Matsushita et al, Nat Commun 14, 2383, 2023). Periosteal and muscle SSPCs showed increased accessibility of chondrogenic genes compared to bone marrow SSPCs, including Sox9 and Col2a1. Inactivation of Sox9 in bone marrow SSPCs in AdipoQCreERT2;R26tdTom;Sox9fl/fl mice did not affect their contribution to repair and healing outcome. In contrast, inactivation of Sox9 in muscle and periosteal SSPCs via a local tamoxifen induction protocol in PdgfraCreERT2;R26tdTom;Sox9fl/fl mice severely impaired healing. We observed an absence of endochondral ossification, although intramembranous bone formation by periosteal SSPCs was unaffected. These results indicate that the chondrogenic program in periosteum and muscle SSPCs is required for endochondral ossification, while bone marrow and periosteal SSPCs can undergo intramembranous ossification independently of Sox9 expression. Focusing on the comparison between muscle and periosteal SSPCs, we noted similar transcriptomic profiles, but periosteal SSPCs displayed an osteogenic priming, characterized by increased chromatin accessibility in genomic loci associated with genes involved in osteogenic differentiation as well as Wnt signaling (such as Wnt5a and Lrp6) and BMP signaling (such as Bmp2 and Bmpr1b). The increased accessibility of these osteogenic genes in the periosteum at steady state correlated with their higher expression in activated periosteal cells than in activated muscle cells in response to fracture. Among the periosteal-specific osteogenic factors, we identified the transcription factor DLX5, which positively regulates the master regulator of osteogenesis, RUNX2. Dlx5 overexpression in SSPCs using PdgfraCreERT2; R26tdTom/Dlx5 mice results in increased intramembranous bone formation at the periosteal surface, highlighting the key role of Dlx5 in regulating the periosteal osteogenic program. Overall, the diverse fates of SSPCs from muscle, periosteum, and bone marrow during fracture healing are controlled by their epigenetic state at steady state.

Mots clés : Bone regeneration, Skeletal Stem/Progenitor cells, Epigenetic regulation

Thème de recherche : Génétique et Physiologie

O22* L'AUGMENTATION D'INTERLEUKINE 1-B DANS LA CYSTINOSE A UN IMPACT SUR LES POPULATIONS CELLULAIRES DE LA NICHE STROMALE : DU MODELE MURIN A L'HUMAIN

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La cystinose est une maladie rare autosomique récessive causée par des mutations du gène CTNS codant la cystinosine, un transporteur lysosomal de la cystine. Elle entraîne un rachitisme hypophosphatémique, une maladie rénale chronique, un retard de croissance et des anomalies squelettiques. Nous avons précédemment montré, in vitro, des défauts intrinsèques des cellules osseuses, avec un nombre plus élevé d'ostéoclastes générés à partir des PBMC (cellules mononucléées du sang périphérique) des patients, et ayant un profil inflammatoire particulier avec une surexpression du récepteur de l'interleukine-1. Dans le modèle murin Ctns-/-, les ostéoblastes présentaient une augmentation de l'Il1β, indépendamment du système RANKL/OPG, ce qui pourrait expliquer l'augmentation de l'ostéoclastogenèse. L'augmentation d'IL1B dans la moelle osseuse des souris agées a un effet sur les populations cellulaires de la niche stromale et impacte les populations de précurseurs de l'ostéolinéage, nous avons donc exploré cette voie dans la cystinose.

L'expression d'IL1B dans les cellules CD45- de la moelle de souris ctns-/- de 4 semaines était significativement augmentée par rapport aux souris ctns+/+ (n=16, p <0.05). Les différentes populations cellulaires présentes dans la niche stromale ont été étudiées par cytométrie en flux sur des souris ctns +/+ et -/- jeunes et âgées. Nous avons observé une augmentation des cellules stromales mésenchymateuses (MSC) peri-sinusoidales (LepR+/PDGFRa+) dans les souris jeunes ctns-/- par rapport aux ctns+/+ (augmentation comparable au taux obtenu pour les souris +/+ âgées).

La cystinose étant une maladie pédiatrique rare et sévère, les biopsies osseuses ne peuvent pas être réalisées chez les patients. Nous avons besoin de nouveaux modèles cellulaires humains, tels que les cellules souches pluripotentes induites (iPSC), afin d'avoir un accès illimité à des ostéoblastes porteurs de différentes mutations de CTNS et à ses précurseurs.

Des iPSC ont été générées à partir de trois patients atteints de cystinose (délétion complète du gène ou mutations ponctuelles), puis ont été différenciées en MSC et en ostéoblastes, avec une lignée corrigée par CRISPR. Celle-ci présentait moins d'IL-1β que les trois autres (p < 0,05) tandis que celle portant une mutation ponctuelle avait une expression augmentée de 10 à 100 fois.

L'IL-18, marqueur substitutif de la voie IL-1, a également été mesuré dans le sérum de patients atteints de cystinose sous traitement conservateur. Chez les 8 patients, les concentrations étaient légèrement augmentées, en moyenne 1,9 fois supérieures à la limite normale supérieure.

L'outil iPSC confirme les résultats murins montrant une activation accrue de la voie IL-1β dans les ostéoblastes cystinotiques, avec une pertinence clinique chez les patients présentant des taux élevés d'IL-18. Ces résultats ouvrent des perspectives thérapeutiques potentielles pour les patients présentant une atteinte osseuse sévère.

Mots clés : maladie rare, cellules souches, progéniteur ostéoblastique

Thème de recherche : Génétique et Physiologie

O23* IMMOBILISATION PASSIVE DE VESICULES EXTRACELLULAIRES SUR IMPLANTS EN TITANE TEXTURÉS PAR LASER FEMTOSECONDE POUR LA RÉGÉNÉRATION TISSULAIRE

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Les vésicules extracellulaires (EVs, 50-500 nm) dérivées de cellules souches mésenchymateuses humaines (hMSC) émergent comme des nanovecteurs naturels de choix en médecine régénérative, grâce à leurs propriétés ostéo-inductrices et immunomodulatrices. Leur intégration à la surface d'implants en titane constitue une stratégie prometteuse pour conférer une bioactivité locale. Cependant, les méthodes d'immobilisation conventionnelles, comme le greffage chimique ou le piégeage dans des hydrogels, risquent d'altérer l'intégrité des EVs et de limiter leur capture ultérieure par les cellules hôtes, compromettant ainsi leur efficacité thérapeutique.

Pour relever ce défi, nous proposons une approche originale de texturation de surface par laser femtoseconde. Cette technique permet de générer des architectures multiéchelles contrôlées (motifs de 50 nm à 1 µm) capables de piéger passivement les EVs, les protégeant lors de l'implantation, tout en préservant leur accessibilité pour les cellules. Plusieurs configurations de texturation (longueurs d'onde du laser : 1030 nm et 515 nm, textures simples ou 2D) ont été évaluées. L'efficacité de rétention des EVs a été quantifiée par Nanoparticle Tracking Analysis (NTA) des solutions avant dépôt et après élutions, et corrélée par microscopie confocale super-résolution et électronique.

Nos résultats démontrent que nos meilleures surfaces texturées retiennent entre 75 et 90 % des EVs déposées, une performance nettement supérieure à celle du titane lisse (rétention de 15-50 %), qui n'offre aucune protection. Ces performances sont reproductibles, que les EVs soient d'origine commerciale ou isolées au laboratoire à partir de cultures de hMSC. Fait intéressant, la longueur d'onde de structuration semble également influencer la sélectivité : les nanotextures réalisées à 515 nm favoriseraient une capture préférentielle des "small EVs" (< 150 nm), tandis que celles obtenues à 1030 nm retiennent l'ensemble de la population vésiculaire.

Les investigations en cours se concentrent sur la confirmation de l'internalisation efficace des EVs immobilisées par les cellules cibles et du maintien de leurs propriétés biologiques. Ces travaux pionniers valident la texturation laser femtoseconde comme une méthode robuste, sans altération chimique, pour fonctionnaliser des implants. Ils ouvrent la voie au développement d'une nouvelle génération d'implants bioactifs, capables d'immobiliser passivement et efficacement une variété de nanovecteurs d'intérêt pour la régénération tissulaire.

Mots clés : Vésicules extracellulaires, texturation laser, implants en titane

Thème de recherche : Biomatériaux

O24* IMPACT DE L'ACTIVITÉ DE LA COMT SUR L'HOMÉOSTASIE OSSEUSE

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Les catécholamines sont connues pour être des médiateurs de la perte osseuse induite par le stress. Leur dégradation dépend de l'enzyme catéchol-O-méthyltransférase (COMT). Des études de cohorte ont montré qu'une variante courante du gène COMT, Met158, est associée à une réduction de 40 % de l'activité enzymatique par rapport à Val158. Cette variante est associée à un risque accru de fracture chez les patients ostéoporotiques, bien que les mécanismes sous-jacents à ce phénotype osseux restent flous.

Les objectifs de cette étude étaient de caractériser le phénotype osseux associé aux variants Val158 et Met158 et d'analyser les mécanismes cellulaires sous-jacents.

Nous avons utilisé des souris humanisées porteuses du variant Met158 ou Val158. La microarchitecture osseuse a été analysée à 3, 6, 10 et 15 mois par micro-tomographie, ainsi que par des évaluations histologiques. In vitro, des lignées cellulaires ostéoblastiques (MC3T3) et ostéoclastiques (RAW) ont été différenciées en présence ou en l'absence de tolcapone, un inhibiteur de la COMT.

In vivo, dans le fémur, la densité minérale osseuse trabéculaire et le rapport BV/TV étaient significativement plus faibles chez les variants Met que chez les variants Val entre 3 et 10 mois (rapport BV/TV de 14 % pour Met contre 20 % pour Val, $P < 0,05$ à 6 mois). La coloration TRAP a révélé une augmentation du nombre d'ostéoclastes chez les souris Met158. Cependant, l'épaisseur corticale a augmenté (243,3 µm pour Met contre 232,2 µm pour Val $p < 0,048$).

La coloration immunofluorescente a montré que l'expression de la COMT est similaire entre les groupes. In vitro, le tolcapone a augmenté l'expression de l'ostéocalcine et de la phosphatase alcaline au jour 7, tant au niveau de l'ARNm que de l'activité ALP. De plus, le tolcapone a amélioré la différenciation ostéoclastique des cellules RAW par rapport aux témoins (augmentation de 2 fois dans les cellules traitées au tolcapone par rapport au témoin, $P < 0,05$).

Ensemble, ces résultats suggèrent qu'une activité réduite de la COMT accélère la différenciation des ostéoblastes tout en augmentant simultanément la différenciation des ostéoclastes, ce qui conduit finalement à une diminution du rapport BV/TV. Ces données éclairent le mécanisme de fragilité osseuse observé chez les porteurs du variant Met158.

Mots clés : Os, COMT, catécholamines

Thème de recherche : Génétique et Physiologie

O25 L'ADMINISTRATION AU LONG TERME DE DAPAGLIFLOZINE (SGLT2I) AMELIORE LA QUANTITE D'OS TRABECULAIRE DES SOURIS OVARIECTOMISEES

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La ménopause et l'ovariectomie s'accompagnent du développement d'une obésité, d'une perte de l'homéostasie glycémique et de l'adiposité médullaire dont les contributions à la fragilité osseuse sont encore mal comprises. Les inhibiteurs du transporteur SGLT2 (SGLT2i) favorisent l'excrétion rénale du glucose et sont employés comme anti-diabétiques. Toutefois, les études cliniques et pré-cliniques rapportent des effets contrastés des SGLT2i sur la composante osseuse et n'ont pas testé leur impact dans le contexte de la carence oestrogénique. Nos objectifs sont donc d'étudier les effets de la Dapagliflozine (DAPA, SGLT2i aux effets prolongés) chez les souris ovariectomisées (Ovx) et leurs contrôles Sham.

L'obésité, l'adiposité médullaire et l'état prédiabétique sont bien établis chez les Ovx au bout de 8 semaines à partir desquelles la DAPA (1µg/g BW/jour) est administrée pendant 1.5 et 3 mois. La glycémie et l'intolérance au glucose des Ovx sont significativement diminuées dès 1.5 mois avec DAPA ; les masses grasses corporelle et périgonadique sont réduites seulement après 3 mois de traitement. Les effets métaboliques de la DAPA chez les Sham sont peu marqués. Chez les Ovx, 3 mois de DAPA augmentent le gain de contenu minéral osseux corporel (x3, p=0.043), le volume osseux trabéculaire (+33%, p=0.0006) et le nombre de travées (+28%, p=0.0025) du tibia proximal, sans modifier la perte d'épaisseur de l'os cortical. Ce même temps de traitement des Sham empêche la perte trabéculaire liée au vieillissement. L'analyse histologique après double marquage montre une augmentation du taux d'apposition du minéral chez les Sham (+36%, p=0.021) et de la surface minéralisée chez les Ovx (+29%, p=0.013) des travées du fémur distal avec 3 mois de DAPA. L'analyse de la qualité osseuse par spectroscopie Raman de ces travées révèle une élévation de la cristallinité chez les Ovx sans impact du DAPA et chez les Sham à 6 semaines de DAPA. L'analyse histologique confirme une élévation de la densité (x2.6 à 5.5, à 1.5 et 3 mois, p <0.01) et du diamètre (~40%, p<0.0002) des adipocytes médullaires pour les Ovx vs Sham sans effet de la DAPA. De premières analyses d'expression génique des cellules osseuses du fémur indiquent que les niveaux d'expression de marqueurs osseux (Alp, Bglap) et anti-résorptif (Opg) augmentent pour les Ovx à 3 mois de DAPA en comparaison des Ovx ou Sham. L'expression de ces marqueurs reste diminuée dans les cellules médullaires des Ovx traitées ou non.

L'administration de DAPA pendant 3 mois améliore la masse osseuse trabéculaire sans en changer la qualité dans l'ovariectomie. Cette amélioration -concomitante à la réduction des tissus adipeux périphériques et non de l'adiposité médullaire- impliquerait une meilleure formation osseuse associée à une ostéoclastogenèse réduite. Outre de nouvelles alternatives thérapeutiques, notre étude offrira une meilleure compréhension de l'adaptation métabolique de l'os dans la ménopause et le vieillissement.

Mots clés : ovariectomie, anti-diabétique, os

Thème de recherche : Génétique et Physiologie

O26 CAPN6+ CANCER STEM CELLS DRIVE METABOLIC REPROGRAMMING AND IMMUNE DEACTIVATION IN OSTEOSARCOMA

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This study investigated mechanisms regulating immune compartment activity in osteosarcoma (OS) by characterizing intratumoral inflammation. We analyzed transcriptomic data from bulk and single-cell RNA sequencing of OS using R-based bioinformatics tools. Inflammation was assessed using an enrichment score for the HALLMARK_INFLAMMATORY_RESPONSE signature (INF). INF scores were primarily driven by macrophage activity which correlated with hypoxia signaling but inversely correlated with mitochondrial activity in tumor cells.

Previous studies identified calpain-6 as a biomarker for cancer stem cells (CSC). Of note, CAPN6-expressing CSCs constituted only 15–30% of the population of OS cell cultures and were detected in 50% of analyzed human tumors. However, we found that variations in CAPN6 expression in bone tumors were differently associated with better 5-year survival rates: a -4.13 $\log_2$ fold change ($p = 9.8 \times 10^{-6}$) for patients with high INF and a $+2.85$ $\log_2$ fold change ($p = 3.2 \times 10^{-5}$) for patients with low INF.

Bulk RNA-seq analyses revealed that CAPN6 expression positively correlated with glycolysis and hypoxia signatures in high-INF OS, but inversely correlated with mitochondrial activity in low-INF OS. ScRNA-seq data revealed that, within high-INF tumors, those lacking CSC exhibited significantly reduced glycolysis signature in their tumor cells—in contrast to high-INF tumors containing even minimal CAPN6+ cell populations. However, comparisons of metabolic gene sets between CAPN6+ and CAPN6- cells within the same culture or tumor showed no significant differences. In silico predictions of metabolic fluxes indicated that calpain-6 knockdown with shRNA in OS cell cultures suppressed glycolysis and altered mitochondrial respiration. These effects were consistent across both CAPN6+ and CAPN6- cells. Knockdown also increased cellular ATP levels in OS cells in a HIF-1α- and glutamine-dependent manner, an effect abolished by the complex II inhibitor Atpenin A5. These findings suggest that CSCs coordinate the suppression of mitochondrial activity and promotion glycolysis in the other tumor cells, potentially explaining why CAPN6 serves as a favorable prognostic marker in low-INF tumors.

Conversely, in high-INF tumors, CAPN6 expression was associated with reduced M1 macrophage infiltration. In hypoxic culture, OS cells suppressed TNF expression in THP1 macrophages—a effect reversed by calpain-6 shRNA in OS cells.

Collectively, our study illustrates that CSCs contribute to immunosuppression and metabolic dysfunction depending on the inflammatory context. Our findings define distinct osteosarcoma subgroups based on inflammatory and metabolic profiles and CAPN6 expression. They suggest that tumors with low INF may be vulnerable to agents targeting metabolism. Moreover, elucidation of mechanisms involved in CSC-dependent immunomodulation could pave the way for strategies to reactivate the immune compartment and sensitize osteosarcomas to immunotherapy.

Mots clés : Osteosarcoma, Cancer Stem Cells, Calpain-6

Thème de recherche : Biologie cellulaire et moléculaire

O27 AIRWAY CALCIFICATION: AN OVERLOOKED PHENOMENON WITH MAJOR RESPIRATORY IMPACT?

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Tracheobronchial calcification is a rare condition observed in elderly individuals during normal aging and in younger patients with Keutel Syndrome (KS), a genetic disorder caused by loss-of-function mutations in Matrix Gla Protein (MGP), a key inhibitor of ectopic calcification. While elderly subjects are often asymptomatic, KS patients develop significant respiratory complications, including dyspnea and airway infections. However, the mechanisms driving tracheobronchial calcification and its functional consequences remain poorly understood.

Using complementary morphological, molecular, functional, and transcriptomic approaches in wild-type (WT, Mgp+/+) and MGP-deficient (Mgp-/-) mice, we provide an integrated characterization of airway calcification. Histological stainings (Alcian blue/Alizarin red, Von Kossa), in situ hybridization, qPCR, and high-resolution micro-CT imaging reveal that calcification of tracheal cartilage rings is an early physiological event in mice, beginning at postnatal day 30 (P30) in WT animals and progressing rostro-caudally with age. This process is associated with terminal differentiation of chondrocytes expressing the hypertrophic marker collagen X. In Mgp-/- mice, mineralization is markedly accelerated, starting at P14 and extending throughout the tracheobronchial tree.

Strikingly, we also uncover an additional and previously unrecognized calcification within the airway mucosa of Mgp-/- mice. This mucosal calcification is restricted to the trachea and bronchi and absent in WT mice, even at advanced age when cartilage rings are fully mineralized. It is accompanied by structural alterations of the overlying epithelium, suggesting a direct impact on epithelial integrity.

Functional assessment using mucociliary clearance assay, combined with mucin quantification, demonstrates that mucosal calcification correlates with epithelial dysfunction. Indeed, Mgp-/- mice exhibit increased mucin production, notably Muc5ac upregulation and impaired mucociliary clearance. Bulk RNA sequencing at P21 further reveals widespread transcriptional modification in Mgp-/- tracheas. Gene ontology enrichment highlights activation of inflammatory pathways, mucin biosynthesis, lipoxygenase signaling, ion transport, and extracellular matrix remodeling. qPCR validation confirms upregulation of key genes including Muc5ac, Mmp12, and CtsS, linking MGP deficiency to elastocalcinosis and altered airway function.

Altogether, this work provides the first comprehensive and integrated description of tracheal calcification in mice and identifies MGP as a key factor in this phenomenon. Beyond accelerating cartilage ring calcification, MGP deficiency induces a previously overlooked mucosal calcification that disrupts epithelial structure and function. These findings suggest that respiratory complications in KS may not solely result from cartilage ring calcification, but from mucosal alterations that compromise airway function and defense mechanisms.

Mots clés : calcification, trachea, mouse model, rare disease

Thème de recherche : Autre

O28 BIOMINERAL PIGMENTATION IN SEA URCHINS

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Red-spherule cells (RSCs) are key players of the innate immune system of sea urchins through the release of polyhydroxylated naphthoquinones (PHNQs) initially enclosed in their cytoplasmic vesicles as dense red granules (Coates et al., 2018). Beyond their antimicrobial activity, PHNQs are responsible for sea urchin biomineral coloration. In Paracentrotus lividus, purple biomineral results from the incorporation of deprotonated spinochrome A, which shifts from red to purple at basic pH (Ferreira et al., 2025). However, how PHNQs are released from RSCs and incorporated into biominerals during crystal growth remains unclear.

Here, we investigated biomineral pigmentation during the regeneration of mineralized spines of P. lividus sea urchins. Fractured spines were allowed to regenerate for several days in seawater, with or without 20 µM calcein. In vivo confocal imaging showed active RSC movement around growing micro-spines, likely providing ideal conditions for biomineralization to occur. Numerous Ca-vesicles (500 nm to 10 µm) were observed, although RSCs did not appear to contain calcium.

Tips of regenerated spines were further high-pressure-frozen, freeze-substituted, and analyzed by cryo-SEM and FIB-SEM. Epidermis, dermis, skeletogenic cells (sclerocytes), phagocytes and RSC were identified (Heatfield & Travis, 1975, Dubois & Ameye, 2001). Serial FIB-SEM enabled the 3D reconstruction of the different cellular features observed at the vicinity of growing micro-spines. Both sclerocytes and RSCs were present at the mineralization front. They connect to micro-spines through a sheath containing isolated pigment vesicles touching the mineral surface, supporting PHNQ release from the cells and incorporation within the mineral.

In addition, TEM of ultrathin sections revealed pigment vesicles having different PHNQs granule density and internally coated by a polysaccharide layer, possibly protecting the cell from acidic pH. Indeed, preliminary measurements of intracellular pH, showed a neutral RSC pH (7.4), while red vesicles darkened at basic pH, suggesting their acidic pH. We therefore propose that vesicle opening may be regulated through pH variations, allowing for PHNQ release at the site of mineralization.

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Mots clés : biomineralization, pigmentation, sea urchins

Thème de recherche : Biominéralisation

P1* SEX-DEPENDENT MOLECULAR REPROGRAMMING DEFINES PHEX-DRIVEN SKELETAL PATHOLOGY IN X-LINKED HYPOPHOSPHATEMIA

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X-linked hypophosphatemia (XLH) is a rare X-linked dominant disorder caused by loss-of-function mutations in PHEX (phosphate-regulating endopeptidase homolog, X-linked), resulting in renal phosphate wasting, impaired skeletal mineralization, rickets, and osteomalacia. Excess FGF23 (fibroblast growth factor 23) is central to disease expression, but the molecular and cellular mechanisms linking PHEX deficiency to disrupted phosphate homeostasis and bone pathology remain incompletely understood.

To define PHEX-dependent signaling networks, we performed integrated transcriptomic profiling and targeted qPCR of tibial cortical bone from one-month-old Hyp (Phex mutant) hemizygous males (Hyp/y), heterozygous females (+/Hyp), and wild-type mice. Differential expression, pathway enrichment, and protein–protein interaction network analyses were used to identify coordinated molecular programs, with qPCR validating key regulators of bone tissue. Differential expression analysis revealed distinct sex-dependent transcriptional signatures in Hyp tibial cortical bone. Male Hyp bone showed enrichment of extracellular matrix (ECM) organization, collagen fibrillogenesis, skeletal morphogenesis, and ossification pathways, consistent with canonical structural pathology in XLH. This was accompanied by induction of Fgf23 and upregulation of metabolic regulators, suggesting involvement of a previously underappreciated metabolic–neuroendocrine axis. In contrast, female Hyp bone displayed profound repression of muscle-related and bioenergetic pathways, alongside enrichment of contractile fiber, ion channel, and muscle system processes, indicative of phosphate-sensitive energetic stress and contractile remodeling distinct from male ECM-dominant responses. Preliminary qPCR data revealed modest sex differences in wild-type bone, with females exhibiting higher Cathepsin K, Bsp (bone sialoprotein), TGF-β (transforming growth factor beta), and a five-fold increase in RANKL (receptor activator of nuclear factor κB ligand), consistent with elevated basal remodeling. In Hyp mice, sex divergence was amplified: female Hyp bone showed markedly elevated RANKL (8.3-fold vs male Hyp, $p<0.001$) with reduced Osteocalcin, Bsp, Cathepsin K, and TGF-β, indicating severe remodeling uncoupling. Increased Osterix (2.2-fold, $p=0.02$) suggested enhanced osteoblast commitment but impaired maturation, while OPN (osteopontin) was five-fold lower than in males ($p<0.001$), reflecting sex-specific disruption of mineralization. Collectively, these data indicate female Hyp bone exhibits amplified osteoclastogenic signaling alongside compromised matrix maturation and defective osteoblast differentiation.

In conclusion, XLH pathogenesis is established early during skeletal development and is strongly sex-dependent at the molecular level. Male Hyp bone is primarily characterized by ECM remodeling, whereas female Hyp bone shows pronounced metabolic dysregulation and increased osteoclastogenic signaling. These findings indicate that beyond the canonical FGF23–phosphate axis, XLH involves distinct sex-specific molecular adaptations in bone. Recognizing these differences will be essential for developing precise, mechanism-based, sex-informed therapeutic strategies.

Mots clés : X-linked hypophosphatemia (XLH), Sex-specific bone remodeling , Osteoclastogenic signaling

Thème de recherche : Biologie cellulaire et moléculaire

P2* NANO-HOLOTOMOGRAPHY IMAGING OF THE SUB-MICROSCOPIC POROSITY NETWORK IN DENTIN

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Tooth sensitivity is a key topic in dental research, but its mechanisms remain unclear. According to the hydrodynamic theory, external stimuli induce fluid flow inside dentinal porosity, activating the odontoblast-nerve complex in the pulp. Thus, the topology of dentinal porosity is crucial to understand fluid-flow activation. Using confocal microscopy [1], it was recently shown that dentinal porosity forms a complex network, suggesting mechanosensing could be more complex than previously thought [2].

While the biggest branches measure 300 to 700 nm in diameter, the smallest branches range from 25 to 200 nm [3], i.e. beyond optical resolution. Therefore, optical microscopy leads to interconnection errors in the network analysis. A higher-resolution ground truth is thus required to validate confocal data and refine error rates. Imaging 100-200 nm branches requires at least 50 nm resolution, along with sufficient field of view (FOV) and short acquisition time to capture representative regions of the porosity network (e.g. a 50×50 µm² FOV contains at least 20 tubules).

As an extension of clinical Computed Tomography (CT), X-ray nano-CT can image dentin tubules [4], but its low absorption contrast never demonstrated sufficient signal-to-noise ratio to visualize branches (SNR > 10 dB). X-ray phase contrast enhances pore interfaces sharpness. Deyhle et. al. [5] visualized tubules using nano-holotomography, but lacked the resolution (0.33 µm pixel size) to image branches. Zanette et. al. [6] used Ptychographic X-ray nano-CT to quantify mineral distributions in human dentin and were able to visualize tubules and branches. However, the long acquisition time limits the number of acquisitions (62×25×30 µm3 at 65 nm pixel size in ~5h30 [6]), preventing statistically robust medical analysis.

Taking advantage of recent advances in nano-holotomography, the present study imaged the dentin porosity network to assess whether a 50 nm resolution could be achieved, allowing visualization of 100 nm branches. Experiments were performed at ESRF ID16B beamline with an energy of 29.6 keV. For this preliminary study, 9 samples were extracted from 2 human molars (19 and 55 year old), 7 from the crown near the dentin-enamel junction and 2 from the root for comparison. 100 scans were acquired at 25 nm pixel size on 50×50×50 µm3 region and 59 scans at 100 nm pixel size on 200×200×200 µm3. Preliminary results demonstrate visualization of ~100 nm branches (SNR ~ 15 dB), the best results to date. This unique dataset will allow to revisit dentin histology with unrivaled resolution and will be available in open- access in June 2027.

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Mots clés : Dentin, Cellular porosity, Nano-holotomography

Thème de recherche : Autre

P3 DYNAMIQUE DES SYNCHONDROSES DE LA BASE DU CRANE ET ACHONDROPLASIE : APPROCHE MULTI-ECHELLE DE LA SOURIS A L'HOMME

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L'achondroplasie (ACH), forme la plus fréquente de nanisme, est due à des mutations faux-sens activatrices du Fibroblast Growth Factor Receptor 3 (FGFR3), régulateur majeur de l'ossification endochondrale. Cette pathologie est caractérisée par un nanisme rhizomélique associé à des anomalies crâniofaciales. La fusion prématurée des jonctions cartilagineuses de la base du crâne, les synchondroses, cause en partie de la dysmorphie faciale caractéristique de l'ACH. La croissance des synchondroses est un processus hautement coordonné et dynamique, dépendant de la régulation de la chondrogenèse, de la croissance des os qu'elles relient, ainsi que des forces mécaniques qui leur sont appliquées. Cependant, les dynamiques tridimensionnelles (3D) des populations cellulaires des synchondroses au cours du développement ainsi que leurs réponses aux stimuli mécaniques sont mal caractérisées. Ce projet vise à décrypter ces processus dans un contexte physiologique et dans le cadre l'ACH, en combinant 1) une analyse 3D de la dynamique des populations cellulaires des synchondroses de souris contrôles et ACH (Fgfr3Y367C/+) au cours du développement, 2) l'étude de l'impact des stimuli mécaniques sur le transcriptome de ces populations cellulaires à partir de culture ex vivo et, 3) la modélisation de l'évolution des synchondroses au cours du développement humain, à partir de données scanographiques de sujets sains et ACH.

Pour répondre à ces objectifs, nous mettons en place un protocole de clarification de bases du crâne de souris âgées de E14.5 à P14 combiné à l'analyse de marqueurs de la chondrogenèse et de l'ostéogénèse tels que Sox9, Col2a1, Col10a1 et Col1a1 par RNAscope et immunomarquage suivi de l'acquisition d'images par microscopie à feuilles de lumière et de l'analyse 3D des populations cellulaires. A ce jour les protocoles de clarification, RNAscope et immunofluorescence sont validés, permettant une visualisation 3D des synchondroses murines embryonnaires. De plus, afin d'étudier l'influence des forces mécaniques sur la croissance des synchondroses, nous développons un système ex vivo permettant de soumettre des bases crâniennes explantées à une compression cyclique (≈2 Hz, <2 N, durant 6 jours). Cette compression est réalisée grâce à un ballonnet de Fogarty actionné par un pousse-seringue électrique. Quant à l'analyse de données humaines, des scanners pré et postnataux de patients sains et atteints d'achondroplasie jusqu'à 19 ans ont été collectés. Le protocole de marquage de repères anatomiques est établi et permettra de caractériser les variations de forme des synchondroses et du crâne de manière objective et quantitative.

Cette approche multi-échelle permettra une caractérisation nouvelle des synchondroses dans le modèle murin d'ACH. À terme, la compréhension des mécanismes de mécanotransduction au sein de ces structures pourrait ouvrir la voie à des stratégies thérapeutiques non chirurgicales, fondées sur la stimulation mécanique de la base du crâne.

Mots clés : Achondroplasie ; Synchondroses de la base du crâne ; Mécanotransduction

Thème de recherche : Autre

P4* CIRCULATING EVS FROM ZUCKER DIABETIC FATTY RATS' PLASMA DIFFERENTIALLY MODULATE MESENCHYMAL STROMAL CELL FUNCTIONALITY AND OXIDATIVE STRESS

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Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder associated with increased bone fragility, delayed fracture healing, and impaired bone regeneration. Parallel to the increasing incidence of T2DM, skeletal complications represent an escalating clinical challenge, while effective therapeutic strategies remain limited. Bone marrow mesenchymal stem cells (BMMSCs) are key regulators of bone homeostasis and repair, but their functionality seems compromised in the T2DM microenvironment. Recently, extracellular vesicles (EVs), a heterogeneous group of small membranous structures, have gained attention as they can modulate intercellular communication during bone homeostasis and repair. Emerging evidence indicates that circulating EVs contribute to the pleiotropic effects of T2DM. However, their influence on the functional properties of BMMSCs remains poorly investigated.

The present study aimed to characterize the profile of circulating EVs in the plasma of Zucker Diabetic Fatty (ZDF) rats and evaluate their effects on the functions of diabetic and healthy rat BMMSCs.

Blood was harvested from 24-week-old ZDF and healthy controls, Zucker Lean (ZL) rats. Plasma was isolated by centrifugation, and its biochemical profile was characterized. A highly enriched EVs fraction was obtained by filtration. EVs concentration and size distribution were analyzed using nanoparticle tracking analysis. The effects were evaluated on ZDF-BMMSCs and ZL-BMMSCs migration, adhesion, and proliferation. Moreover, intracellular and mitochondrial reactive oxygen species (ROS) in both cell populations were assessed.

Plasma from ZDF rats exhibited higher levels of glucose (40.68 ± 1.3 mmol/l), glycated hemoglobin C (11.9 ± 2.01%), and an altered lipid profile. Compared to the ZL- plasma-enriched EVs fraction (ZL-PEF), the ZDF-PEF contained 3.2-fold more EVs (7.4x1011±1.6x1011 Vs 2.4x1012 ± 9.1x1011 particles/ml, $p<0.01$), while EVs size was inferior to 200 nm with no mean size differences (91.7 ± 6.3 x vs 88.5 ± 6.2 nm). In contrast to ZL-PEF, the ZDF-PEF added in culture medium reduced migration (21.9%; $p<0.0001$), and delayed adhesion (at 4H, 52.3% $p<0.01$) of ZDF-BMMSCs. Moreover, it inhibited ZL and ZDF-BMMSCs proliferation, while under the same conditions, ZL-PEF increased the proliferation rate by 1.6-and 3.3-fold ($p<0.001$), for ZDF and ZL-BMMSCs, respectively. Exposure of ZDF-BMMSCs to ZDF-PEF significantly increased cytosolic ROS levels by 25% and 23% compared to baseline and ZL-PEF, respectively ($p < 0.001$ for both comparisons). In contrast, both ZL-PEF and ZDF-PEF significantly increased mitochondrial ROS levels compared to baseline (by 30% and 50%, respectively; $p < 0.001$ for both), with no significant differences observed between them.

These findings show that circulating EVs in plasma alter BMMSCs functionality and oxidative stress status and may have implications in autologous and/or allogenic cell-based therapies in the T2DM context.

Mots clés : Diabetes Mellitus, Mesenchymal Stromal Cells, Plasma circulating extracellular vesicles

Thème de recherche : Biologie cellulaire et moléculaire

P5* IN VITRO CHARACTERIZATION OF BIOACTIVE 3D-PRINTED BIOMATERIALS FOR MANDIBULAR REGENERATION

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Reconstruction of large mandibular defects caused by tooth extraction, trauma, or disease remains a major clinical challenge, particularly for vertical bone augmentation. Key challenges include maintaining scaffold volume and stability to support bone regeneration, promoting vascularization and osteogenesis, and allowing timely and spontaneous biodegradation, while supporting soft tissue healing. As part of the ANR MandiBone3D (24-CE17-6811-02) project, our collaborators (Team IEM) are developing bioactive materials that incorporate Dental Pulp Stem Cells (DPSC)-derived secretome in conditioned medium (CM-Sc), embedded into 3D-printed hydrogels or polymer microspheres forming scaffolds. These CM-Sc scaffolds are designed to provide osteogenic cues and support tissue repair, highlighting the potential of CM-Sc-based strategies for mandibular bone regeneration.

Our objective is to assess the in vitro biocompatibility of these bioactive materials, ensuring their safety, functionality, and translational relevance. This involves assessing cytotoxicity and osteogenic differentiation potential. To achieve this, primary human oral cells — including osteoprogenitors from periosteum and alveolar bone, and gingival fibroblasts — have been collected from healthy donors through the ORCELL biobank (DC-2021-4509, Team Santé Orale).

Using these cells, 2D and 3D in vitro models were developed to mimic the post-extraction alveolar socket environment. In the 2D models, cellular responses were evaluated under three conditions: CM-Sc alone, scaffolds alone, and CM-Sc combined with scaffolds. Cell viability was assessed using Live/Dead staining, proliferation by cell counting and DNA/RNA quantification, and cell morphology by scanning electron microscopy (SEM). 3D models using cell-printing techniques are currently under development to further assess biomaterial performance and biocompatibility in a more physiologically relevant environment prior to preclinical studies.

Preliminary 2D experiments indicate that CM-Sc partially compensates for low serum conditions, improving cell survival, but no proliferation-enhancing effects were observed in fibroblasts or periosteal cells. Future experiments will also assess differentiation potential in primary oral cell types. Additionally, preliminary testing of 3D-printed hydrogels with periosteal cells indicated that cell viability was preserved. Ongoing experiments will evaluate the addition of the CM-Sc to these 3D-printed hydrogels to further assess their regenerative potential. Future in vivo studies will assess bone repair, vascularization, and integration within host tissue in mandibular defects, bridging the translational gap toward clinical application (Team LBN).

Mots clés : Mandibular bone defects, in vitro, 3D-printed hydrogels, secretome

Thème de recherche : -

P6 L'INHIBITION DU TRANS-SIGNALLING DE L'INTERLEUKINE 6 PREVIENT LA CALCIFICATION DES CELLULES INTERSTITIELLES DE LA VALVE AORTIQUE INDUITE PAR L'INDOXYL-SULFATE

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Introduction. Le rétrécissement aortique calcifié (RAC) est une pathologie dégénérative caractérisée par une calcification progressive des feuillets de la valve aortique. Chez les patients atteints de maladie rénale chronique (MRC), le RAC est plus fréquent, évolue plus rapidement et est associé à un pronostic plus défavorable qu'en population générale. À ce jour, aucun traitement n'existe pour prévenir la progression du RAC. Les études de notre laboratoire montrent que l'indoxyl-sulfate (IS), une toxine s'accumulant dans le sang des patients souffrant de MRC, favorise la calcification des cellules interstitielles de la valve aortique (VICs) en augmentant la sécrétion d'interleukine 6 (IL6) par les macrophages. L'IL6 peut agir sur les cellules via deux voies de signalisation : cis et trans. Dans la voie cis, l'IL6 se lie à son récepteur membranaire IL6Ra, qui se dimérise avec la protéine transmembranaire gp130 pour activer la voie JAK/STAT. Dans la voie trans, l'IL6 se lie à la forme soluble d'IL6Ra (sIL6Ra), formant un complexe qui fixe ensuite gp130 pour déclencher la signalisation. L'objectif de notre étude était de déterminer si le ciblage de l'IL6 permet de prévenir la minéralisation des VICs induite par les macrophages exposés à l'IS.

Méthodes. L'expression de gp130, IL6Ra et sIL6Ra a été évaluée dans des VICs primaires et des macrophages dérivés de THP1 par qPCR et western blot. La capacité des cellules à sécréter l'IL6 et sIL6Ra a été mesurée par ELISA. Les VICs ont ensuite été exposées à un milieu conditionné (MC) provenant de macrophages non traités (MC-CT) ou traités par IS (MC-IS), en présence ou non de sgp130Fc (un antagoniste de la voie trans). La phosphorylation de STAT3 et l'expression de RUNX2 ont été suivies par western blot. La minéralisation des VICs a été quantifiée par O-cresolphthalein complexone.

Résultats. Les VICs expriment gp130 mais pas IL6Ra. Ceci indique que ces cellules ne sont pas capables de transduire le signal via la voie cis, mais qu'elles peuvent répondre via la voie trans lorsque sIL6Ra est présent dans le milieu. Confirmant cette hypothèse, l'exposition à une forme recombinante du complexe IL6/sIL6Ra induit la phosphorylation de STAT3, l'expression de RUNX2 et la minéralisation des VICs. Cet effet est bloqué par sgp130Fc. Les macrophages exposés à l'IS ne sécrètent pas sIL6Ra, mais l'exposition des VICs au MC-IS induit la sécrétion de sIL6Ra. L'usage de sgp130Fc bloque l'activation de STAT3, l'induction de RUNX2 et la minéralisation des VICs induites par le MC-IS.

Conclusion. Le blocage du trans-signalling de l'IL6 prévient la minéralisation des VICs induite par les macrophages exposés à l'IS. À l'avenir, nous vérifierons si l'usage de sgp130Fc permet de ralentir la progression du RAC dans un modèle animal de MRC. Des études sont en cours afin de vérifier si une corrélation existe entre les concentrations circulantes de sgp130 et la sévérité du RAC en clinique.

Mots clés : Rétrécissement aortique calcifié, Maladie rénale chronique, Interleukine 6

Thème de recherche : Biologie cellulaire et moléculaire

P7* POTENTIATING ENDOGENOUS BMP SIGNALING VIA PEPTIDE-MEDIATED INHIBITION OF MGP AND NOGGIN FOR BONE REPAIR

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Critical-sized bone defects are associated with impaired regenerative capacity and frequently require specialized therapeutic intervention. Successful healing depends on the restoration of vascularization, which in turn fosters effective bone formation. Over the years, numerous strategies have been explored to optimize this process. Among them, bone morphogenetic proteins (BMP-2/4/7), particularly BMP-2, have emerged as strong candidates due to their well-established pro-osteogenic and pro-angiogenic properties. However, exogenous administration of BMPs at supraphysiological doses has been associated with significant adverse effects, including ectopic calcification, which often requires secondary surgical intervention.

In this context, the present project aims to harness BMPs' potential by enhancing their endogenous bioavailability and biological activity. To achieve this objective, we propose to prevent their interaction with endogenous inhibitors, with a particular focus on matrix Gla protein (MGP), a potent inhibitor of vascular calcification. Our strategy entails the release of BMP-2/-4/-7 from inhibitory sequestration, thereby potentiating BMP signaling and promoting the angiogenic and osteogenic responses required for efficient bone regeneration.

In silico structural modeling and molecular docking analyses were conducted to design peptides targeting the interaction interfaces between BMPs and their antagonists. A dedicated screening method was subsequently implemented to identify candidates capable of modulating these interactions. This approach enabled the identification of three lead peptides that enhanced BMP-mediated signaling by interfering with binding to MGP and another key BMP inhibitor, Noggin. Next, the regenerative potential of these peptides was evaluated in vitro through RT-qPCR and tube formation assays.

In parallel, the lead peptides are being incorporated into a silanized hyaluronic acid (Si-HA) hydrogel developed as a local delivery system for the impaired bone niche. This injectable biomaterial is designed to enable sustained release, thereby prolonging BMP signaling and supporting angiogenic and osteogenic regeneration.

Together, these results support a novel peptide-based strategy to potentiate endogenous BMP activity and provide a promising foundation for future regenerative therapies for critical bone defects and complex conditions such as osteoradionecrosis where both angio- and osteo-genesis processes are impaired.

Mots clés : Osteogenesis, Bone Morphogenetic Protein, Inhibitory peptide

Thème de recherche : Biologie cellulaire et moléculaire

P8 DIFFUSE INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS AND REHUMATOID ARTHRITIS: IDENTIFICATION OF NEW BIOMARKERS OF FIBROSIS AND/OR INFLAMMATORY FORMS

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Diffuse interstitial lung diseases (ILDs) comprise a heterogeneous group of disorders characterized by inflammatory and fibrosing involvement of the pulmonary parenchyma. They are a common manifestation of systemic sclerosis (SSc) and rheumatoid arthritis (RA) and represent the third leading cause of death after cardiovascular diseases and cancers, with a median survival of 3 to 10 years in symptomatic patients. Available therapeutic options remain limited, and improving both survival and functional outcomes remains a major challenge in patient management. This requires early diagnosis to enable timely initiation of treatment, as well as rapid detection of disease progression and/or treatment failure in order to allow prompt adjustment of therapy.

To identify innovative preclinical biomarkers capable of predicting progression of ILD toward a fibrosing phenotype, we use two murine preclinical models. The transgenic Fra-2 (TgFra2) model reproduces the main features of SSc, including a progressive fibrosing ILD that develops between 14 and 18 weeks of age, associated with worsening respiratory symptoms, abnormalities on thoracic micro-CT, impaired lung function, and characteristic histological lesions. The second model consists of transgenic mice expressing human TNF 3647 (TghTNF). These mice develop a polyarthritic phenotype leading to progressive functional impairment, which is fully controlled by anti-TNF treatment (infliximab). They also exhibit a non-fibrosing inflammatory lung involvement detectable by micro-CT, which worsens between 14 and 18 weeks and is likewise reversible under infliximab treatment.

Our objective is to better characterize the molecular mechanisms leading to fibrosing progression of ILD, and also to identify molecules specific to inflammation and fibrosis whose expression increases over time in murine extracellular vesicles (mEVs) isolated from sera and lungs of TgFra2 and TghTNF mice. Our preliminary results show that serum-derived TghTNF mEVs do not activate the expression of fibrosis markers (αSMA, LOX, Col1α, and TGFβ), but do induce the expression of inflammatory markers (IL-6 and NF-κB). Comparison with lung-derived mEVs, and with mEVs isolated from TgFra2 mice, is ongoing. In parallel, we have begun the biochemical characterization of the different mEV populations by nanoparticle tracking analysis and transmission electron microscopy. Their composition will subsequently be investigated using a comprehensive multi-omics approach: transcriptomics by RNA sequencing (RNA-Seq), proteomics by high-resolution mass spectrometry (LC–MS/MS), and metabolomics by nuclear magnetic resonance (NMR). This strategy should enable a better understanding of the pathophysiology of fibrosing progression in ILD and help identify innovative biomarkers.

Mots clés : Rheumatoid Arthritis, Extracellular Vesicles, Fibrosis

Thème de recherche : Génétique et Physiologie

P9 3D BIOPRINTING OF OSTEOCHONDRAL UNIT WITH INDUCED NEURAL CREST CELLS USING A NATURAL TRI-COMPONENT BIOINK

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Due to its avascular nature, articular cartilage has an extremely limited capacity for regeneration, making degenerative or traumatic lesions particularly prone to progressing toward osteoarthritis. This condition currently affects more than 500 million people worldwide and, to date, no curative treatment is available underscoring the need for biologically relevant cell-based regenerative strategies. Nasal chondrocytes which embryologically derived from neural crest cells have emerged as a promising cell source for articular cartilage repair, demonstrating promising superior chondrogenic potential than mesenchymal stromal cells and the ability to generate hyaline-like cartilage closely resembling native tissue.

In this study, we established a stepwise differentiation protocol to derive skeletal lineage cells from human induced pluripotent stem cells (iPSCs) via a neural crest intermediate. Human iPSCs were first differentiated into induced neural crest cells (iNCCs), which exhibited stable expression of canonical NCC markers. These iNCCs were subsequently committed to a mesenchymal stromal-like phenotype (iMSC-NCC), expressing relevant mesenchymal markers.

The iMSC-NCCs multilineage differentiation capacity was assessed using standardized growth factor-based protocols for 21 days. Under chondrogenic conditions, gene expression analysis revealed a significant upregulation of key cartilage markers, including collagen type 2B, aggrecan and SOX9. Under osteogenic conditions, bone markers such as alkaline phosphatase and osteocalcin were markedly increased, confirming their skeletal differentiation potential.

Following validation of their differentiation potential, iMSC-NCCs were successfully bioprinted in a fibrin–gelatin–alginate bioink crosslinked with a transglutaminase/calcium chloride/thrombin solution. These cell-laden constructs were cultured for 21 days in the respective induction media. Cell viability was maintained over time, as demonstrated by Live/Dead staining on days 1 and 21. In vitro characterization of the rheological and biological properties of the constructs is ongoing.

In conclusion, we have demonstrated that iNCC-MSCs have a higher capacity than MSCs to generate chondrocytes in vitro and a reduced capacity to form hypertrophic chondrocytes. Further in vivo validation using a subcutaneous mouse model will follow to assess therapeutic efficacy and tissue integration.

Mots clés : Bioprinting, Neural Crest Cells, Cartilage

Thème de recherche : Développement et différenciation

P10* IN VITRO MODELING OF OSTEOGENESIS IMPERFECTA USING MECHANICALLY STIMULATED 3D BONE-ENGINEERED CONSTRUCTS AND ASSESSMENT OF THE RESPONSE TO SETRUSUMAB

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Osteogenesis imperfecta (OI) is a rare genetic skeletal disorder characterized by defective type I collagen and impaired bone matrix organization, leading to severe bone fragility. Robust in vitro models that recapitulate both the mechanical and structural features of pathological bone are still lacking. This study aims to develop mechanically stimulated 3D bone–engineered constructs reproducing OI.

Dental Pulp Stem cells from permanent teeth (DPSCs) or exfoliated deciduous teeth (SHEDs), derived from healthy donors and OI patients were cultured within perfusion bioreactors. Prior to cell seeding, commercially obtained decellularized human bone fragments were shaped to fit the bioreactor and subsequently demineralized, yielding 3D human bone-derived matrices. Control and OI cells were then seeded onto the scaffolds and cultured for 28 days in osteogenic induction medium. The bioreactors provided controlled dynamic mechanical stimulation and culture medium perfusion, mimicking physiological conditions exerted on bone. A subset of the OI-derived constructs was treated with setrusumab, a humanized monoclonal antibody targeting sclerostin. Acellular constructs were used as negative controls. After 28 days of culture, constructs were characterized using complementary multi-scale approaches, including mechanical stiffness testing, micro-computed tomography (µCT), and histological analyses to assess the organization of the extracellular matrix and bone tissue mineralization.

Regardless of cell type, cells were predominantly localized at the periphery of the constructs. Analysis of bone volume fraction (BV/TV) and mechanical stiffness revealed a cell type– and treatment-dependent response over time. After 28 days of culture, an increase in both BV/TV and mechanical stiffness was observed in constructs seeded with healthy DPSCs, OI DPSCs, and setrusumab-treated OI DPSCs, compared with the initial time point (D0). In contrast, no detectable BV/TV was measured at D28 in constructs seeded with SHEDs, regardless of donor status or treatment. Notably, despite the absence of detectable BV/TV, constructs seeded with antibody-treated OI SHEDs exhibited a significant increase in mechanical stiffness at D28 compared with D0.

Our preliminary histological analyses using Alizarin Red S, von Kossa, and Sirius Red staining, restricted to the central region of the constructs, did not reveal any mineralized areas, regardless of cell type or treatment condition. Further investigation of additional regions of the scaffolds, particularly the peripheral zones where the cells were predominantly localized are needed. Complementary analyses are currently underway and will be performed across multiple scaffold regions. These analyses include Raman spectrometry and immunohistochemical characterization of extracellular matrix components.

Mots clés : Osteogenesis imperfecta, 3D bone–engineered constructs, bioreactor

Thème de recherche : Biomatériaux

P11 THE ROLE OF GLUCOSE METABOLISM IN THE PATHOPHYSIOLOGY OF OSTEOARTHRITIS

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Introduction. Osteoarthritis (OA) is a whole joint degenerative disease mainly characterized by progressive articular cartilage degradation. Cartilage is an avascular matrix produced and renewed by chondrocytes, the only cells present in cartilage. In this hypoxic environment, chondrocytes mainly use glycolysis as their principal source of energy. In OA, the ratio between glycolysis and Tricarboxylic acid cycle (TCA) is dysregulated. Interestingly, many investigations demonstrated that glucose metabolism has a key role in the progression of OA, but the mechanisms are not well understood. We hypothesize that glucose metabolism dysregulation in chondrocytes induces cartilage degradation and inflammation.

Methods. Primary chondrocytes extracted from femoral heads and knee joints of 4/6-day-old WT mice pups were cultured for 24 hours with or without IL-1β to mimic OA in vitro (n=4). Gene expression was evaluated by RT-qPCR. Extracellular glucose concentration was evaluated in the supernatant of primary chondrocytes. GLUT1 subcellular localization was analyzed by immunofluorescence. Femoral heads from 10-week-old WT mice were stimulated for three days with IL-1β in presence or absence of mitochondrial pyruvate carrier (MPC) inhibitor, UK-5099. Samples were fixed for histological analyses (n=4). After ethical approval, OA was induced in vivo by destabilization of the medial meniscus (DMM) surgery in 10-week-old WT mice. Eight weeks post-surgery, mice were sacrificed for histological analysis (n=6). Human cartilage explants were stimulated for 6 days with or without IL-1β in the presence or absence of UK-5099 and prepared for histological analysis (n=3).

Results. In chondrocytes stimulated with IL-1β, glucose consumption and glycolytic genes expression were upregulated, but TCA genes expression was downregulated. GLUT1, GLUT3 and GLUT6 genes expression were increased. Surprisingly, GLUT1 was relocated from the plasma membrane to the cytoplasm of cells. Ex vivo and in vivo, we confirmed that GLUT1 and GLUT3 protein expression were upregulated and an overexpression of PFKFB3 expression, a key enzyme in the regulation of glycolysis. In murine cartilage explants, inhibition of MPC increased proteoglycan production observed after Safranin-O staining, reduced 8-OHdG (oxidative stress marker) and MMP13 expression. In human explants, we observed a loss of alcian blue staining after IL-1β stimulation but not in the ones treated with UK-5099. 8-OHdG, IL-18 and MMP13 protein expression were increased post IL-1β stimulation but not in explants treated with UK-5099.

Conclusion. In OA models, glucose metabolism was dysregulated with an increased glucose consumption associated with GLUT3 and GLUT6 upregulation, upregulation of glycolytic genes with higher PFKFB3 protein expression. Moreover, inhibiting MPC reduces cartilage degradation, inflammation and oxidative stress, suggesting that pyruvate entry in the mitochondria could be deleterious in OA.

Mots clés : Osteoarthritis, glucose metabolism

Thème de recherche : Biologie cellulaire et moléculaire

P12 LA LEUCETTAMINE B ET LE PINCTAZOLE, DERIVE DE LA NACRYLINE, FAVORISENT L'OSSIFICATION ENDOCHONDRALE : ISOLEMENT, SYNTHESE DES ANALOGUES, ANALYSE IN SILICO ET ACTIVITES BIOLOGIQUES

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De nos jours, nous manquons de solutions pharmacologiques conçues pour stimuler l'ossification endochondrale, qui joue un role crucial dans la réparation des fractures des os longs.

Dans la recherche de nouveaux composés actifs, les organismes marins, en particulier les éponges calcaires et les huîtres perlières ont été étudiés. Deux composés naturels, la leucettamine B et la nacryline, ont été isolés respectivement de l'éponge Pericharax orientalis et de la nacre de l'huître perlière Pinctada margaritifera. Il est intéressant de noter que la leucettamine B et la nacryline présentent des similitudes structurelles significatives. Une bibliothèque de 20 dérivés des deux molécules a été synthétisée. Une nouvelle voie de synthèse a été développée pour accéder à la leucettamine B et à ses dérivés par fonctionnalisation tardive.

Trois composés ont démontré une activité sur le test ColX-MetLuc-ATCD5 à 0,2 mM. Parmi eux, le pinctazole, un analogue synthétique de la nacryline, a significativement stimulé l'ossification endochondrale et la minéralisation matricielle par les cellules ATDC5. L'analyse in silico a révélé que ce composé exerce des effets régulateurs multicibles et multivoies sur l'ossification endochondrale. Des études de docking moléculaire ont montré que le pinctazole avait la plus grande affinité de liaison avec Src. De plus, une évaluation pharmacocinétique in silico a indiqué que ce composé pourrait être bien absorbé.

Dans l'ensemble, nos résultats suggèrent que le pinctazole pourrait être un candidat prometteur pour promouvoir la réparation osseuse.

Mots clés : Leucetamine B, Eponges, Nacre, ossification endochondrale

Thème de recherche : Autre

P13* ROLE OF I-BAR PROTEINS IN OSTEOCLAST FORMATION AND FUNCTION

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Bone is a dynamic tissue that undergoes continuous remodeling through the coordinated actions of osteoblasts, which are responsible for bone formation, and osteoclasts, which mediate bone resorption. Osteoclasts are large, multinucleated cells that are derived from myeloid precursors and are specialized in degrading the mineralized bone matrix. Disruptions in osteoclast formation or function, due to aging, chronic inflammation, or bone tumors, can deregulate this balance and lead to skeletal disorders such as osteoporosis. Current treatments for osteoporosis, such as bisphosphonates, reduce osteoclast viability. However, because osteoblast and osteoclast functions are closely interconnected, these treatments can also impair bone formation, highlighting the need for more targeted therapeutic strategies.

Osteoclastogenesis involves the fusion of myeloid precursors through the formation of tunneling nanotubes and the acquisition of bone-resorbing capacity, both of which depend on dynamic actin cytoskeleton remodeling. My project focuses on I-BAR proteins, key regulators of membrane curvature and actin dynamics. In particular, IRSp53 has been described as a crucial linker between Rho-GTPase signaling and the actin cytoskeleton, regulating protrusion and migration in other cell types. However, their involvement in osteoclast differentiation and function remains poorly explored.

To investigate this, we use two osteoclast models, human osteoclasts derived from peripheral blood monocytes and murine osteoclasts derived from immortalized myeloid precursors. Using siRNA and CRISPR–Cas9 approaches, we individually knock out I-BAR proteins, including IRSp53, to study their roles in osteoclast fusion, cytoskeletal organization, and bone-resorbing capacity.

By identifying novel regulators of osteoclast function, this project aims to provide new mechanistic insights and should pave the way for the development of more precise therapies for bone diseases.

Mots clés : osteoclasts, actin dynamics, membrane curvature

Thème de recherche : Biologie cellulaire et moléculaire

P14* SCHWANN CELLS REGULATE TRANSCRIPTIONAL AND TRANSLATIONAL PROFILES OF STEMNESS MARKERS IN STEM CELLS FROM HUMAN EXFOLIATED DECIDUOUS TEETH

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Schwann cells (SCs) are glial cells of the peripheral nervous system that are essential for axonal maintenance and regeneration. SCs seem to play an important role in promoting angiogenesis and osteogenesis, implying a broader role in tissue regeneration. Stem cells from human exfoliated deciduous teeth (SHEDs) exhibit high proliferative and differentiation potential and display robust pro-angiogenic and pro-osteogenic properties. Our aim is to evaluate the impact of SCs on SHEDs' stemness and osteogenic potential. In order to assess SCs' impact on SHEDs under direct contact, we produced spheroids of SCs and SHEDs (1:1 proportion) and cultured them in basal or osteogenic conditions for 7 days. Histological and immunofluorescence analyses showed that SHEDs+SCs spheroids were bigger and less dense than SHEDs-only spheroids with SHEDs predominantly localized in the spheroid's core while SCs were at the periphery. After dissociating the spheroids, gene expression of each cell type was analyzed. In basal conditions, SHEDs co-cultured with SCs (SHEDs-co) had a panel of stemness markers (OCT4, SOX2, NANOG, and KLF4) upregulated at a gene level relative to SHEDs-only. At a protein level, no differences were detected in NANOG level, SOX2 was upregulated, while OCT4 was downregulated. Under osteogenic conditions, no differences were observed for KLF4, and the early osteogenic markers COL1A1 and RUNX2 were downregulated in SHEDs-co relative to SHEDs-only, while no differences were detected for ALPL and BGLAP. At a protein level, OSX was downregulated in SHEDs-co relative to SHEDs-only. A different scenario was observed when investigating the paracrine effect of SCs on SHEDs. After culturing SHEDs in 2D for 7 days in SCs-conditioned medium, we detected a downregulation of the stemness markers OCT4, KLF4, and NANOG. At a protein level, SOX2 and NANOG were upregulated, whereas OCT4 was downregulated. Concerning SCs, to determine the molecules through which SCs impact SHEDs' stemness markers, gene expression of functional candidate markers (VEGFA, CNTF, PDGFA, and PTH) was assessed in SCs and SCs co-cultured with SHEDs (SCs-co). No differences were detected for VEGFA and PTH, while CNTF and PDGFA were downregulated. Our preliminary findings suggest that SCs regulate SHEDs' stemness through direct contact while the paracrine effects of SCs do not produce the same results. However, the factors mediating SCs' mechanism of action remain unidentified. Further analyses are required to confirm our results and to uncover the mechanism of SCs' regulatory functions on SHEDs' stemness.

Mots clés : Innervation, tissue homeostasis, paracrine signaling

Thème de recherche : Biologie cellulaire et moléculaire

P15 QUANTITATIVE PHOSPHOPROTEOMICS ANALYSIS TO DETERMINE THE ROLE OF INTEGRIN ALPHA 10 IN CHONDROCYTE MECHANOTRANSDUCTION

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Introduction. Integrins function as key mechanotransducers in multiple cell types, and notably the chondrocytes. This study focuses on integrin α10, the most abundantly expressed integrin in chondrocytes, whose role in cartilage mechanobiology is still unknown. The objective of this project was to determine the phosphoproteomic profile of the chondrocytes under dynamic compression in order to decipher the integrin α10–dependent and –independent signaling, thereby advancing our understanding of the molecular mechanisms governing cartilage responses to mechanical loading.

Methods. We established an original cellular model in which murine chondrocytes—wild-type (WT) or integrin α10 knockout (KO)—were cultured under static conditions or subjected to cyclic compression for 5, 15, or 30 minutes within an agarose gel matrix. Quantitative proteomics and phosphoproteomics analyses were performed to identify compression-responsive proteins and integrin α10–dependent signaling events (14 experimental conditions). Following protein digestion, samples were analyzed by label-free quantification while the peptides were enriched using Zr-IMAC HP beads prior to LC–MS/MS analysis. Raw data were processed using Proteome Discoverer version 3.1 (Thermo Scientific) with the Chimerys search engine.

Results and Conclusion. Our comparative phosphoproteomic profiling of WT and KO chondrocytes revealed that loss of α10 significantly alters the molecular signaling in response to dynamic compression. KEGG pathway enrichment analysis highlighted a prominent involvement of focal adhesion kinase–associated signaling pathways. These initial findings will be integrated with transcriptomic data obtained from WT and KO chondrocytes subjected to the same dynamic compression regimen.

Mots clés : chondrocytes; integrin α10; phosphoproteomics; mechanotransduction;

Thème de recherche : Biologie cellulaire et moléculaire

P16* ENGINEERING LIPID NANOPARTICLES: FROM TUMOR CELL TARGETING TO BIOMINERAL VESICLE SYSTEMS

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Nanomedicine aims to improve anticancer therapies by enhancing drug selectivity while limiting systemic toxicity. However, most targeting strategies rely on passive accumulation or ligand–receptor recognition, often overlooking intrinsic physicochemical differences between tumor and healthy cell membranes. Cancer cells exhibit altered lipid composition, membrane organization, and fluidity, which influence nanoparticle interactions and cellular uptake. During my PhD, I investigated whether tuning liposomal membrane fluidity could enhance selective drug delivery through physicochemical compatibility with tumor cell membranes.

Lipid-based nanocarriers with controlled membrane rigidity were engineered by modulating phospholipid composition to encapsulate vincristine. Physicochemical characterization (size, surface charge, membrane fluidity, encapsulation efficiency) and biological evaluation on prostate, colon, and breast cancer cell lines versus non-tumor controls were performed using viability assays, flow cytometry, and confocal microscopy, with complementary diffusion studies in 3D printed hydrogel tumor models. Our results demonstrate that membrane fluidity is a key determinant of liposome–cell interactions: fluid vincristine-loaded liposomes significantly decreased cancer cell viability while sparing non-tumor cells, as confirmed by confocal evidence of intracellular drug release and mitotic spindle disruption. In 3D models, fluid formulations showed improved diffusion and maintained selective tumor cell interaction, highlighting membrane biophysics as a critical design parameter for selective nanocarrier development.

Building on this expertise in vesicular systems and membrane-controlled processes, my postdoctoral research shifts toward pigmentation of biominerals in sea urchins. The project focuses on pigment-containing vesicles involved in color regulation during calcium carbonate formation. By isolating native vesicles and developing biomimetic microcompartments, we aim to investigate how physicochemical parameters such as pH, Ca^{2+}, and carbonate ions regulate pigment release at the mineralization front and possibly mineral nucleation as well as pigment–mineral interactions. This transition extends my research from therapeutic nanocarriers to biologically driven mineral systems, while maintaining a central theme: understanding how membrane-bound compartments govern selective transport, encapsulation, and functional material formation.

Mots clés : liposome, tumor cell, sea urchins pigmentation

Thème de recherche : Autre

P17* EXTL3 DYSFUNCTION IDENTIFIED AS A DRIVER OF ABERRANT BONE DEVELOPMENT IN SEVERE FAMILIAL ANKYLOSING SPONDYLITIS

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Severe forms of axial spondyloarthritis (SpA) are characterized by excessive ossification leading to complete ankylosis of the spine and sacroiliac joints (SIJ), defining ankylosing spondylitis (AS). The molecular drivers of this pathological ossification remain poorly understood. Here, we identify a rare missense variant in EXTL3, a gene involved in heparan sulfate (HS) biosynthesis, in a family with multiple cases of severe AS with bamboo spine. Functional modeling in heterozygous knock-in mice (Extl3mut/+) recapitulated key features of the human phenotype, including trabecular bone defects, osteoid accumulation, and early sacroiliac joint bridging. Mechanistically, the mutation induced accelerated chondrocyte hypertrophy and delayed osteoblast maturation, both linked to dysregulated Wnt signaling, decreased mineralization, and altered HS metabolism. Transcriptomic and biochemical analyses confirmed disruption of the glycosaminoglycan balance and increased heparanase expression. Our results reveal a previously unexplored and conceptually novel mechanism of pathological ossification in spondyloarthritis, centered on EXTL3-mediated heparan sulfate regulation in skeletal remodeling. More broadly, they support an innovative dual genetic model in which HLA-B27 confers disease susceptibility, while a rare EXTL3 variant acts as a modifier driving structural severity, illustrating how distinct genetic factors can differentially shape disease risk and phenotype.

Mots clés : Ankylosing spondylitis, heparan sulfate, endochondral ossification

Thème de recherche : Ostéoimmunologie

P18 STRAIN-DEPENDENT DIFFERENCES IN RAT CALVARIA BONE DEFECT REPAIR

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The surgical management of large bone defects remains a clinical challenge. While autologous bone graft is the gold standard for small defects, its efficacy diminishes for larger or complex injuries, driving the need for tissue engineering-based therapies. Preclinical animal models, particularly the rat calvaria bone defect model, are essential for evaluating these therapies due to their ability to replicate the dynamic, multifactorial nature of bone healing—including cellular interactions, vascularization, and inflammatory responses. However, the widespread use of different rat strains across studies has led to inconsistencies in data reproducibility and comparability, complicating the translation of findings.

This study addresses this gap by systematically comparing bone repair, inflammatory status, vascularization, and osteoprogenitor functionality across four commonly used rat strains: Fisher F344 (F), Lewis (L), Wistar (W), and Sprague-Dawley (SD). Its objectives are to enhance the understanding of these preclinical models for better cross-study comparisons, and uncover potential molecular and cellular mechanisms driving successful or failed bone repair.

After creating 3- and 5-mm calvaria bone defects, we evaluated: bone formation using micro-CT imaging over 8 weeks, neovascularization using baryum sulfate perfusion and micro-CT imaging at W2, inflammatory status at the systemic (plasma) level using Milliplex assays for rat chemo-/cyto-kines at D-7, D+1, D+3, and D+8 and at the local (granulome, pooled cDNA) level using RT2 Profiler PCR arrays at D+3 and D+8. Osteoprogenitor functionality was assessed using CFU-F assays on cells isolated from bone marrow and calvaria periosteum.

Preliminary data reveal strain-specific differences in repair mechanisms. W and SD rats exhibited greater bone volume than F and L rats in 3-mm-defect, starting at W4, with W rats maintaining superior repair in 5-mm defects (N=6/strain). F rats showed higher blood vessel volume at W2, though this does not correlate with improved bone formation (N=1/strain, to be completed at N=6). On the 12 chemo-/cyto-kines analysed in plasma only CXCL-1 and IL-18 were robustly detected. Although not affected by the defect creation, F rats constantly displayed higher plasma level of CXCL1 (N=6-10/strain). Locally, W rats showed the highest expression of inflammation- and M1-related genes, particularly at D+8, while SD rats exhibited the highest expression of bone repair-related genes at D+3 (N=6/strain). These findings require confirmation at the individual level using RT-qPCR. W-derived bone marrow cells formed more CFU-F colonies than F-derived cells, with no significant differences observed in periosteal-derived CFU-F across strains ((N=3/strain).

These findings, though preliminary, highlight the impact of genetic background on bone repair and prompt further investigation into the role of angiogenesis and inflammation in this context.

Mots clés : Bone repair, Animal model, Inflammation

Thème de recherche : Biologie cellulaire et moléculaire

P19* HETEROGENEITE ET IMPLICATION DES VESICULES MATRICIELLES DERIVEES DE CHONDROCYTES DANS L'ARTHROSE

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L'arthrose (OA) est la maladie musculosquelettique la plus répandue, et associée à une surmortalité. Aucun traitement modificateur de la maladie n'existe. Elle se caractérise par une inflammation synoviale, un remodelage pathologique de l'os sous-chondral et une dégradation du cartilage. A l'interface os-cartilage, la matrice extracellulaire (MEC) se minéralise et de nouveaux vaisseaux et terminaisons nerveuses se forment. La différenciation hypertrophique (Hyp) des chondrocytes est centrale dans ce processus : le nombre de chondrocytes Hyp corrèle à celui de chenaux vasculaires qui contiennent des microvaisseaux et des nerfs sensitifs, associés à la dégradation du cartilage et la douleur des patients. Les chondrocytes Hyp sécrètent aussi des vésicules matricielles (VM), ancrées à la MEC, où elles initient sa minéralisation.

Nos données suggèrent que dans le cartilage arthrosique humain, des populations hétérogènes de VM existent. Comme les exosomes, les VM sont des cargos moléculaires riches en protéines et acides nucléiques. Nous émettons l'hypothèse que les VM des chondrocytes en cours de différenciation Hyp favorisent la progression de l'arthrose à la fois en permettant la minéralisation de la matrice mais aussi via leur rôle de cargo moléculaire.

Les objectifs de cette étude étaient de caractériser à l'échelle moléculaire l'hétérogénéité des VM. Pour cela, nous avons isolé par ultracentrifugation différentielle des VM de la MEC de chondrocytes murins différenciés au stade préhypertrophique (PreHyp, n=5) et Hyp (n=5), ainsi que des VM de cartilage de patients arthrosiques (n=5). Les ARN et protéines totales de ces échantillons ont été extraits pour une analyse transcriptomique et protéomique.

Les profils transcriptomiques et protéomiques varient selon le stade de maturation des chondrocytes. Sur 2132 protéines identifiées, 67 sont différentiellement exprimées. L'analyse d'enrichissement fonctionnel (GeneOntology) révèle leur implication dans la biominéralisation, la morphogenèse et le développement cartilagineux. De plus, 711 protéines orthologues ont été détectées dans les VM humaines. Par ailleurs, 192 miARN ont été identifiés dans les VM des cultures PreHyp et Hyp, dont 53 différentiels. La littérature montre l'implication de certains de ces miARN dans des processus biologiques liés au développement et au remodelage tissulaire.

Cette étude fournit la première caractérisation moléculaire des VM dans l'OA, leur suggérant des fonctions plus vastes que la minéralisation seule. Une analyse multiomique permettra d'identifier des cibles moléculaires spécifiques dans les VM susceptibles de contribuer à la progression de l'OA.

Mots clés : Arthrose, Maturation chondrocytaire, Vésicules matricielles

Thème de recherche : Biologie cellulaire et moléculaire

P20* AUTOPHAGY AND BONE MINERALIZATION: ULTRASTRUCTURAL STUDY USING TRANSMISSION ELECTRON MICROSCOPY. IN VITRO AND EX VIVO APPROACHES

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The main characteristic of bone tissue is its highly mineralized extracellular matrix, the formation of which is mainly regulated by osteoblast cells. The mineralization process is documented as the result of the release of matrix vesicles by osteoblasts, leading to the deposition of calcium phosphate (CaP) along an organic matrix, giving the tissue its mechanical and structural rigidity. However, a paradigm yet to be fully elucidated suggests that the release of CaP nodules also uses the autophagy machinery. Known for its conventional role in recycling and maintaining intracellular homeostasis, macroautophagy (called here « autophagy ») is a well described process: in this process, cytoplasmic components are sequestered within double-membrane vesicles called autophagosomes. These vesicles then fuse with lysosomes to form autolysosomes, where the acidic environment and hydrolases ensure the enzymatic degradation of the cargo. The resulting elementary metabolites are then released back into the cytoplasm for reuse. In the model of CaP secretion via autophagy pathways, the conventional degradative way seems to be used in favor of a secretory mechanism dedicated to mineral export, as described for the secretion of various factors. In this case, autophagosomes act as intracellular shuttles sequestering CaP precursors to transport them toward the cell membrane thereby contributing to matrix mineralization. The objective of this Master 2 internship is part of the recent trend of exploring the link between autophagic flux and mineralization using transmission electron microscopy (TEM). This project is based on a dual approach, combining in vitro and ex vivo models. In the in vitro approach, we use stem cells from apical papilla (SCAPs), differentiated into osteoblasts. Autophagic flux is modulated by pharmacological agents (activators/inhibitors) in order to characterize autophagosomes (proportion, shape, origin, and CaP content) using TEM. In the ex vivo approach, our first challenge lies in optimizing the preparation of mineralized bone samples for TEM visualization of secretory vesicles and autophagosomes. This task is performed using long bones from young mice, as this is an active process during the skeleton developmental stages.

Mots clés : Autophagy, Mineralization, Transmission electron microscopy

Thème de recherche : Biominéralisation

P21 LA PLATEFORME ECELLFRANCE MODELES NON-CLINIQUES DE MONTPELLIER : IMAGERIE DE POINTE ET ANALYSE DU MOUVEMENT POUR VOS MODELES DE PATHOLOGIES OSTEO-ARTICULAIRES

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La plateforme ECELLFrance Modèles non-cliniques, labellisée ISO9001, est dédiée à l'évaluation préclinique de biothérapies et à la caractérisation de modèles murins génétiquement modifiés. Spécialisée dans l'analyse de modèles de pathologies ostéo-articulaires et auto-immunes, elle s'appuie sur des technologies de pointe pour analyser les paramètres cliniques, biologiques, fonctionnels et structuraux associés au développement de ces pathologies.

La plateforme propose une large gamme de prestations incluant la mise en œuvre de modèles expérimentaux murins (arthrites inflammatoires, arthrose, sclérodermie systémique,...), le suivi clinique (scores cliniques validés), l'analyse du mouvement (Catwalk, Openfield, DWB,...), ainsi que l'imagerie et l'analyse histomorphométrique des altérations osseuses (microtomographie ; µCT) et cartilagineuses (microscopie laser confocale ; CLSM).

La plateforme s'est récemment équipée du nouveau scanner µCT haute résolution N80 (NEOSCAN). Dédié à l'imagerie ex vivo des structures osseuses, ce système permet une reconstruction tridimensionnelle précise des compartiments trabéculaire et cortical, et optimise la quantification des paramètres morphométriques classiques (volume, surface, caractérisation des travées, dégradation de surface) grâce à une qualité d'image considérablement augmentée (résolution jusqu'à 2 µm) et une visualisation de la micro-architecture des tissus minéralisés.

La plateforme développe également des approches dédiées à l'évaluation de la toxicité et à l'étude de la biodistribution des biothérapies. Les études de tolérance, systémique et locale, sont complétées par une analyse histologique des organes (>30) afin d'établir le profil de sécurité des thérapies. La biodistribution peut être évaluée par la quantification de marqueurs moléculaires (dPCR) ou par imagerie corps entier ex vivo via le système CryoViz®. Cette technologie permet une visualisation tridimensionnelle quantitative de la distribution tissulaire de cellules fluorescentes, facilitant l'identification des sites d'accumulation à l'échelle de l'organisme.

De plus, notre plateforme est associée à la plateforme ECELLFrance d'immunomonitoring clinique dédiée à la caractérisation des réponses immunitaires et des mécanismes inflammatoires. L'acquisition récente d'un cytomètre spectral de dernière génération (Cytek AURORA, 5 lasers) permet d'identifier différentes sous-populations immunitaires et leur évolution après traitement.

Cette organisation intégrée assure un suivi global de l'évolution des pathologies et l'effet de traitements au niveau individuel. S'appuyant sur une expertise et connaissance approfondie des modèles que nous proposons ainsi que des compétences opérationnelles efficaces, nos services s'inscrivent dans les principes éthiques de réduction et de raffinement des modèles animaux et sont ouverts aux équipes académiques et privées qui souhaitent répondre à des questions biologiques reposant sur l'expérimentation animale.

Mots clés : Modèles murins ostéo-articulaires, imagerie de l'os et du cartilage, paramètres histomorphométriques

Thème de recherche : Autre

P22* PROTEOMIC AND TRANSCRIPTOMIC MATRISOME PROFILING OF ORAL MESENCHYMAL CELLS REVEALS DISTINCT FUNCTIONAL SIGNATURES

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The extracellular matrix (ECM) is a dynamic and instructive microenvironment that regulates cell behavior, differentiation, and tissue-specific functions. The ensemble of ECM and ECM-associated proteins, known as the matrisome, plays a central role in controlling mineralization, structural organization, and signaling processes. However, the functional matrisome signatures of distinct oral mesenchymal cell populations remain incompletely characterized. This study aims to define and compare the matrisome profiles of gingival fibroblasts (GF), oral periosteum cells (OP), and alveolar bone cells (AB) under proliferative (N-ECM) and mineralizing (OM-ECM) conditions, and to functionally validate key ECM components associated with cell-specific behaviors. Primary human oral mesenchymal cells isolated from healthy donors (ORCELL biobank) were cultured under proliferative or osteogenic conditions for 21 days. ECM proteins were enriched and analyzed by proteomics, as well as gene expression, analyzed by transcriptomics. Identified targets were cross-checked with the human matrisome database. Differential expression and pathway enrichment analyses (DAVID, Reactome) were performed to identify condition-specific and cell-enriched ECM targets. Selected ECM markers are to be further validated at the gene and protein levels using RT-qPCR and Western blotting, with tissue localization assessed in murine and human samples. Preliminary results identified 186 ECM proteins, and showed all three cell types conserved a core matrisome composition under proliferative conditions, with enrichment in pathways related to collagen biosynthesis, fibril assembly, and integrin-mediated interactions. Under mineralizing conditions, OP and AB cells displayed a marked shift toward matrisome-associated proteins consistent with calcium-binding and mineralization-supportive functions, including annexins, whereas gingival fibroblasts exhibited a more limited response to osteogenic cues. These findings indicate that oral mesenchymal cell populations exhibit distinct and condition-dependent matrisome signatures reflecting their functional specialization. Ongoing transcript and protein-level validation will further clarify ECM components involved in matrisome-driven disease mechanisms and identify potential therapeutic targets.

Mots clés : Matrisome, Omics, Mineralization

Thème de recherche : Biologie cellulaire et moléculaire

P23* DETERMINATION DU ROLE DES OSTEOCYTES DANS LA MALADIE OSSEUSE ASSOCIEE A LA MUCOVISCIDOSE

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La maladie osseuse associée à la mucoviscidose (CFBD) touche 20 à 35 % des patients adultes [Putman, 2019] et impacte directement leur qualité de vie. L'élucidation complète des mécanismes à l'origine de ce défaut osseux, en lien avec la perte de fonction de CFTR, est essentielle pour développer de nouvelles stratégies thérapeutiques. Si les effets du dysfonctionnement de CFTR sur les ostéoblastes [Delion, 2016 ; Dumortier, 2025] et les ostéoclastes [Jourdain, 2021] sont documentés, son impact sur les ostéocytes, cellules sentinelles de l'intégrité du tissu osseux et de l'homéostasie minérale, reste inexploré. Ce travail a pour objectifs, 1) d'utiliser un modèle in vitro innovant pour étudier l'impact du dysfonctionnement de CFTR sur les ostéocytes, et 2) d'analyser les ostéocytes ex vivo, chez des souris CF (porteuses de la mutation F508delCFTR) et non-CF, dans un modèle d'ostéoporose induite par ovariectomie (OVX).

Des cellules souches squelettiques (CSS) primaires humaines (n=6 réplicats biologiques indépendants) ont été différenciées sur des biocéramiques macrotexturées durant 28 jours, sans ou avec inhibiteurs pharmacologiques de CFTR (Inh172, BPO-27). Le tissu formé in vitro a été visualisé grâce à une coloration phalloïdine-AlexaFluorTM488/DAPI tandis que la formation et la maturation des ostéocytes ont été analysées par RT-qPCR et dosage ELISA. Des souris de huit semaines CF et non-CF ont subi une ovariectomie (mimétique d'une ostéoporose post ménopause) ou une intervention chirurgicale contrôle (Sham). Les tibias ont été prélevés, colorés à la rhodamine 6G, coupés et transparisés pour une observation en microscopie confocale du réseau lacuno-canaliculaire des ostéocytes.

L'observation des coupes de biocéramiques indique la présence de cellules avec un réseau dense de fibres d'actine sur toute la profondeur des sillons, même en présence d'inhibiteurs. L'analyse du profil d'expression génique, associée à la détection de SOST dans les surnageants de culture, suggère l'obtention d'une population hétérogène composée d'ostéoblastes matures et d'ostéocytes ostéoïdes. L'effet des inhibiteurs reste à explorer plus avant pour pouvoir conclure quant à l'impact de la dysfonction de CFTR sur l'engagement ostéocytaire. L'imagerie confocale des échantillons osseux murins a montré une distribution différente des lacunes ostéocytaires pour les souris OVX comparativement aux souris Sham dans les quatre régions étudiées et pour les deux phénotypes, avec, pour autant, un nombre total de lacunes similaire.

De futurs travaux utiliseront in vitro des CSS dérivées d'iPSC issues de patients CF et de donneurs sains afin d'évaluer l'impact de mutations natives de CFTR sur les ostéocytes. La densité et la connectivité du réseau ostéocytaire seront plus largement étudiées avec le support d'analyses pilotées par intelligence artificielle. Les résultats générés permettront ainsi une meilleure compréhension du rôle des ostéocytes dans la CFBD.

Mots clés : ostéocytes, CFBD, modèle in vitro

Thème de recherche : Biologie cellulaire et moléculaire

P24 MACROPHAGE CHARACTERIZATION IN THE MASQUELET-INDUCED MEMBRANE: ENVIRONMENT-RELATED DISTRIBUTION HETEROGENEITY

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The use of biomaterials presents a promising approach to enhance bone tissue regeneration. When these materials are implanted into bone defects, they stimulate the formation of a membrane and influence macrophage differentiation, which is crucial for tissue repair. Macrophages release various cytokines that facilitate the healing process, although the exact mechanisms behind this action are not fully understood.

The Masquelet Induced Membrane (MIM) technique enhances bone regeneration by creating a bioactive membrane around implanted biomaterials. Our rat model study observed distinct morphological differences between the membrane at the bone-biomaterial interface (MIMB) and the muscle-biomaterial interface (MIMM).

OPTIR microspectroscopy offers a non-destructive method for biochemical analysis of tissues, enabling differentiation between biomaterial-associated membranes based on spectral data. This technique confirmed the presence of collagen fibers in the MIMB, while the MIMM contained both collagen and additional proteins. Sirius Red staining highlighted differences in protein organization.

We also assessed macrophage distribution and found a predominance of M2-like macrophages in the injured area, with fewer M1-like macrophages. In situ hybridization revealed that M2-like macrophages in the MIMM exhibited characteristics associated with b-type cells. These findings enhance our understanding of the role of macrophages in biomaterial-mediated bone regeneration and highlight the biochemical and cellular distinctions between MIMB and MIMM. This knowledge may improve the therapeutic potential of the Masquelet technique in clinical bone repair.

Mots clés : macrophages, bone, in situ hybridization, cytokines, Optical Photo-thermal Infrared Spectroscopy (OPTIR)

Thème de recherche : Biomatériaux

P25* FGFR3-ACTIVATING MUTATION UNDER THE TRANSCRIPTION FACTOR OSTERIX REVEALS DIFFERENT EFFECTS ON CORTICAL AND TRABECULAR BONE FORMATION

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Hypochondroplasia (HCH) is an autosomal dominant skeletal disorder characterized by short-limb dwarfism, and scoliosis. This disease is caused by missense mutations in fibroblast growth factor receptor 3 (FGFR3), with the majority of cases resulting from a heterozygous p. Asn540Lys gain-of-function mutation. FGFR3 is a negative regulator of bone growth and missense FGFR3 mutations induce defective long bone elongation due to abnormal proliferation and differentiation of growth plate chondrocytes. Currently, there are limited studies carried out to understand the specific impact of the HCH variant on osteogenesis.

In the present study, we took advantage of the recently generated CMV-Fgfr3Asn534Lys/+ mice which ubiquitously expresses the mutant N534K FGFR3 protein and exhibits mild dwarfism and mimicking human condition. We sought to determine the impact of Fgfr3 overactivation in bone physiology in this mouse model of HCH, to achieve this, we targeted the mutation specifically in osteoblasts using the Osx-cre mouse strain.

To adress this question we performed macroscopic measurements at 1-year-old female and male mice. Morphometric analyses with microCT (Skyscan 1272) were used to determine bone structure under physiological and pathological conditions. We compared our data with both controls and Osx-Cre mice.

Our results showed that in both sexes, we observed a significant decrease of 7% ($p<0.0001$) in length for long bones. The dwarfism observed in Osx-Fgfr3Asn534Lys/+ mice is much less severe than when the mutation is expressed ubiquitously (CMV-Fgfr3Asn534Lys/+) showing a 23% decrease in femur and tibia length at the same age.

Considering the microCT data, we did not observe a difference in the volume or architecture of cortical or trabecular bone in 1-year-old Osx-Fgfr3Asn534Lys/+ mice compared with Osx-cre mice.

However, we observed sex-related changes in cortical and trabecular bone architecture by microCT. Cortical thickness in females is low compared to male mice by 10% ($p=0.0086$). We also observed a marked osteopenia in female mice, the trabecular thickness and trabecular number were lower than in males by 33% p (≤ 0.0001) and 64% ($P \leq 0.0001$), respectively, whereas trabecular separation was higher (+40%; $p \leq 0.0001$).

Comparative analyses between CMV-Fgfr3Asn534Lys/+ and Osx-Fgfr3Asn534Lys/+mice showed similar significant data in the cortical bone more precisely for BV/TV increase of around 7% ($p=0.0299$) in both mouse models but opposing trends on trabecular bone for Osx-Fgfr3Asn534Lys/+.

Altogether these results seem to indicate that the Fgfr3 gain-of-function mutation responsible for HCH will damage bone physiology depending on gender and bone ossification processes.

Mots clés : FGFR3, Hypochondroplasia, bone

Thème de recherche : Génétique et Physiologie

P26* REPORT OF DENTAL PHENOTYPE IN FAMILIAL HYPOCALCIURIC HYPERCALCEMIA

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Background: Familial Hypocalciuric Hypercalcemia (FHH) is a rare autosomal dominant genetic disorder characterized by PTH-dependent hypercalcemia. It results from loss-of-function of CASR, GNA11, or AP2S1, corresponding to FHH types 1, 2, or 3, respectively. FHH represents the main differential diagnosis for primary hyperparathyroidism (PHPT) and is traditionally distinguished from PHPT by lower urinary calcium excretion and by less skeletal and renal complications. However, overlap in biochemical presentation may lead to misdiagnosis. A better understanding of the tissue-specific manifestations may improve its differential diagnosis from PHPT and enhance patients management.

Objective: To characterize clinical and biological phenotypes of patients with FHH to optimize follow-up, establish genotype-phenotype correlations and propose new diagnostic criteria.

Patients and Methods: A prospective cohort of patients with FHH and of their disease-free relatives was established. Clinical, biochemical, genetic, skeletal, renal, and dental assessments were performed.

Results: To date, a cohort of 27 patients with confirmed or suspected FHH from 13 families has been established. Five, three, and two families were diagnosed with FHH types 1, 2, and 3, respectively, while whole-genome sequencing is ongoing for three families with negative initial genetic testing. Patients with FHH have higher serum calcium concentrations than their disease-free relatives (2.68±0.26mM vs. 2.37±0.11mM, p=0.0008), while PTH levels were similar (0.72 vs. 0.62 times the upper limit of normal range, ULN, p=0.33). Fractional excretion of calcium, which is classically used to differentiate FHH from PHPT, exceeded 1% in nearly half of the patients with FHH, while the pro-FHH score, designed to better distinguish FHH from PHPT and calculated from calcemia, renal function and bone remodeling markers (BRM), was in favor of FHH for all FHH patients. BRM, bone mineralization, and presence of nephrolithiasis did not differ significantly between patients with FHH and their disease-free relatives. Patients with FHH exhibited enamel defects consistent with hypomineralized Amelogenesis Imperfecta, which were absent in disease-free relatives.

Discussion and conclusion: We describe a dental phenotype associated with FHH that appears consistent across the three genetic subtypes. Ongoing expansion of our cohort will allow to confirm these findings. In addition, study of rheumatological consequences of FHH must be further described and better diagnostic criteria are needed. Furthermore, heterozygous Gna11 loss-of-function mice, modeling type 2 FHH, display

lower enamel volume and density, raising questions about the underlying mechanisms of these defects. Collectively, our data support the need for improved, multidimensional diagnostic criteria integrating biochemical, genetic, and dental features.

Mots clés : familial hypocalciuric hypercalcemia, dental phenotype, mouse model

Thème de recherche : Génétique et Physiologie

P27 OSTEODIFFERENTIATION OF SCAPS: GENE EXPRESSION MODIFICATIONS UPON AUTOPHAGY REGULATION BY DRUGS

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SCAPs (Stem Cells from Apical Papilla) derived from the apex of forming wisdom teeth possess multipotent properties that make them an interesting model of mesenchymal stem cells for studying bone mineralization and regeneration. In a previous work [Le Nihouannen, Cells, 2025], we showed that transient inhibition of autophagy, a catabolic process, strongly disrupted the mineralization process of osteodifferentiating SCAPs: verteporphin, which blocks the formation of autophagosomes, induced the release of smaller mineralized nodules, while the treatment with bafilomycin A1, an inhibitor of autophagosome fusion with lysosomes, resulted in a lack of secretion of the mineralized nodules that thus remained in the cytoplasm. The present study, based on the expression analysis of genes associated with mineralization and autophagy, aims at understanding how repetitive but transient inhibition or stimulation of autophagy (twice a week for five hours) can permanently affect the secretion of mineralized nodules.

Mots clés : Bone mineralization, Autophagy regulation, Mesenchymal stem cells

Thème de recherche : Biologie cellulaire et moléculaire

P28* TARGETING DISC CELLULAR SENESCENCE: AN EFFICIENT THERAPEUTIC STRATEGY TO ADDRESS PATHOLOGICAL CALCIFICATION DURING INTERVERTEBRAL DISC DEGENERATION?

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Intervertebral disc degeneration (IVDD) is a major contributor to low back pain (LBP)[1], a health burden affecting millions of people worldwide2, for which no curative treatment is available[3]. Convergent in vitro and in vivo studies highlight a potential pathogenic role of senescent cells accumulation in IVDD[4,5].

Our research aims to assess the involvement of cellular senescence in the onset and progression of IVDD, and its relevance as a therapeutic target. We are developing an in vitro model using primary rat nucleus pulposus cells induced to senescence, in order to decipher the underlying mechanisms of this cellular state, and evaluate the benefit of modulating senescence on delaying the degenerative process.

Though frequently observed in cadaveric samples and in clinical setting of spine disorders care, aberrant calcification processes of interverbal discs have been somehow over-looked so far[6]. A bioinformatic analysis of scRNAseq datasets obtained from human degenerated disc samples revealed an upregulation of several molecular actors know to promote osteogenesis and calcification/mineralization processes, in the senescent cells' transcriptome. In line with this observation, some of these markers were also detected both at the transcriptional and protein expression levels in our in vitro model of nucleus pulposus cellular senescence. It was notably the case of Spp1, the osteopontin-encoding transcript, whose expression has been related to disc degeneration[7,8]. These preliminary results support the concept that the detrimental influence of senescent cells and their pro-degenerative function might be mediated, at least in part, through the disruption of calcification homeostasis in intervertebral discs. Such findings bring original mechanistic insights into the pathogenic function of senescent cells, and strengthen the rationale of seno-therapeutic strategies for IVDD treatment.

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Mots clés : Intervertebral disc degeneration, senescence, calcification

Thème de recherche : Biologie cellulaire et moléculaire

P29* CHARACTERIZATION OF NEUTROPHIL PHENOTYPES IN THE DEVELOPMENT OF PERIODONTITIS

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Periodontitis is a highly prevalent chronic inflammatory disease, characterized by an irreversible destruction of the tooth-supporting tissues. It is triggered by the oral dysbiosis involving a keystone pathogen Porphyromonas gingivalis. Neutrophils, the most abundant immune cells in periodontal lesions, play a crucial role in disease progression and may exhibit distinct phenotypes across different stages of periodontitis. This study aims to identify and characterize neutrophil phenotypes based on their location within the periodontal tissue to better understand their functions in periodontitis development.

Experimental periodontitis was induced on C57BL/6 mice using ligatures soaked with P. gingivalis. The ligatures were placed into the palatal sulcus of the first maxillary right molar, while the left molars served as negative control. Alveolar bone resorption was monitored by micro-CT before, during, and at the end of the experiment. Mice were sacrificed for histological and immunostaining analysis.

In mice gingiva, the targeting of neutrophils expressing serine proteases (NE, CatG, PR3) significantly increased over time with distinct tissue distribution: PR3+ neutrophils were homogeneously distributed in the periodontal tissue, while NE+ neutrophils were mostly localized around the alveolar bone and generally exhibited an inflammatory phenotype [NLRP3+, PD-L1-], and CatG+ neutrophils were mostly localized near the sulcus, exhibiting a regulatory phenotype [NLRP3-, PD-L1+]. Interestingly, a pool of neutrophils expressing the osteoclast activation factor RANKL was observed, suggesting an important role for neutrophils in alveolar bone resorption. Importantly, we confirm the existence of these neutrophil phenotypes within gingival tissue from patients with periodontitis. Finally, the use of a neutrophil serine proteases inhibitor in mice led to a significant decrease of bone resorption, suggesting that serine proteases may contribute to alveolar bone resorption during periodontitis.

These findings indicate that, within periodontal tissues, neutrophils adjust their phenotypes and functional properties, including protease expression and pro-inflammatory or regulatory activities, in response to the local microenvironment.

Mots clés : Neutrophils, Periodontitis, Alveolar bone resorption

Thème de recherche : Ostéoimmunologie

P30 DE LA KÉRATOPATHIE EN BANDE À LA CALCINOSE AIGÜE : LA CORNÉE COMME MODÈLE MINIMAL POUR DÉCRYPTER NUCLÉATION ET SUPERSATURATION

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La minéralisation ectopique correspond au dépôt pathologique de sels de calcium, principalement sous forme de phosphate de calcium, dans des tissus non destinés à se minéraliser. Dans de nombreux organes, ce phénomène s'accompagne de mécanismes actifs de reprogrammation ostéogénique. La cornée constitue un contre-modèle particulièrement instructif : tissu avasculaire, transparent et finement organisé, elle peut se calcifier sans signature d'ostéogenèse, permettant d'isoler le rôle des déterminants passifs physico-chimiques.

Cliniquement, deux entités emblématiques illustrent la calcification cornéenne. La kératopathie en bande représente une forme chronique dystrophique, caractérisée par des dépôts de phosphate de calcium au niveau de la membrane de Bowman et du stroma antérieur, survenant dans un contexte d'inflammation chronique, de sécheresse sévère ou d'exposition prolongée, le plus souvent sans désordre systémique majeur du métabolisme phosphocalcique. À l'opposé, la calcinose cornéenne aiguë correspond à une minéralisation rapide, fréquemment iatrogène, déclenchée par une rupture épithéliale associée à un apport exogène excessif en phosphate, conduisant à une précipitation brutale de sels calciques.

Malgré des cinétiques et des déclencheurs distincts, ces deux tableaux convergent vers des mécanismes biophysiques communs : perte de la fonction barrière, exposition de la matrice stromale, nucléation hétérogène sur collagène altéré et micro-environnements localement supersaturés. L'absence de différenciation ostéogénique, de marqueurs de minéralisation active et de vésicules matricielles renforce le caractère principalement passif de la minéralisation cornéenne.

Nous proposons d'exploiter la cornée comme modèle expérimental minimaliste de minéralisation ectopique afin de tester, de façon contrôlée, l'impact des paramètres clés gouvernant l'initiation et la propagation des dépôts (intégrité épithéliale, altération du collagène, disponibilité en phosphate, conditions de supersaturation). Ce cadre vise à relier directement observations cliniques et principes physico-chimiques, et à fournir une base mécanistique transférable à l'étude des calcifications pathologiques dans d'autres tissus. En pratique, ce modèle pourrait orienter des stratégies de réduction du risque (contrôle des apports phosphatés topiques, restauration de la barrière, modulation des conditions de supersaturation) avant la précipitation massive.

Mots clés : Cornée, minéralisation ectopique

Thème de recherche : Biominéralisation

P31 PROLONGING MESENCHYMAL STROMAL CELL SURVIVAL IN ISCHEMIA WITH A FULLY HYDROLYSABLE NUTRITIVE HYDROGEL

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Human mesenchymal stromal cells (hMSCs) are promising candidates for regenerative medicine owing to their multipotency and immunomodulatory properties. However, post-implantation survival remains a major hurdle, as these cells are exposed to ischaemic microenvironments that rapidly compromise their viability. Nutrient-releasing hydrogels based on glucose polymers have shown potential to enhance short-term survival (up to 7 days), but often lack full hydrolysability, potentially leading to steric hindrance and impaired tissue integration.

Here, we report the development of a fully hydrolysable fibrin-based hydrogel designed to sustain nutrient delivery over 21 days. We evaluated the enzymatic hydrolysis of five starch-derived glucose polymers, and identified wheat starch, amylopectin, and maltodextrin as fully degradable by amyloglucosidase. Incorporation into fibrin hydrogels was dependent on polymer viscosity and only maltodextrin demonstrated a loading capacity high enough to fuel hMSCs for 21 days. By adjusting maltodextrin/amyloglucosidase compositions, we achieved glucose release kinetics aligned with hMSC metabolic demand over a 21-day period. In vitro assays confirmed the ability of selected compositions to sustain hMSC viability up to 21 days in near-anoxic conditions. In vivo, subcutaneous implantation demonstrated enhanced hMSC survival at day 7 compared to glucose-free controls, although the effect declined by day 14.

Overall, maltodextrin provided twice the storage capacity of other polymers tested, was completely hydrolysable in vitro, and not recovered in vivo, supporting its full hydrolysis. Further optimization, however, will be needed to prevent component leakage and maximize therapeutic potential.

Mots clés : MSC, Cell survival, Glucose

Thème de recherche : Biomatériaux

P32* MANIFESTATIONS CRANIOFACIALES ASSOCIÉES A L'HYPOPHOSPHATÉMIE LIÉE A L'X CHEZ LA SOURIS HYP

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L'hypophosphatémie liée à l'X (XLH) est la forme héréditaire d'hypophosphatémie la plus fréquente, touchant environ une naissance sur 20 000. Cette maladie résulte de mutations perte de fonction du gène PHEX (phosphate regulating endopeptidase X-linked). Outre les anomalies du squelette axial et appendiculaire causées par une diminution sévère des taux circulants de phosphate, la prévalence de la craniosynostose chez les patients atteints d'XLH est estimée à 22 %. Cette affection résulte d'une altération de l'ossification intramembranaire, bien que les mécanismes sous-jacents demeurent encore mal compris.

L'objectif de ce travail est de caractériser les manifestations crâniofaciales chez les souris Hyp, un modèle murin de l'XLH, afin d'étudier les mécanismes physiopathologiques impliqués.

Le développement du crâne a été étudié à des stades clés du développement par imagerie microCT. Des analyses craniométriques ont été réalisées à 2 semaines, 3 semaines, 2 mois et 3 mois, et complétées par des approches histologiques à 2 et 3 semaines chez des souris Hyp et contrôles (n = 4–6 par groupe).

Les analyses craniométriques ont mis en évidence un phénotype crâniofacial altéré dès 3 semaines chez la souris Hyp, confirmé et accentué à 2 mois puis 3 mois. La souris Hyp présentait une brachycéphalie avec un crâne plus court et plus large, une voute crânienne plus élevée, bombée et arrondie. L'analyse microCT a également mis en évidence une altération de la morphologie des sutures coronales, sagittales et lambdoïdes des souris Hyp dès 2 semaines, confirmée à 3 semaines. Enfin, les analyses histologiques ont confirmé ces altérations de morphologie, avec en particulier une altération importante de la structure de la suture lambdoïde à 2 semaines.

L'ensemble de ces résultats permettent pour la première fois de caractériser le phénotype crâniofacial des souris Hyp mettant en évidence chez ces souris, un crâne plus court et plus bombé, associées à des anomalies de fermeture des sutures. L'analyse des différentes populations cellulaires intervenants lors de la formation des sutures est en cours. Ces résultats permettront d'améliorer notre compréhension du rôle de Phex dans l'ossification intramembranaire et de mieux appréhender les anomalies crâniofaciales observées chez les patients atteints de XLH.

Mots clés : -

Thème de recherche : Génétique et Physiologie

P33 EVALUATION OF THE THERAPEUTIC POTENTIAL OF SEVERAL CANDIDATE MOLECULES FOR THE TREATMENT OF HYPOCHONDROPLASIA

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Hypochondroplasia (HCH), is a mild dwarfism compared to achondroplasia (ACH). Both chondrodysplasia are caused by Fibroblast Growth Factor Receptor 3 (FGFR3) gain-of-function variants. HCH patients are characterized by short stature, stocky build, disproportionately short arms and legs, short hands and feet and macrocephaly.

Previously, our team has generated and characterized the first mouse model (Fgfr3Asn534Lys/+) of HCH(1). The mutant mice mimic the human pathology, we observed cartilage abnormalities in Fgfr3Asn534Lys/+ mice which explains the reduced size of the long bones.

Today, several treatments are available for FGFR3-related disorders (ACH and HCH). These include BMN111 (Vosoritide/ CNP analog) was approved for use in patients with ACH in 2021. BGJ398 (Infigratinib/ tyrosine kinase inhibitor), which obtained positive phase 3 results in children with achondroplasia and recombinant human growth hormone (rhGH) which is commonly used in patients with HCH. Here, our goal is to identify the best drug able to correct the growth deficit in HCH. We evaluated the efficacy of candidate drug using organotypic cultures of embryo femur (E16.5) isolated from HCH mouse model. We treated the femur with BMN-111 (10-6 M), BGJ-398 (10-6 M) and rhGH (2.24 10-7 M). The measurements of the HCH femurs after 6 days of ex vivo culture show that femur length increased by + 10.5 % for BMN111 (n=10), + 16.3 % for BGJ398 (n=8) and 4.24 % for rhGH (n=9) compared to HCH femur treated with vehicle. The different effects of treatment on bone growth can be explained by the mechanism of action of these candidate molecules. The molecules target either the receptor itself or signaling pathways downstream of FGFR3. Histological analyses confirm these organotypic culture results. We observed a different impact of the molecules on chondrocyte proliferation or differentiation. Immunohistochemical analyses of specific cartilage markers are currently being analyzed.

All these results should enable us to identify the best therapeutic approach for HCH.

(1)-Loisay L, et al. Hypochondroplasia gain-of-function mutation in FGFR3 causes defective bone mineralization in mice. JCI Insight. 2023;8(12):e168796.

Mots clés : Hypochondroplasia, organ culture, treatments

Thème de recherche : Développement et différenciation

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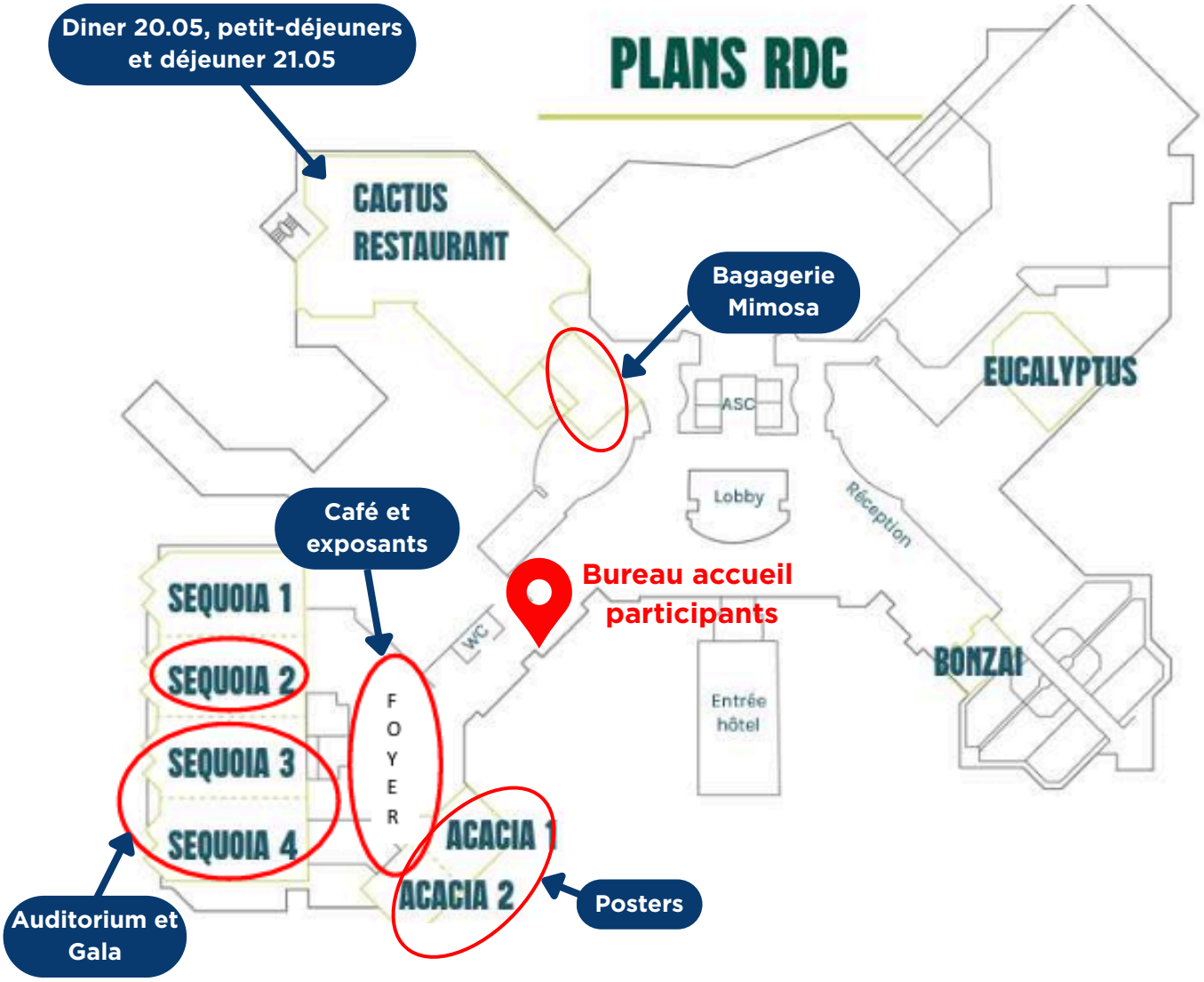
Les posters sont affichés dans les salles Acacia du mercredi 20 Mai 13h jusqu'au Jeudi 21 Mai 19h.



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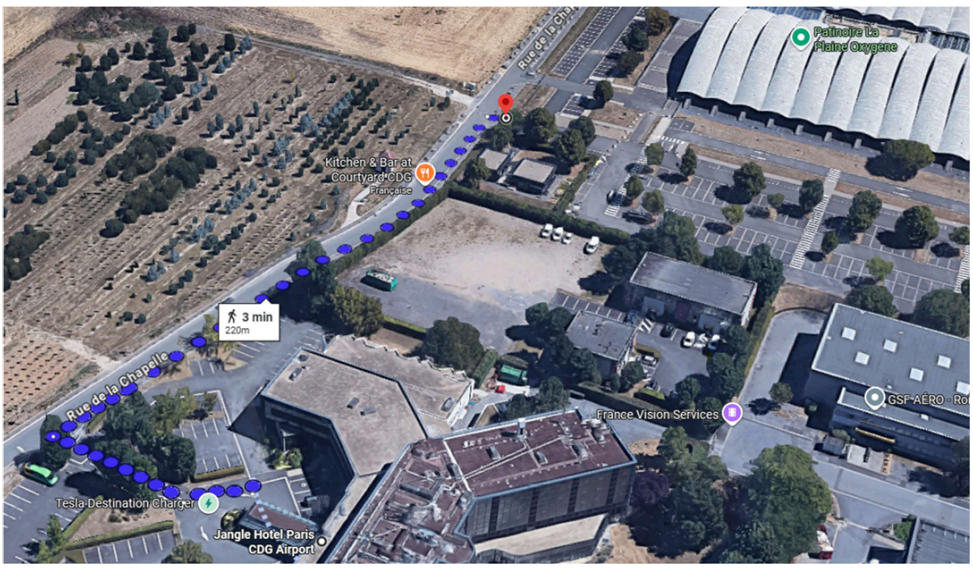

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