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Inflammation, Remodeling & Fibrosis in Human Diseases

Scientific day

Friday, 10th April 2026
Cochin Hospital, Paris

Theme

From cellular interactions to organ crosstalk

Conferences

Short talks

Round table

Two Junior Prizes
Best oral communication

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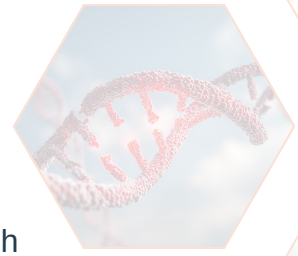
Programme



9:00 - 9:30am **Welcoming and breakfast**

9:30 - 9:45am **INFIBREX & INFIRE introduction**
Prof. Bruno Crestani - Prof. Luc Mouthon
Prof. Raphael Borie - Dr Camille Cohen

Session 1 – Inter-organ communication

9:45 - 10:45am **KEYNOTE**
Kidney inflammation and fibrosis
Dr Bryan Conway - University of Edinburgh

10:45 - 11:30am **Lung–joint crosstalk, the example of rheumatoid arthritis**
Prof. Raphael Borie – **Prof. Philippe Dieudé** - Bichat Hospital

11:30 - 11:50 **Coffee break**

SHORT COMMUNICATION

11:50 - 12:00 **Senescence in the kidney — Drivers of lesion development in monoclonal immunoglobulin deposition disease**
Samuel Chauvin - Centre de Recherche sur l'Inflammation

12:00 - 12:10 **POT1 variants are associated with telomere biology disorder including interstitial lung diseases: a multicentric retrospective cohort study**
Clémence Paillat - Bichat Hospital

12:10- 12:20 **Somatic genetic rescue in ZCCHC8-associated telomere biology disorders**
Sophie de Tocqueville - Institut Imagine

12:20- 12:30 **Analysis of autoantibody and extracellular matrix–mediated inflammation in scleroderma**
Lou Segarra - Centre de Recherche des Cordeliers

12:30- 12:40 **From GWAS to function and treatment: genetic regulation of CARD9 at the 9q34 locus in axial spondyloarthritis and related diseases**
Prof. Félicie Costantino - Ambroise Paré Hospital

12:40- 12:50 **Proinflammatory strains of Mediterraneibacter gnavus are enriched during spondyloarthritis (SpA) and modulate disease during experimental SpA**
Manon Jacoutot - Université de Versailles Saint-Quentin-en-Yvelines

12:50- 1:00pm **Impact of miRNAs in host-microbiota interface establishment and long-term effects on intestinal inflammation**
Louis Berthet - Centre de Recherche sur l'Inflammation

1:00 - 2:00pm **Lunch**

Session 2 – Cellular crosstalk and innovative tools

2:00 - 3:00pm **KEYNOTE**

Autologous immune organoids to investigate pediatric cancer development

Dr Alessia Bagattin, Gustave Roussy

3:00 - 3:30pm **The complement system, a key player in intercellular crosstalk**

Dr Anne Grunenwald – Dr Idris Boudhabhay

Centre de Recherche des Cordeliers

3:30 - 3:50pm **Coffee break**

SHORT COMMUNICATION

3:50 - 4:00pm **A complement atlas of HNSCC reveals intratumoral complement control and identifies factor H as a therapeutic target in oral cavity and HPV-negative oropharyngeal tumors**

Joey Martin - Centre de Recherche des Cordeliers

4:00 - 4:10pm **Tumour cell-intrinsic complement C1r and C1s regulate cancer cell fitness and shape the immune microenvironment in triple-negative breast cancer**

Andrea Minery - Centre de Recherche des Cordeliers

4:10 - 4:20pm **Role of mechanical stress in educating the microenvironment in Chronic Lymphocytic Leukemia**

Lola Ozenne - Université Sorbonne Paris Nord

4:20 - 4:30pm **Evaluating the Immune Checkpoint TIGIT as a Novel Target in Pulmonary Fibrosis**

Anna Curioni - Centre de Recherche sur l'Inflammation

4:30 - 4:40pm **STING-mediated autophagy in lung macrophages limits pulmonary fibrosis**

Dr Nicolas Riteau - CNRS IRL2029 Immune Health

4:40 - 5:20pm **ROUNDTABLE**

Crosstalk and tools: spatial transcriptomics, imaging

Dr Alessia Bagattin, Gustave Roussy

Dr Idris Boudhabhay, Centre de Recherche des Cordeliers

Dr Camille Cohen, Bichat Hospital

Dr Lubka Roumenina, Centre de Recherche des Cordeliers

5:20 - 5:30pm **Best Oral Presentation Prizes**

Conclusion

9:30 - 9:45am

INFIBREX & INFIRE introduction

Prof. Bruno Cretsani

Pulmonologist
Chef de service
Coordinator INFIBREX
Bichat Hospital, Paris

Prof. Luc Mouthon

Expert médecine interne
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Dr Camille Cohen

Nephrologist
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Session 1 – Inter-organ communication

9:45 - 10:45am **KEYNOTE**

Dr Bryan Conway

Honorary Consultant Nephrologist
Senior Clinical Fellow
Centre for Cardiovascular Science
Research University of Edinburgh

THE UNIVERSITY of EDINBURGH

Kidney inflammation and fibrosis

Chronic kidney disease affects ~10% of the global population and is a major risk factor for progression to dialysis or transplantation and for cardiovascular disease. To learn more about the underlying mechanisms that promote kidney disease, our group employs multiomic analysis of human kidney tissue, blood and urine, with causality subsequently determined in pre-clinical disease models.

We have recently identified an inflamed tubular cell phenotype that is observed exclusively in injured kidneys and may promote transition from acute kidney injury to chronic kidney disease. Inflamed tubular cells are enriched in the fibrotic niche, where they signal to adjacent fibroblasts and immune cells to mediate fibrosis. ATAC-seq highlighted the AP-1 transcription factor family as a core driver of the inflamed tubular cell phenotype and inhibition of AP-1 reduces fibrosis in a pre-clinical model of kidney disease.

We have also employed small RNA-seq to identify miR-190-5p as key to maintaining a healthy proximal tubular cell phenotype. Mir-190-5p can be employed as a biomarker of kidney prognosis and may also be exploited therapeutically, with administration of a miR-190-5p mimic reducing fibrosis in a pre-clinical model of kidney disease.

10:45 - 11:30am

Prof. Raphael Borie

Pulmonologist
Bichat Hospital, Paris

Prof. Philippe Dieudé

Rheumatologist
Bichat Hospital, Paris

Lung–joint crosstalk, the example of rheumatoid arthritis

Rheumatoid arthritis (RA) may be associated with pulmonary involvement, particularly interstitial lung disease, which can be indistinguishable from idiopathic pulmonary fibrosis.

We have demonstrated a continuum in the genetic causes of pulmonary fibrosis associated with RA and those of idiopathic pulmonary fibrosis, suggesting that therapeutic management may sometimes be similar, while also highlighting the importance of RA-specific treatment.

These findings support the concept of a shared pathophysiological framework between joint and lung involvement, driven by common inflammatory and fibrotic pathways. Understanding this lung–joint crosstalk is essential for improving early diagnosis and patient stratification. It may also open new avenues for targeted therapies that address both articular and pulmonary manifestations of the disease.

SHORT COMMUNICATION SESSION 1

Senescence in the kidney
Drivers of lesion development in monoclonal immunoglobulin deposition disease

Chauvin Samuel[1] ; Thomas Loeffler ; Ariane Coutrot[2] ; Léa Chapart[2] ; Sébastien Bender[3] ; Christophe Sirac[3] ; Camille Cohen[4]
[1] INSERM U1149, Centre de Recherche sur l'Inflammation, Université Paris Cité, Paris, France
[2] INSERM U1149, Centre de Recherche sur l'Inflammation, Paris, France
[3] CRIBL Unit, UMR CNRS 7276 INSERM 1262, University of Limoges, Limoges, France
[4] INSERM U1149, Centre de Recherche sur l'Inflammation, Université Paris Cité, Nephrology Department, Bichat Hospital, APHP, FHU INFIRE, Paris, France

BACKGROUND
Monoclonal Immunoglobulin Deposition Disease (MIDD) is characterized by the deposition of pathogenic monoclonal immunoglobulins (MIg) in the kidney, leading to tubulointerstitial fibrosis and glomerulosclerosis. The mechanisms linking deposits to kidney lesions remain poorly understood. Cellular senescence—a state of stable cell-cycle arrest associated with a senescence-associated secretory phenotype (SASP)—has been implicated in glomerulosclerosis of other causes. Here, we identify an upregulation of cellular senescence in MIDD, associated with the development of glomerulosclerosis and the recruitment of Trem2⁺ macrophages, which may drive lesion progression.

METHODS
We combined the analysis of human MIDD kidney biopsies with transgenic mice recapitulating MIDD lesions (10.1182/blood.2020005980). Tissue characterization was performed using immunofluorescence, complemented by high-resolution spatial transcriptomics.

RESULTS
In both mouse and human kidney tissues, we observed a marked accumulation of senescent cells, evidenced by the presence of p21-positive nuclei in both glomerular and tubular epithelial cells. Spatial transcriptomic analysis revealed that these senescent glomeruli exhibited a pronounced upregulation of genes associated with the matrisome, consistent with an active fibrotic process and sclerosis. Further analysis indicated a selective enrichment of myofibroblasts, key effectors of fibrosis, and Trem2⁺ macrophages, a subset associated with tissue remodelling and chronic injury, around senescent glomeruli, suggesting potential paracrine interactions.

CONCLUSION
These findings support a role for cellular senescence in MIDD-associated renal injury. As senescence induces SASP, we hypothesize that SASP factors recruit macrophages, which in turn promote fibrosis and glomerulosclerosis. Ongoing work aims to determine whether targeting senescent cells with navitoclax can mitigate lesion development, opening new therapeutic perspectives in MIDD.

POT1 variants are associated with telomere biology disorder including interstitial lung diseases: a multicentric retrospective cohort study

Clémence Paillat, Ibrahima Ba, Marie-Pierre Debray, Godelieve Morel, Nathalie Allou, Yurdagul Uzunhan, Hilario Nunes, Jean-Marc Naccache, Josephine Amar, Clement Massonaud, Arthur Mageau, Pauline Chaumet, Hélène Morel, Thomas Cluzeau, Antoine Froidure, Aurélie Plessier, Pierre-Emmanuel Rautou, Vincent Cottin, Christine Kim Garcia, Caroline Kannengiesser, Bruno Crestani, Raphaël Borie, Quentin Philippot and OrphaLung

Protection of telomere 1 (POT1) germline variants have been associated with two opposite syndromes: telomere biology disorders (TBD) including interstitial lung disease (ILD) and long telomere syndrome. The aim of this retrospective, observational study, was to characterize the phenotype of patients with TBD and an heterozygous POT1 pathogenic variant.

Among 14 patients from 7 families with an heterozygous POT1 pathogenic variant, 12 patients were diagnosed with ILD, with a median age at diagnosis of 65 years (min 47 – max 74). Six of them had a smoking history and/or a fibrogenic exposure. The pulmonary phenotypes were heterogenous, but the most frequent diagnosis was idiopathic pulmonary fibrosis (IPF n=8, other diagnoses were idiopathic NSIP, unclassifiable ILD, asbestosis and ILA), associated with pulmonary hypertension in 3 patients. The median FVC and DLCO at ILD diagnosis were 56% and 37%, respectively. None had a diagnosis of lung cancer, and one had a diagnosis of extrathoracic cancer. Six patients received a specific treatment for ILD, antifibrotic (n= 5) and steroids (n=1). The median decline of FVC for the whole population was - 54 ml/year (min -588 – max 572). After a median follow-up of 2 years 5 patients had died. The median survival was 2.7 years. A myelodysplastic syndrome was identified in 3 patients and liver disease (including porto-sinusoidal vascular disease in one patient) in 3 patients.

We confirmed that POT1 pathogenic variant may be associated with TBD. The most frequent pulmonary diagnosis was IPF, but other ILD may be observed as well as hematological and hepatic involvement. No disease suggestive of long telomere syndrome was observed in this cohort. Larger cohorts are needed to further delineate the TBD phenotype associated with POT1 variation.

Somatic genetic rescue in ZCCHC8-associated telomere biology disorders

Sophie de Tocqueville[1], Mina Nouri, Caroline Kannengiesser[2], Patrick Revy[1]

1 Laboratory of Genome Dynamics in the Immune System, Laboratoire labellisée Ligue Nationale contre le Cancer, INSERM UMR 1163, Université de Paris, Imagine Institute, Paris, France.
2 Université Paris Cité, AP-HP, Bichat-Claude Bernard Hospital, Genetic Department, INSERM
UMR1152, Paris, France

In Mendelian diseases, somatic genetic rescue (SGR) events can partially or completely counteract the harmful effects of a pathogenic germline mutation. Telomere biology disorders (TBDs), a group of rare Mendelian conditions that include pulmonary fibrosis and bone marrow failure, arise from dysfunctional or critically short telomeres. Telomere maintenance relies on telomerase, a ribonucleoprotein complex minimally comprised of a reverse transcriptase, TERT, and a template containing RNA, TERC/hTR. ZCCHC8 is part of the NEXT complex, which regulates the processing and abundance of many RNAs, including TERC. Recently, ZCCHC8 mutations were found to be etiologic in TBDs.
I will discuss seven heterozygous germline missense variants in ZCCHC8, five of which are novel, that we identified in association with TBDs and frequent SGR events. Two unrelated patients with severe hematological defects harbored a distinct de novo ZCCHC8 variant affecting the same residue, G184. A subset of leukocytes from both patients exhibited a direct SGR corresponding to a copyneutral loss of heterozygosity of chromosome 12q, which replaced the mutated ZCCHC8 gene with its wild-type counterpart. This SGR was associated with a progressive hematological improvement in one of the patients. Additionally, we detected in blood cells from four other patients indirect SGR affecting the TERT promoter as well as the POT1 and DIS3 genes. The observation of direct and indirect SGRs highlights the critical, cell-intrinsic role of ZCCHC8 in human hematopoiesis and provides a potential mechanism for disease modification in TBDs. These findings provide new insights into telomere biology and suggest that somatic rescue may represent a natural adaptive process with therapeutic implications.

12:20 - 12:30am

Analysis of autoantibody and extracellular matrix–mediated inflammation in scleroderma

Lou SEGARA
Centre de recherche des Cordeliers - U1138

Excessive accumulation of extracellular matrix (ECM) is a major hallmark of the fibrosis observed in systemic sclerosis (SSc). Certain matrix proteins contribute to maintaining the inflammatory process by interacting with innate immunity receptors or by modulating the recruitment of immune cells. In addition, autoantibodies directed against matrix proteins or fibroblasts have been identified in patients with SSc. However, their potential role in the initiation, progression, or resolution of fibrosis remains poorly understood. To explore these mechanisms, we developed a three-dimensional model of human fibroblast spheroids that reproduces a pro-fibrotic environment characterized by ECM overexpression. Exploration of the matrisome using a multiplex RT-PCR panel allowed us to show that IgG isolated from patients with SSc specifically modulates the expression of several genes encoding matrix proteins. In a second step, the capacity of this remodeled matrix to influence immune cell activation will be evaluated using a co-culture system with human immune cells.

12:30 - 12:40am

From GWAS to function and treatment: genetic regulation of CARD9 at the 9q34 locus in axial spondyloarthritis and related diseases.

Prof. Félicie Costantino[1,2]
1Ambroise Paré Hospital (AP-HP), Rheumatology Division, Boulogne-Billancourt
2Université Paris Saclay, UVSQ, Inserm, UMR1173 Infection & Inflammation, Montigny le Bretonneux,

Background
Axial spondyloarthritis (axSpA) is a chronic immune-mediated inflammatory disease with a strong genetic component. Beyond the major contribution of HLA-B27, genome-wide association studies have identified multiple additional susceptibility loci, most of which lie in non-coding regions and are difficult to interpret. One such locus at chromosome 9q34 is associated with axSpA as well as inflammatory bowel diseases (IBD), and IgA nephropathy (IgAN). This region contains several genes, including CARD9, a key adaptor in innate immune signalling, but the causal variants and mechanisms underlying the association remain unclear.
Objective
To identify the causal variants at the 9q34 locus and determine how genetic variation influences CARD9 regulation and immune cell function.
Methods: We integrated GWAS data for axSpA, IBD and IgAN with molecular QTL datasets and epigenomic annotations. Bayesian fine-mapping and colocalization analyses were used to identify shared causal variants and link disease associations with gene expression and chromatin accessibility, with cell-type specificity assessed using immune cell–resolved eQTL and ATAC-seq datasets. Additional analyses evaluated the impact of candidate variants on DNA shape, nucleosome positioning, and transcription factor binding at regulatory elements. Functional consequences of CARD9 variation were assessed using single-cell transcriptomics of stimulated PBMCs, flow cytometry, cytokine measurements, and pharmacological inhibition in PBMCs.
Results
Fine-mapping identified a shared credible set of 32 variants at the 9q34 locus, consistent with a single causal signal. Colocalization analyses linked this signal to CARD9 cis-eQTLs specifically in myeloid cells. Integration with chromatin accessibility data identified a myeloid-specific distal enhancer harboring disease-associated variants, where risk alleles were associated with increased enhancer accessibility and higher CARD9 expression. Chromatin analyses suggested that the risk haplotype alters DNA shape, nucleosome positioning, and PU.1 binding. Functionally, higher CARD9 expression was associated with distinct myeloid transcriptional states, enhanced monocyte activation, and increased production of cytokines including IL-6 and IL-23, while pharmacological inhibition partially reduced inflammatory cytokine responses.
Conclusion
Common variants at the 9q34 locus increase axSpA susceptibility by enhancing activity of a myeloid-specific enhancer that upregulates CARD9 expression, leading to increased myeloid activation and inflammatory cytokine production. These findings link genetic risk to immune cell function and highlight CARD9 as a potential therapeutic target in inflammatory diseases.

Proinflammatory strains of Mediterraneibacter gnavus are enriched during spondyloarthritis (SpA) and modulate disease during experimental SpA

Manon Jacoutot
UVSQ/INSERM
Infection et Inflammation, UMR1173

Introduction.
Spondylarthritis (SpA[MB1.1]) is a chronic inflammatory disorder characterized by osteoarticular and extra-articular manifestations, including inflammatory bowel disease (IBD). It is well-established that intestinal microbiota dysbiosis plays an important role in IBD pathophysiology. We recently evidenced an intestinal dysbiosis during SpA characterized by a decreased bacterial diversity associated to an increased relative abundance of the bacterium Mediterraneibacter gnavus (MG). In this study, our goal was first to determine if specific MG strains are present during SpA. Second, we tested if MG strains isolated from SpA patients were more toxic and proinflammatory than those from healthy controls (HC). Finally, we assessed in vivo pathogenicity of those MG strains.

Methods.
MG colonies were isolated from colonic biopsies and/or stools from SpA patients and HCs. Isolated MG strains were sequenced by next generation sequencing-. Functional assays were conducted by stimulating peripheral blood monocytes from SpA patients with the isolated strains to assess MG toxicity and pro-inflammatory function through tumor necrosis factor (TNF) induction. Germ-free SKG mice were monocolonized with MG strains isolated either from SpA patients or HC, challenged with curdlan and the development of arthritis and colitis were evaluated.

Results.
A total of 44 MG strains were isolated and sequenced (37 from SpA patients and 7 from HC), with no shared strains between groups. Phylogenetic analysis revealed 2 clades with one containing exclusively strains from SpA patients. Functional studies showed that SpA patients were enriched in MG strains displaying toxic and proinflammatory functions on monocytes. MG monocolonization restored SpA susceptibility in GF SKG mice. MG strains from SpA patients were associated with higher arthritis severity and bone remodeling than MG strains from HCs.

Conclusions.
Our work demonstrates a broad MG diversity in stools and biopsies from SpA patients and HCs. Enhanced toxic and proinflammatory potential of MG strains isolated from SpA patients was associated with higher pathogenicity in SKG mice in vivo supporting a possible pathogenic role of MG during SpA. Further research will investigate the underlying pathogenic mechanism to clarify the contribution of MG strains to SpA.

12:50 - 1:00pm

Impact of miRNAs in host-microbiota interface establishment and long-term effects on intestinal inflammation

Louis Berthet
INSERM U1149, Centre de Recherche sur l'Inflammation, Université Paris Cité, Paris, France
Team Host-Environment interface in chronic inflammatory disorders

Accumulating findings highlight the crucial role of the first thousand days of life in structuring the gut-microbiota interface. This early developmental window appears as a critical period for establishing lasting physiological trajectories. Early disruption of this interface would significantly increase vulnerability to pathologies associated with dysbiosis, immune system alterations, and impaired intestinal barrier function. At the host-microbiota interface, numerous elements suggest that microRNAs (miRNAs), small non-coding RNAs resistant to digestion, play a major regulatory role. Our team has demonstrated that high levels of certain fecal miRNAs, let-7b and miR-21, are associated with inflammation in IBDs, affecting various key digestive system functions, such as barrier function and the onset of dysbiosis. However, their influence during the early stages of life remains unexplored. In a neonatal animal model, we have just demonstrated that supplementation with the pro-colitogenic miRNA, let-7b, induces significant effects on the development of the gut-microbiota interface in the short and long term, with the development of a predisposition to dysbiosis and colitis. This supplementation appears to have different effects on the modulation of colonic inflammation and microbiota, depending on whether it occurs before or during the period of dietary diversification. In parallel with this approach, we observed, in a murine model of colitis, a significant correlation between colon inflammation and alteration of the milk miRNA profile. Since breast milk is a major source of exogenous miRNAs, our results could suggest a possible regulatory role for miRNAs in the development of the host-microbiota interface from the neonatal period onward.

Session 2 – Cellular crosstalk and innovative tools

2:00 - 3:00pm **KEYNOTE**

Dr Alessia Bagattin

Scientific Researcher
PhD in Genetics and Molecular Biology
Inserm U1356
Laboratory of Florent Ginhoux “Myeloid cell biology”
Gustave Roussy, Villejuif

Autologous immune organoids to investigate pediatric cancer development

Pediatric cancers, including brain tumors, neuroblastomas, sarcomas, and kidney tumors, remain challenging to treat due to their biological complexity and the limited efficacy of current therapies. A major limitation in preclinical models is the inability to accurately recapitulate the pediatric tumor microenvironment (TME), particularly its immune components such as tissue-resident macrophages, which play crucial roles in tumor progression and immune regulation. In the laboratory of Dr. Florent Ginhoux, we are developing advanced models that better reflect the complexity of pediatric cancer by integrating immune cells into three-dimensional (3D) organoid and tumoroid cultures. We have established a protocol to generate patient-derived macrophages (iMacs) from induced pluripotent stem cells (iPSCs). These iMACs closely resemble tissue-resident macrophages and can differentiate into microglia-like cells in the context of brain tumors. Using autologous immune-organoid models that integrate induced pluripotent stem cell (iPSC)-derived macrophages (iMacs) with patient-derived brain organoids and tumor cells in 3D co-cultures and applying multiomic approaches, including single-cell RNA sequencing, spatial transcriptomics, and light-sheet microscopy, we investigate how immune cells influence tumor growth, immune suppression, and treatment resistance. Our aim is to identify key molecular mechanisms within the TME in order to develop effective immunotherapies that could improve outcomes for pediatric cancer patients.

3:00- 3:30pm

Dr Idris Boudhabhay

Nephrologist
Centre de Recherche des Cordeliers

Dr Anne Grunenwald

Nephrologist
Centre de Recherche des Cordeliers

The complement system, a key player in intercellular crosstalk

The complement system, traditionally viewed as a key component of innate immunity, is now recognized as a central mediator of intercellular communication across multiple tissues. Beyond its role in host defense, complement activation shapes cellular responses by modulating inflammation, tissue repair, and fibrosis. Recent evidence highlights its involvement in complex crosstalk between immune cells, stromal cells, and parenchymal cells, thereby influencing disease progression in chronic inflammatory and fibrotic conditions. In particular, complement-derived effectors such as C3a and C5a act as signaling molecules that orchestrate cellular recruitment, activation, and differentiation. Dysregulation of these pathways contributes to maladaptive remodeling and organ dysfunction. This presentation will provide an overview of the emerging roles of the complement system in intercellular communication, with a focus on its implications in inflammatory diseases, and discuss potential therapeutic strategies targeting complement pathways.

SHORT COMMUNICATION SESSION 2

3:50 - 4:00pm

A complement atlas of Head and Neck Squamous Cell Carcinomas reveals intratumoral complement control and identifies factor H as a therapeutic target in oral cavity and HPV-negative oropharyngeal tumors.

Joey Martin
Equipe 4 Isabelle CREMER
INSERM 1138 Inflammation, Complement and Cancer Team, Paris

Background: Oral Cavity Squamous Cell Carcinoma (OCSCC) and Oropharyngeal Squamous Cell Carcinoma HPV-independent (OPSCC HPV-negative) remain an unmet clinical need among head and neck squamous cell carcinomas (HNSCC), with poor prognosis and limited benefit of multimodal therapies, including immune checkpoint inhibitors. The innate immune complement system has emerged as a druggable pathway in cancer, with strategies targeting C3a/C5a signaling or tumor-bound complement regulators to restore membrane attack complex (MAC)–mediated cytotoxicity. GT103, an antibody targeting tumor cell–associated complement regulator Factor H (FH), exemplifies this approach and is currently being evaluated in lung cancer in combination with anti-PD1. However, the role and regulation of complement activation across HNSCC subtypes remain poorly defined.
Methods: We established a comprehensive complement atlas of HNSCC using an integrated Complementomics approach combining hyperplex imaging, plasma profiling, and clinical annotation from an institutional longitudinal biobanking cohort: SCANDARE (NCT03017573).
Results: We enrolled 159 patients with early-stage HNSCC in the SCANDARE study. Plasma profiling of 17 complement proteins and activation fragments revealed selective alternative pathway activation in OCSCC and OPSCC, with coordinated elevation of Ba, C3a, and C5a, Contrary to hypopharyngo-laryngeal SCC (HLSCC). Tumor profiling revealed a dense infiltration by C5aR1-positive macrophage and neutrophil subsets, attracted in part via the C5a generation in OCSCC and OPSCC tumors, but not HLSCC. In situ complement cascade did not reach the terminal step with formation of cytotoxic membrane attack complex. This could be explained by the binding of FH to tumor cells surface of OCSCC and OPSCC HPV-negative, but not OPSCC HPV-positive and HLSCC. This FH was likely derived from the circulation, as local expression was minimal and it was elutable from our ex vivo preclinical model (Patient Tumor-Derived Fragment), indicating active local inhibition of alternative pathway–mediated cytotoxicity. As autoantibodies against this form of tumor-bound FH tumor neoantigen were protective in lung and renal cancer, we searched them in HNSCC. Only isolated patients appeared positive, especially in the FH-rich OCSCC and OPSCC HPV-negative tumors, hence this potentially protective autoimmunity was a rare event.
Conclusions: OCSCC and OPSCC HPV-negative exhibit a distinctive complement phenotype characterized by systemic anaphylatoxin generation without intratumoral complement-mediated cytotoxicity, mediated by tumor cell-associated FH. Targeting this FH with GT103 may overcome the regulatory barrier, restore immunogenic cell death mediated by the membrane attack complex, and enhance responses to immunotherapy, supporting clinical evaluation in these HNSCC subsets.

4:00 - 4:10pm

Tumour cell-intrinsic complement C1r and C1s regulate cancer cell fitness and shape the immune microenvironment in triple-negative breast cancer

Andrea Minery 1, Lubka T. Roumenina 1,2

1 Centre de Recherche des Cordeliers, Institut National de la Santé et de la Recherche Médicale, Sorbonne Université, Université de Paris Cité, Team Inflammation, Complement and cancer, F-75006 Paris, France

2 University Hospital Federation (FHU) COMET, Paris, France

Emerging evidence positions tumour cell-intrinsic complement proteins as regulators of cancer cell behaviour and immune crosstalk, yet their role in triple-negative breast cancer (TNBC) remains undefined. Here, transcriptomic profiling across breast cancer molecular subtypes reveals that C1R, C1S and C3 are preferentially expressed in TNBC cells, both in patient tumours and in vitro, and that their expression is upregulated by pro-inflammatory cytokines. In situ mRNA hybridization and hyperplex SeqIF immunofluorescence demonstrate that C1R and C1S share more closely matched expression patterns with one another than with C3 within TNBC cell populations. These patterns associate with distinct transcriptional programs: metabolic and cell cycle gene sets are enriched in C1R-, C1S- and C3-high cells, whereas inflammatory and apoptotic signatures are specifically linked to C1R and C1S. Functionally, silencing of C1r or C1s modestly impairs TNBC cell proliferation, viability and tumoursphere formation — effects not rescued by extracellular protein supplementation, supporting an intracellular mechanism. C3 silencing exerts minimal effects. C1R- and C1S-high tumour cells are enriched in chemoattractant chemokines including CCL2 in patient tumours, and their secretion decreases upon complement gene silencing in vitro. C1R and C1S expression further correlates with cytotoxic T cell infiltration and improved patient survival. Together, these findings indicate that whilst cell-intrinsic C1r and C1s enhance modestly tumour cell fitness, their more consequential contribution lies in shaping the tumour immune microenvironment through regulation of chemokine secretion and cytotoxic T cell infiltration, highlighting their role as enhancers of anti-tumour immunity in TNBC.

4:10 - 4:20pm

Role of mechanical stress in education the microenvironment in Chronic Lymphocytic Leukemia

Lola OZENNE, Emeline SAINDOY-TAULERA, Laure AUBARD, Antonin OUDAR, Nadine VARIN-BLANK, Grégory LAZARIAN, Laura GARDANO

UMR U1349 INSERM-Université Sorbonne Paris Nord (USPN)
Signalisation, Microenvironnement et Hémopathies Lymphoïdes B (SIMHEL)
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Chronic Lymphocytic Leukaemia (CLL) is a lymphoproliferative malignancy characterized by the accumulation of tumor B cells in the blood, lymph nodes, and bone marrow. The tumor microenvironment plays a crucial role in the support and development of the CLL as, when purified from patients' blood CLL cells show limited survival in vitro.Thus, co-cultures of CLL with stromal cells are employed to extend CLL cells survival and to study the cross-talk of tumor cells with the microenvironment.
Infiltration of CLL cells into lymphoid tissues generates a mechanical stress, evidenced by extracellular matrix (ECM) remodelling, that contributes to tumor cells retention and survival. Extracellular matrix remodeling is known to activate the Hippo signaling pathway. Activated by the cell-cell contact or cell-ECM, this pathway regulates the activity of a transcriptional co-activator YAP important for cell survival, adhesion and differentiation. YAP deletion in a mouse model showed to cause lymph node disorganisation and loss of the stromal dependent immune cells trafficking, similar to the nodal disorganisation observed in CLL lymph node biopsies. Thus, we investigate the role of the stromal YAP dependent signaling in the cross-talk of the stroma with CLL cells and their abnormal retention within the microenvironment.
We generated stable stromal cells overexpressing YAP by mutating its regulatory phosphorylation sites (HS-5 YAP5SA) These transgenic stromal cells were co-cultured with CLL cells, and tumor cells adhesion was analysed. Indeed we found that CLL cells adhere more strongly to stromal cells overexpressing YAP, indicating that the signaling pathway linked to mechanical stress has an impact on CLL cells retention. In parallel, we generated 3D models, such as spheroids, containing transgenic HS-5 cells and CLL cells to analyse the cellular dialogue in a microenvironment reproducing the 3D architecture of the lymph node. In these 3D models, we show that YAP modulation changes the structure and solidity of the spheroids. We are currently analysing whether this YAP-dependent change of architecture affects CLL cells survival and trafficking.
Our data suggest that CLL cells cause a mechanical stress on stromal cells, resulting in the remodelling of the ECM and regulating the Hippo/YAP signaling pathway to increase CLL cells retention within the microenvironment. Targeting the YAP signaling could reveal to be a promising therapeutic strategy to favour the release of CLL cells from the microenvironment impacting their survival. Current therapeutic molecules, such as Ibrutinib, target the dialogue of CLL cells with the microenvironment but resistance phenomena often develop, thus the need of alternative strategies.

Evaluating the Immune Checkpoint TIGIT as a Novel Target in Pulmonary Fibrosis

A. V. Curioni*, D. Pokhreal*, X. Li□, P. Le Guen||, Y. Castier||, B. Crestani*,||, G.D. Helou*

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Introduction Idiopathic pulmonary fibrosis (IPF) represents the most frequent and severe type of lung fibrosis, with limited therapeutic options (PMID: 32145831). While the immune system's role in IPF remains debated, its contribution via the production of key fibrotic mediators is established. In particular, regulatory T cells (Tregs) secrete transforming growth factor beta (TGF-β) and interleukin (IL-) 10, promoting the proliferation of fibroblasts. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is an immune checkpoint implicated in different pathological contexts, notably cancer. High TIGIT expression marks enhanced Tregs' suppressive functions, associated with fibrinogen-like protein 2 and IL-10 production upon ligation (PMID: 34367161). Building on this, we aimed to characterize TIGIT expression in the lungs of IPF patients and to investigate its role in lung fibrosis progression.

Methods Transcriptomic data from the IPF atlas were reanalysed to characterize TIGIT gene expression in human lung immune cells. TIGIT levels were also quantified in bronchoalveolar lavage fluid (BAL) cells and correlated with disease severity. Pulmonary fibrosis was induced in FoxP3-GFP and humanized TIGIT (hTIGIT) knock-in mice. Lungs and BAL were collected 7 or 14 days (D) after intranasal exposure to bleomycin (BLM), and immunophenotyping was performed using flow cytometry. hTIGIT mice were injected at D8 and D11 with a human TIGIT antagonist "Tiragolumab" or an isotype control, and lung fibrosis was assessed.

Results TIGIT is most highly expressed by Tregs in the lungs and is significantly upregulated in IPF relative to healthy donors. The percentage of TIGIT+ Tregs is elevated in the BAL of IPF patients, but no correlation is revealed with respiratory function, sex, or smoking status. In both mouse models, Treg count increases upon BLM stimulation, and the percentage of TIGIT+ Tregs is significantly enhanced during the fibrotic phase (D14). Interestingly, TIGIT+ cells display an upregulated expression of activation markers CD69, ICOS, and CD25 as compared to TIGIT- cells, and an increased secretion of IL-13, IL-10, amphiregulin (Areg), and TGF-β in the lungs at D14. Treatment of hTIGIT mice with Tiragolumab does not affect the development of lung fibrosis. Specifically, no changes were observed in body weight, collagen production, or in the number and activation status of pulmonary myeloid and lymphoid cells.

Conclusion TIGIT emerges as a promising marker of a pulmonary pro-fibrotic Treg subpopulation in IPF, although treatment of humanized mice with TIGIT antagonist Tiragolumab does not affect lung fibrosis progression under our experimental conditions. More studies are needed to evaluate whether depletion of TIGIT+ Tregs would dampen fibrosis development, both in preclinical mouse models and in primary human lung cells.

4:30 - 4:40pm

STING-mediated autophagy in lung macrophages limits pulmonary fibrosis

Dr Nicolas Riteau
IRL2029 Immune Health; CNRS

The STimulator of INterferon Genes (STING) pathway represents a fundamental component of the innate immune system, orchestrating the detection of cytosolic DNA and the initiation of immune responses. We previously showed a type I interferon-independent protective function of STING in bleomycin (BLM)-induced lung fibrosis, the classical experimental model of Idiopathic Pulmonary Fibrosis (IPF). IPF is the most common interstitial lung disease with poor survival prognostic and limited treatment efficacy. Single cell RNA sequencing revealed a strong induction of STING in monocyte/macrophage populations upon BLM treatment. These results were confirmed using STING reporter animals (Tmem173 one strep tag), which showed that BLM treatment induces STING upregulation mainly in macrophage/dendritic cell subsets but not in lymphoid cells nor neutrophils. We hypothesize that STING in these cells may trigger protection against lung fibrosis through autophagy regulation. Our results indicate that BLM induces autophagy in lung myeloid cells and autophagy-related proteins ATG5 and LC3B-II are reduced while P62 is increased in BLM-treated Sting-deficient mice in comparison to their WT relatives, indicating that BLM-induced autophagy depends on STING. Furthermore, BLM-treated C57BL/6J wild type (WT) mice receiving the autophagy inducer Carbamazepin display a significant decrease in lung fibrosis associated with a reduction of recruited CD45+ immune cells, remodeling factors and collagen deposition suggesting positive effects of autophagy on lung fibrosis. Together, our data support an immunoregulatory function of STING in myeloid subsets through the induction of autophagy, possibly by modulating macrophage polarization and fibroblast function.

4:40 - 5:20pm ROUNDTABLE

Crosstalk and tools: spatial transcriptomics, imaging

How can new technologies reveal cellular crosstalk in human diseases?

How spatial transcriptomics and advanced imaging are reshaping our understanding of cell-to-cell communication.

Dr Camille Cohen

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Dr Lubka Roumenina

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