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NOVOTEL MONTE CARLO



BOOK OF ABSTRACTS

POSTERS

French Society of Vascular Biology (SFBVa) – Inaugural Meeting

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26 selected posters

[P-01] Aggrecan forms a non-classical Blood-Brain barrier in the medio-basal hypothalamus, a critical brain region for metabolic regulations

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Background: Energy homeostasis relies on a constant communication between the periphery and the brain, mediated by circulating signals (hormones, nutrients). This communication takes place in the medio-basal hypothalamus, notably the arcuate nucleus (ARH), where critical metabolic neurons (regulating feeding, satiety, and glycemia) are located, close to the median eminence (ME), a circumventricular organ with fenestrated capillaries. This highly permeable fenestrated vasculature passively allows the entry of circulating molecules (including metabolic hormones like stomach-derived ghrelin) into the brain parenchyma. However, an unidentified structure limits their diffusion from the ME to the ARH, possibly playing a decisive role in the central control of metabolism. Our aim was to identify this structure, to assess its possible plasticity with the physiological state, and to determine its role in the regulation of food intake.

Methods: The distribution of blood-borne molecules extravasating from the fenestrated ME vasculature was studied by immunostaining of endogenous albumin, alongside mapping of the extracellular matrix (aggrecan). The role of aggrecan was tested using genetic (hypomorphic and knock-out mice) and enzymatic approaches (stereotaxic digestion with the aggrecanase ADAMTS-5), combined with hormonal challenges (ghrelin) and food intake measurements. The plasticity of the deposit was assessed in relation to the animal nutritional state (fasting or refeeding), circadian timing, and its association with local vascularization.

Results: Blood-borne molecules extravasating from the fenestrated ME vasculature display a specific spatial distribution at the ME/ARH border, with unique features along the rostral-caudal axis of the hypothalamus. Aggrecan, deposited as perineuronal nets at this interface, plays a key role in this distribution: its genetic or enzymatic disruption leads to unregulated diffusion of blood-borne molecules into the ARH, alters ARH neuron sensitivity to ghrelin, and modifies post-fasting food intake. This deposit is plastic: it expands towards the ARH after fasting, reinforcing diffusion restriction. A diurnal plasticity was also observed, with maximal extension during the hours following the light phase, correlating with the animal feeding rhythm and the ghrelin secretion peak.

Conclusion: This study identifies aggrecan as a novel extracellular component forming a blood-brain barrier distinct from the classical vascular one, thereby regulating the entry of circulating molecules into the medio-basal hypothalamus. This novel cerebral barrier is located at the interface between a fenestrated capillary network and the classical blood-brain barrier and appears to adapt to local vascular plasticity.

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[P-02] Blood–Nerve Barrier Alterations in Acute and Chronic Oxaliplatin-Induced Peripheral Neuropathy

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Background: Chemotherapy-induced peripheral neuropathies (CIPN) are frequent, dose-related toxic effects of anticancer therapies, notably oxaliplatin, a platinum-based agent commonly used in gastrointestinal cancers. CIPN presents with sensory disturbances such as paresthesias and mechanical allodynia. These symptoms may be reversible at early stages but can evolve into long-lasting, debilitating chronic neuropathy over time. The mechanisms underlying this transition from acute to chronic neuropathy remain incompletely understood. Increasing evidence suggests that CIPN development involves neurovascular dysfunction, potentially driven by blood-nerve barrier (BNB) alterations and disruption of peripheral nerve homeostasis. However, the temporal dynamics of BNB impairments across acute and chronic stages remain poorly characterized.

Hypothesis: We hypothesized that oxaliplatin induces early functional alterations of the BNB during the acute phase of neuropathy and that persistent or progressive disruption of the BNB contributes to chronic, potentially irreversible peripheral nerve damage. We further hypothesized that vasodilator treatments can modulate early neurovascular dysfunction and that these effects correlate with behavioral outcomes assessed by Von Frey and Catwalk analyses.

Results: In acute CIPN model, mice received three injections of oxaliplatin over ten days. Mechanical sensitivity was assessed by Von Frey test, while locomotor function was evaluated using Catwalk automated gait analysis. Oxaliplatin-treated mice developed significant mechanical hypersensitivity and gait alterations compared to control animals which is consistent with CIPN onset. In this acute CIPN model, co-administration of vasodilator reduced mechanical hypersensitivity and seem to show an improvement of gait parameters compared with oxaliplatin alone. Previous results from our laboratory showed that acute oxaliplatin-induced neuropathic symptoms peak within approximately two weeks following treatment initiation and gradually recover within one month after cessation of treatment, indicating a largely reversible phase. In contrast, chronic CIPN model (up to two months) suggest persistent peripheral nerve alterations, including degeneration of intraepidermal nerve fibers which is consistent with a non-reversible component of neuropathy. Based on these observations, ongoing work is focused on comparing BNB integrity at the functional and molecular level in acute and chronic conditions. Preliminary data suggest early functional BNB alterations during the acute phase is not sustained by barrier molecular changes, while chronic exposure may be associated with sustained structural disruption and long-term nerve degeneration.

Conclusions: These findings support the involvement of BNB dysfunction in oxaliplatin-induced peripheral neuropathy and highlight important temporal differences between acute and chronic stages. While acute neuropathy appears partially reversible and modifiable by vasodilator treatment, chronic exposure may lead to persistent structural nerve damage. Understanding BNB dynamics across disease progression may provide new mechanistic insights into CIPN and identify potential therapeutic targets. Future studies will investigate BNB alterations in both acute and chronic settings in relation to antitumor treatment regimens and vasomodulatory strategies in order to better understand their translational relevance to clinical CIPN.

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[P-03] Deciphering extracellular matrix remodeling in brain regions distant from intracerebral haemorrhage

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Abstract (2000 Characters including space)

Background: Intracerebral hemorrhage (ICH) is a life-threatening condition caused by the rupture of a cerebral blood vessel and the entry of blood into the brain parenchyma. Given the absence of a specific therapeutic option, ICH is associated with high mortality rates, but also long-lasting neurological deficits among survivors. While pathophysiology of acute brain damage is emerging, the molecular and cellular mechanisms governing tissue remodeling and functional recovery remain obscure.

Hypothesis: This project tests the hypothesis that extracellular matrix (ECM), a key component of the neurovascular microenvironment, alters beyond the peri-hemorrhagic region, and affects distant brain areas involved in cognitive function.

Results: We adapted a previously validated ICH-inducing experimental method for use in mice, to characterize kinetic changes in both the ECM proteoglycan components and the vascular network across multiple brain regions. Immunostaining and tissue clearing techniques enables us to examine the three-dimensional organization of these remodeling processes. Concurrently, behavioural assessments evaluate the impact of ICH on motor and cognitive functions.

Conclusion: We expect to determine a key step in ECM and vascular remodeling processes, that would influence hematoma resolution and neurological recovery after ICH. Such a knowledge would pave the way for the development of novel therapeutic strategies to slow the progression of neurological deficits.

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[P-04] Endothelial ALK1 is critical for the maintenance of pulmonary and liver integrity beyond endothelial cells

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Abstract (2000 Characters including space)

Background: Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic vascular disorder characterized by recurrent epistaxis, gastrointestinal bleeding, cutaneous and mucosal telangiectasia, and arteriovenous malformations (AVMs), primarily affecting the lungs and liver, with severity increasing with age. HHT is caused by mutations in receptors of the Bone Morphogenetic Protein (BMP) signaling pathway, particularly Activin Receptor-like Kinase 1 (ALK1) or Endoglin (ENG), both of which are essential for maintaining endothelial integrity and quiescence.

Hypothesis&Approach: To specifically investigate the role of ALK1 in the adult vasculature, we developed an inducible endothelial-specific *Alk1* knockout (*Alk1*^{IECKO}) mouse model, in which *Alk1* deletion was triggered in fully mature, two-month-old mice. We also performed single-cell RNA sequencing (scRNAseq) on liver cell suspensions from these mice.

Results: ALK1 deletion in endothelial cells resulted in lethality within 8 days, with mice presenting severe pulmonary and gastrointestinal hemorrhages, highlighting the crucial role of ALK1 in maintaining vascular integrity in adult tissues.

In the liver, *Alk1* loss caused profound alterations in liver sinusoidal endothelial cells (LSECs) (*Gata4*, *Lyve1*, *Wnt2*), which lost their fenestrations and transitioned to a continuous endothelial phenotype. This "capillarization" of LSECs was accompanied by increased secretion of permeability-inducing factors (*Semaphorines*). Notably, these capillarized LSECs also abnormally secreted PDGF-B (platelet derived growth factor) that promote hepatic stellate cells activation, leading to perivascular fibrosis. This disruption of the liver microenvironment impaired hepatocyte zonation, a key determinant of liver metabolic function, and severely affected essential liver functions, including detoxification. Notably, these findings were validated on liver sections from HHT patients.

Conclusion: In conclusion, endothelial ALK1 deletion in adult mice leads to severe hepatic dysfunction. scRNAseq analysis revealed that these effects extend beyond endothelial cells, disrupting liver homeostasis and cellular interactions.

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[P-05] Engineering an *in vivo* and *in vitro* model of primary lymphedema

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Background: Primary lymphedema is an incurable rare disease caused by mutations in genes involved in the development and maintenance of the lymphatic vasculature. It is characterized by impaired lymphatic drainage, leading to the accumulation of fluid and adipose tissue within affected tissues. The lack of curative treatments is partly due to the limited availability of relevant *in vitro* and *in vivo* disease models.

Hypothesis: More than 30 gene mutations have been associated with primary lymphedema. Given that the disease predominantly manifests as a localized pathology affecting the limbs, we hypothesized local induction of disease-causing mutations using genome-integrative lentivectors would recapitulate the development of lymphedema *in vivo*.

Results: We first optimized the injection sites and number of lentivector administrations required to achieve broad coverage of the limb. Intradermal delivery of lentivectors carrying primary lymphedema-associated mutant genes induced the development of limb swelling within 10 days post-injection. In parallel, primary lymphatic endothelial cells were transduced at early passage with mutant lentivector to investigate the cellular consequences of the mutations in functional assays including migration, proliferation, bead sprouting, and vessel-on-chip permeability analyses.

Conclusions: We have developed a novel platform to investigate genetic mutations associated with primary lymphedema both *in vitro* and *in vivo*. This approach enables rapid characterization of mutation-specific phenotypes and provides a valuable tool for studying disease mechanisms. Furthermore, the *in vivo* model offers a platform for the development and evaluation of targeted genome-editing therapies aimed at selectively correcting pathogenic mutations.

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[P-06] Fibrillin-1 is required for endothelial mechanosensing in the aortic subendothelium

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Background: Ficrofibrils serve as a scaffold for elastin deposition. The resulting elastic fibers provide tissue elasticity, as in the media of the aorta, for example. In adult mice, we observed, within the intima, that the basement membrane underlying the endothelium also contains fibrillin-1 fibers that are oriented with the blood flow direction. Fibrillin plays a structural role, but it also contributes to the regulation of homeostasis by modulating the bioavailability of TGF-beta and BMPs. A less well-characterized role of fibrillin-1 is its involvement in mechanosensitivity.

Hypothesis: We hypothesized that fibrillin-1 network located in the aortic basement membrane plays a role in mechanosensation.

Results: We used a mouse model with a fibrillin-1 deficiency to investigate the role of subendothelial fibrillin-1 in the transmission of mechanical forces to endothelial cells. We performed integrin immunostaining labeling and “en face” viewing to study the adhesion of endothelial cells to this fibrillin-1-rich basement-membrane. We used atomic force microscopy to assess the stiffness of the matrix. Through in vitro experiments using endothelial cells silenced for fibrillin-1 expression and bulk-RNA sequencing, we were able to identify the signaling pathways induced or suppressed by fibrillin-1 deficiency. These results were validated by quantitative PCR and Western blotting.

Conclusion: Our results show that subendothelial fibrillin-1 participates in the mechanosensing of forces acting on the endothelium in the aorta, such as wall shear stress.

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[P-07] Functional and molecular characterization of novel GDF2 (BMP9) and BMP10 variants from the French pulmonary arterial hypertension (PAH) and Hereditary Hemorrhagic Telangiectasia (HHT) cohorts

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Background: Hereditary Hemorrhagic Telangiectasia (HHT) and Pulmonary Arterial hypertension (PAH) are two rare vascular diseases involving the BMP/ALK1/Smad signaling pathway. Few mutations in the genes *GDF2* (encoding BMP9) and *BMP10*, which are the high affinity ligands of the endothelial receptor ALK1, have recently been described in these two diseases. We aimed to develop a functional assay discriminating benign from pathogenic variants and to characterize the underlying molecular mechanisms responsible for their loss of function (LOF).

Hypothesis: BMP9 variants (four in suspected HHT patients, ten in the PAH patients) and BMP10 variants (one in HHT and five in PAH) were identified in the French HHT and PAH cohorts. The functional activities of these variants, generated by site-directed mutagenesis, were assessed using a specifically designed one step BMP luciferase reporter assay. Additionally, the impact on BMP9 and BMP10 protein processing and secretion was assessed by Western blot revealing the molecular mechanisms leading to their LOF.

Results: Two out of four BMP9 variants identified in suspected HHT patients were found pathogenic due to a defect in their processing; nevertheless, none of these patients met the Curaçao criteria for HHT. Nine out the ten BMP9 variants identified in PAH patients were found pathogenic and two among the six BMP10 variants identified in PAH patients were found pathogenic. Most of these alterations led to defects in processing/stability of BMP9 or BMP10 proteins. Moreover, we found that LOF GDF2 variants impaired the secretion of BMP10, suggesting a potential dominant negative mechanism.

Conclusion: Together, we present here a functional assay for BMP9 and BMP10 variants that allows to discriminate isomorphic from pathogenic variants and that can be easily transferable to clinical genetic laboratories. Our data do not support the hypothesis of BMP9 variants in HHT, whereas they support the presence of pathogenic BMP9 and BMP10 variants as susceptibility genes in PAH.

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[P-08] Identification of a conserved EndMT gene signature associated with atherosclerosis

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Background: Endothelial-to-mesenchymal transition (EndMT) is a pathological process whereby endothelial cells lose their endothelial identity and acquire mesenchymal characteristics. EndMT contributes to vascular remodelling and disease progression in several pathological contexts, including cancer and cardiovascular diseases such as atherosclerosis^{1,2}. Despite its recognized role in vascular pathology, the molecular programs underlying EndMT remain heterogeneous across experimental models and disease contexts, limiting the identification of robust EndMT-associated markers³.

Aims: To overcome the heterogeneity observed across EndMT models and disease contexts, we performed an integrative analysis of multiple publicly available transcriptomic datasets to identify a conserved EndMT gene signature and uncover novel regulators involved in endothelial plasticity and vascular remodelling.

Results: Rank-based meta-analysis identified a core set of genes consistently upregulated across EndMT datasets. This conserved signature was subsequently validated in independent datasets, with a particular emphasis on atherosclerosis. Gene set enrichment analysis confirmed robust enrichment of the signature in both human and mouse atherosclerotic tissues. In single-cell RNA-sequencing datasets, EndMT signature scoring revealed elevated EndMT-associated transcriptional programs in diseased endothelial cells. Importantly, this enrichment was observed across multiple endothelial subpopulations rather than being restricted to a specific cluster, highlighting the dynamic and heterogeneous nature of EndMT.

To further refine the signature and identify its key contributors, leading-edge analysis was performed across datasets. This approach highlighted both known EndMT markers and previously unrecognized candidate genes that may play important roles in endothelial plasticity, vascular remodelling, and disease-associated adaptation.

Conclusion: Our study identified and validated a conserved EndMT gene signature across independent datasets and species, with robust validation in atherosclerosis. Beyond identifying genes consistently associated with EndMT, our findings suggested that EndMT signatures capture both regulators of the transition and transcriptional responses that may reflect adaptive or protective mechanisms rather than drivers of the process. Together, these results provide a valuable foundation for future functional studies aimed at deciphering the mechanisms underlying endothelial plasticity and remodeling in diseases characterized by EndMT.

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[P-09] Investigating the role of the VEGFC/NRP2 axis in therapeutic strategies for pediatric medulloblastoma

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Background: Medulloblastoma is the most common pediatric brain cancer. Despite advanced therapeutic strategies such as radiotherapy, one-third of patients fail to respond and face fatal treatment resistance [1, 2]. Consequently, studying these resistance mechanisms remains a major clinical challenge. In the brain, meningeal lymphatic vessels participate in the metastatic dissemination of tumor cells. The formation of these vessels is promoted by Vascular Endothelial Growth Factor C (VEGFC), a growth factor secreted by tumor cells that can also be hijacked as a protumoral factor in autocrine signaling loops [3-6]. Additionally, preliminary data from our team linked acute irradiation to an upregulation of the VEGFC/Neuropilin-2 (NRP2) pathway.

Hypothesis: We postulated that whether targeting VEGFC and/or NRP2 in medulloblastoma cells could restrict tumor aggressiveness and radioresistance. Pharmacologically, the VEGFC axis can also be disrupted using a NRP2 receptor inhibitor, NRPa-308, developed by our collaborators [7]. We thus explored the potential of a combinatorial approach simultaneously targeting VEGFC and NRP2.

Results: The *VEGFC* gene was knocked out in Daoy cells (SHH subgroup, *TP53*-mutated), which were subsequently exposed or not to irradiation. The functional impacts of this loss on cell proliferation, migration and invasion were evaluated using clonogenic, wound-healing (scratch), and 3D spheroid assays. Against all expectations, our results revealed an antitumoral role of VEGFC, while the observed radioresistance proved to be independent of this axis, thereby opening new perspectives to study compensatory pathways. However, the NRP2 inhibitor appears highly promising, inducing a drastic collapse of invasive aggressiveness at low concentrations.

Conclusion: These findings establish the VEGFC/NRP2 axis as a key and multifaceted regulator of radioresistance in medulloblastoma and fully justify further preclinical evaluations in an *in vivo* murine model.

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Keywords: Medulloblastoma SHH, Vascular Endothelial Growth Factor C, Neuropilin-2, radioresistance, innovative therapeutic strategies

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[P-10] Is the cerebroprotective function of endothelial PRDM16 during ischemic stroke mediated by controlling the TGF β /BMP signaling balance?

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Background: Ischemic stroke is a leading cause of death and permanent disability caused by cerebral artery occlusion. Restoring cerebral perfusion by functionalizing collaterals and preserving blood-brain barrier (BBB) integrity is a desirable strategy to save ischemic brain tissue. PRDM16 in endothelial cells (ECs) plays a protective role during stroke as its EC-specific loss led to larger infarcts, impaired collateral perfusion and BBB disruption. Targeting EC-PRDM16 or its downstream mediators may therefore be of great interest to ameliorate stroke outcome. PRDM16 interacts with the Transforming Growth Factor (TGF) β /Bone Morphogenetic Protein (BMP) pathway, as it can bind SMADs and inhibits TGF β signaling in cardiomyocytes and smooth muscle cells. It remains to be determined whether PRDM16 also inhibits TGF β signaling in ECs upon stroke.

Hypothesis: During ischemic stroke PRDM16 mediates its protective effects in ECs by modulating the TGF β /BMP signaling balance at the expense of TGF β signaling.

Results: Following ischemic stroke, PRDM16 was compensatorily upregulated in brain ECs along with an increase in BMP signaling. Furthermore, upon EC-PRDM16 loss, phosphoSMAD2 levels were increased in brain ECs 7 days after stroke, suggesting that PRDM16 inhibits the TGF β /SMAD2/3 axis in cerebral vessels upon subacute stroke. Accordingly, functional enrichment analyses of single-cell RNA sequencing datasets identified TGF β /BMP-associated pathways among the significantly enriched terms in ECs upon subacute stroke in mice with EC-PRDM16 loss.

Conclusion: Collectively, these results support that PRDM16 controls the TGF β /BMP signaling pathway in ECs upon ischemic stroke. Future experiments will focus on corroborating the effect of EC-specific loss of PRDM16 on TGF β /BMP signaling reporter activity, and testing whether inhibition of the TGF β /SMAD2/3 pathway, via brain EC-specific viral gene transfer, can rescue cerebrovascular function and hence stroke outcome upon EC-PRDM16 loss.

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[P-11] Loss of endothelial PRDM16 accelerates atherosclerosis and induces a vulnerable plaque phenotype

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Background: Atherosclerosis is a life-threatening arterial occlusive disease initiated by endothelial cell (EC) dysfunction. The transcription factor PRDM16 acts as a guardian of arterial EC function through sustaining blood flow recovery downstream of occluded arteries during peripheral artery disease in mice. However, it remains unknown whether and how endothelial PRDM16 plays a role in the upstream atherosclerosis process.

Hypothesis: We hypothesize that EC-specific loss of PRDM16 aggravates atherogenesis by amplifying EC dysfunction.

Results: EC-PRDM16 knockout mice (*Prdm16-ECKO*) and their wild-type littermates (*Prdm16-ECWT*) on an atheroprone low density lipoprotein (LDL) receptor-deficient background were exposed to 8 or 20 weeks of Western diet, corresponding to early and late-stage atherosclerosis, respectively. In female, but not male, *Prdm16-ECKO* mice, atherogenesis was accelerated. At the early plaque stage, *Prdm16-ECKO* females exhibited an increased burden of collagen-rich lesions compared to *Prdm16-ECWT*, whereas late lesions had larger necrotic cores and less collagen, suggesting a vulnerable plaque phenotype. Single-nucleus RNA sequencing revealed more macrophages and synthetic smooth muscle cells (SMCs) in early and less synthetic SMCs in advanced lesions, compared to *Prdm16-ECWT* females. Early plaque stage ECs of *Prdm16-ECKO* mice featured profound disruption of circadian rhythm pathways evidenced by a significantly decreased expression of core clock genes such as *Bmal1* and *Npas2*. Furthermore, autophagy and senescence-associated genes were dysregulated in PRDM16-deficient ECs, all characteristics of EC dysfunction.

Conclusion: EC-PRDM16 is an atheroprotector by safeguarding EC homeostasis. Loss of PRDM16 in ECs accelerates atherogenesis and promotes plaque instability, which is in contrast to its known role in SMCs. These results uncover a previously unrecognized cell-type specific role for PRDM16 in atherosclerosis.

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[P-12] Loss of ROBO2 stabilizes PLK1 via C-ABL and drives head and neck squamous cell carcinoma (HNSCC) aggressiveness

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Background: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with over 400,000 deaths annually. Despite effective treatment of early-stage disease, advanced and recurrent HNSCC often relapses and develops therapy resistance, emphasizing the need for novel targeted approaches. Polo like kinase (PLK1), a mitotic regulator, is overexpressed in HNSCC and linked to poor survival, while ROBO2 (Roundbound guidance receptor 2) is downregulated and acts as a tumor suppressor. TCGA and an independent cohort showed an inverse ROBO2–PLK1 correlation, where low ROBO2 corresponds to high PLK1 and worse outcomes.

Hypothesis: We hypothesize that the downregulation of ROBO2 leads to PLK1 overexpression, thereby promoting tumor progression in HNSCC. Accordingly, the objectives of this study are to characterize the role of ROBO2 in HNSCC progression, Investigate the molecular relationship between ROBO2 and PLK1, with a particular focus on their inverse expression pattern and finally to assess the therapeutic potential of targeting the ROBO2/PLK1 axis in HNSCC.

Results: ROBO2 expression was significantly reduced in HNSCC and associated with poor overall and disease-free survival. ROBO2 downregulation correlated inversely with PLK1 expression in both TCGA and patient cohorts. In HNSCC cell lines, ROBO2 overexpression significantly inhibited proliferation, clonogenicity, migration, and invasion, together with decreased AKT, ERK, and p38 signaling. Mechanistically, ROBO2 reduced PLK1 expression through modulation of C-ABL activity. Pharmacological inhibition of ABL with imatinib further decreased PLK1 levels and significantly reduced cell viability, clonogenicity, and invasion while increasing cell death in ROBO2-deficient HNSCC cells, highlighting the therapeutic potential of targeting the ROBO2/C-ABL/PLK1 axis.

Conclusion: ROBO2 acts as a tumor suppressor in HNSCC by negatively regulating the ABL–PLK1 pathway. Loss of ROBO2 promotes tumor progression, whereas ABL inhibition with imatinib counteracts the aggressive phenotype of ROBO2-deficient cells, supporting the therapeutic potential of targeting this pathway.

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[P-13] Mesenchymal Nestin⁺ cells in post-myocardial infarction angiogenesis.

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Background: Myocardial infarction remains a leading cause of death worldwide. A coronary vessel blockage results in an exacerbated inflammatory response triggered by nutrient and oxygen deprivation, which initiates a complex reparative process aimed to restore tissue homeostasis. Following an acute myocardial infarction (AMI), the coordinated regulation of inflammation and reparative angiogenesis is essential to limit tissue damage, promote neovascularization, and preserve cardiac function. Dysregulation of these processes contributes to maladaptive remodeling and heart failure.

Hypothesis: Among the cellular populations within the myocardium, there are a particular mesenchymal progenitor cells, characterized by the expression of the intermediate filament nestin. These cells have been extensively studied in different cell niches¹, highlighting their role in both inflammation and angiogenesis. This study aims to characterize the role of Nestin⁺ heart mesenchymal progenitor cells regulating the inflammatory response and promoting reparative angiogenesis following an AMI.

Results: We analyzed available Single Cell RNA-Seq data focusing on the expression of transcription factors related to heart vascularization after AMI, within these expressing nestin mesenchymal stem cells². Therefore, we performed AMI in a transgenic mouse line to study these cells *in vivo*. They express endothelial markers within the infarct zone consistent with a contribution to the post-ischemic heart neovascularization. In *in-vitro* studies, HUAECs incubated with ischemic serum from infarcted patients showed an increase in blood vessel formation, blunted in nestin siRNA treated cells. Moreover, *In-vivo* depletion of chemokine expression in Nestin⁺ cells, showed reduced immune cells recruitment, indicating an active role for this progenitor cell population shaping inflammatory responses post-AMI.

Conclusions: Collectively, these findings suggest that Nestin⁺ cardiac progenitor cells are activated in response to ischemic injury and may contribute to the modulation of post-infarction inflammation and reparative angiogenesis.

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[P-14] Modulation of smooth muscle cell plasticity: implication in severe asthma

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Background: Allergic asthma is a chronic inflammatory disease affecting millions of peoples worldwide and is characterized by airway inflammation, hyperresponsiveness, and bronchial remodeling. While bronchodilators and inhaled corticosteroids effectively control symptoms in many patients, severe asthmatics patients often remains poorly responsive to these therapies. Like the vasculature, the bronchies are covered with smooth muscle cell controlling their diameter. Both vascular and airway SMCs play a key role in the progression of diseases through a phenotypic shift towards a proliferative, extra-cellular matrix producing state. In the case of asthma, airways SMCs contribute to airway remodelling and persistent obstruction. Their contractile properties also promote airway hyperresponsiveness. Current treatments do not reverse this airway remodeling, a phenomenon considered irreversible.

Hypothesis: Over the past decade, development of immunotherapies has considerably improved the treatment of severe asthma. In particular, anti-IL-4/IL-13 (Dupilumab)¹ and anti-IL-5 (Mepolizumab)² therapies effectively reduce pulmonary inflammation and improve lung function in patients. These clinical benefits suggest that bronchial remodeling and airway SMCs phenotypic switching, once considered irreversible, may in fact be reversible. In this context, our work used spatial transcriptomics to investigate, for the first time *in situ*, the impact of pulmonary inflammation on phenotypic dynamics of bronchial and vascular cells.

Results: We used a murine model of severe asthma³ to study bronchial remodeling dynamics. Spatial transcriptomic analysis revealed major phenotypic alterations in epithelial, fibroblastic and airway SMCs populations. Remarkably, one month after allergen withdrawal, the resolution of pulmonary inflammation was accompanied by restoration of epithelial and fibroblast populations toward a control-like composition. Importantly, airway SMCs heterogeneity was also normalized, with the disappearance of the hypercontractile subset and recovery of the physiological balance between contractile and secretory airway SMCs. This represents the first *in vivo* evidence of molecular reversion of airway SMC phenotypes following severe asthma. To determine whether these changes reflected true phenotypic plasticity, primary murine airway SMCs were exposed to PDGF-BB to induce dedifferentiation, followed by growth factor withdrawal. As expected, PDGF-BB downregulated contractile markers (Acta2, Tagln, Cnn1). After its removal, airway SMCs rapidly regained their contractile gene expression profile within 48 hours, demonstrating that airway SMC phenotypic switching is reversible and highlighting the intrinsic plasticity of these cells.

Perspectives: This study provides the first *in vivo* evidence of dynamic and reversible phenotypic changes in airway SMCs during the course of asthma. These findings challenge the notion of irreversibility in SMCs remodeling in general. Thus, our ongoing work focuses on pulmonary inflammatory consequences on vascular SMCs phenotype to determine the common and specific mechanisms involved in phenotype plasticity.

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[P-15] Molecular and Functional Characterization of Cerebral Perivascular Macrophage Diversity in Health and Disease

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Background: Perivascular macrophages (PVMs) are essential immune cells residing within the Virchow-Robin space, where they play a crucial role in neuroimmune surveillance and cerebrovascular homeostasis. Among these subpopulations, Lymphatic Vessel Endothelial Hyaluronan Receptor 1 (LYVE-1) expressing PVMs have garnered attention due to their distinctive lymphatic signature. This subset is essential for brain fluid homeostasis, a function crucial for mitigating toxic amyloid- β (A β) accumulation and hyperphosphorylated tau tangles, the key pathological hallmarks of Alzheimer's disease (AD). Recent research suggests that PVMs, particularly LYVE-1⁺ subsets, may interact with the glymphatic system to facilitate perivascular clearance, highlighting their potential role in cerebrospinal fluid drainage and waste removal in neurodegenerative diseases like AD.

Hypothesis: We hypothesize that LYVE-1⁺ PVMs maintain cerebrovascular homeostasis and glymphatic clearance, and that late-stage AD pathologically deregulates the LYVE-1 transcriptional framework to induce expression loss and morphological alterations. This transcriptional and structural shift drives perivascular drainage failure, accelerating cerebral amyloid angiopathy (CAA) and plaque accumulation.

Results: Leveraging transgenic mouse models, we identified a significant downregulation of LYVE-1 expression in late-stage AD compared to controls, with a pronounced reduction in vessels associated with CAA. Notably, LYVE-1⁺ PVMs in the AD phenotype also exhibit distinct morphological alterations, including increased circularity compared to their WT counterparts, suggesting phenotype-specific adaptations that may influence perivascular immune surveillance and clearance dynamics. Furthermore, we identified a LYVE-1⁺ transcriptional gene signature and potential transcriptional regulators associated with LYVE-1 expression in PVMs.

Conclusion: This molecular framework provides a basis for future strategies aimed at reprogramming LYVE-1 expression in dysfunctional PVMs, potentially restoring their homeostatic functions in AD. Collectively, these findings advance our understanding of PVM biology and identify potential targets for therapeutic modulation of this population in AD.

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[P-16] Neural crest–endothelial crosstalk in VHL-associated hemangioblastomas: development of an iPSC-based vascular tumor model

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Background: Von Hippel-Lindau (VHL) disease is a hereditary tumor syndrome characterized by the development of highly vascularized tumors, including central nervous system and retinal hemangioblastomas (HBs)^{1,2}. HBs are highly vascularized tumors characterized by a prominent network of abnormal blood vessels and the mechanisms underlying their development remain poorly understood. In particular, the contribution of the cellular microenvironment to endothelial cell (EC) activation and vascular remodeling remains to be elucidated. Neural crest cells (NCCs) are transient embryonic cells that migrate extensively during development and give rise to multiple cell types, including neural and vascular-associated cells. We hypothesized that NCCs and their derivatives may contribute to HB development through paracrine interactions with ECs.

Hypothesis: We hypothesized that *VHL*-mutated NCCs may modify endothelial behavior through their secretome and that NCC-derived vascular-associated cells, including pericyte-like cells, may contribute to the HB microenvironment. We therefore aimed to establish an iPSC-based model allowing the study of NCC–EC crosstalk and, ultimately, identify molecular mechanisms involved in *VHL*-associated HB.

Results: We established and characterized an iPSC-based model of *VHL*-associated HB using patient-derived iPSCs carrying different *VHL* gene alterations. Robust differentiation into NCCs was achieved, and functional analyses revealed mutation-dependent differences in NCC transcriptional programs and metabolism. We next optimized EC differentiation and established complementary assays to investigate the effects of NCC-derived soluble factors on endothelial behavior, including wound-healing, adhesion, proliferation and tubulogenesis assays. In parallel, we developed a protocol for differentiation of NCCs into pericyte-like cells, providing an additional cellular component for reconstruction of a more physiologically relevant vascular microenvironment.

Conclusions: Our results support the development of an iPSC-based multicellular model to investigate the mechanisms underlying the highly vascular phenotype of *VHL*-associated HBs. This model will allow us to dissect the molecular dialogue between NCCs/NCC-derived pericyte-like cells and ECs, and to identify secreted factors that may promote endothelial activation. An important future direction will be to investigate the developmental relationship between hemangioblasts and endothelial cells during iPSC differentiation and determine whether this intermediate developmental state may provide new insights into the cellular origin and vascular phenotype of HBs.

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[P-17] ORAI3 calcium channel drives neuro-angiogenic remodeling in prostate cancer

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Background: The progression and therapeutic resistance of prostate cancer (PCa) are driven by dynamic interactions between tumor cells and their microenvironment. Besides tumor cell plasticity, increasing evidence identifies tumor-associated innervation as a key hallmark of aggressive disease. Reciprocal communication between cancer cells, endothelial cells and nerves promotes neuro-angiogenic remodeling, thereby facilitating tumor growth, metastatic dissemination and resistance to therapy. However, the molecular mechanisms orchestrating this crosstalk remain poorly understood.

Hypothesis: We hypothesize that the calcium channel ORAI3, overexpressed in malignant prostate epithelial cells, is a central regulator of tumor cell plasticity and neuro-angiogenic remodeling. We further propose that ORAI3-dependent remodeling is mediated by alterations in the tumor secretome, particularly extracellular vesicles (EVs), which may convey pro-neurogenic and pro-angiogenic signals to the tumor microenvironment.

Results: We implemented an integrated multidisciplinary strategy combining MALDI mass spectrometry imaging, multi-omics analyses and functional assays (calcium signaling, cell migration and proliferation) using human and mouse prostate cancer cell lines, FFPE patient-derived tissues. Our results demonstrate that ORAI3 overexpression contributes both *in vitro* and *in vivo* to tumor microenvironment remodeling by promoting epithelial–mesenchymal transition (EMT) and angiogenesis. Conversely, we show that nerve-derived signals activate ORAI3 and further stimulate EMT, supporting a bidirectional crosstalk between prostate cancer cells and the nervous system. Moreover, conditioned medium experiments using PC3^{WT} and PC3^{OE-ORAI3} cells indicate that ORAI3-overexpressing cells enhance both neuritogenesis and angiogenesis. Ongoing characterization of the tumor secretome, with a particular focus on extracellular vesicles (EVs), aims to identify the molecular mediators responsible for these pro- neuro-angiogenic effects.

Conclusion: Together, these findings identify ORAI3 as a key regulator of tumor cell plasticity and neuro-vascular communication in prostate cancer. To further investigate its role *in vivo*, we generated a genetically engineered mouse model knockout for *Orai3* only in PCa epithelial cells upon tamoxifen injection (project APAFIS #35548-2022020311342894 v3). Combined with comprehensive secretome and EV analyses, (using *in vitro* and *in vivo* models) will allow us to decipher the mechanisms by which ORAI3 remodels the tumor microenvironment and drives neuro-angiogenesis. Ultimately, these studies may identify novel therapeutic targets to limit tumor progression, angiogenesis and metastatic dissemination.

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[P-18] PAI-1, a new therapeutic target in Clear Cell Renal Cell Carcinoma ccRCC

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Introduction Clear cell renal cell carcinoma (ccRCC) accounts for approximately 80% of renal cancers. Although surgical nephrectomy is the standard initial treatment, 30–40% of patients experience recurrence with metastases. SerpinE1 (PAI-1), frequently overexpressed in ccRCC, has been linked to rapid metastatic progression and poor survival. The aim of this study was to characterize PAI-1 expression in ccRCC cells and investigate its role in tumor aggressiveness and metastasis.

Methods: We showed that silencing PAI-1 with siRNA or inhibiting it with TM5441 in ccRCC cell lines led to reduced PAI-1 expression, decreased JNK pathway activity, and significant suppression of cell proliferation, clonogenic potential, migration, and invasion, accompanied by increased apoptosis. In contrast, overexpression of PAI-1 via lentiviral transduction promoted cell proliferation, clonogenicity, migration, invasion, and resistance to apoptosis, effectively reversing the effects of its downregulation.

Results: Beyond its direct effects on tumor cells, PAI-1 also influenced the tumor microenvironment. PAI-1 downregulation decreased the polarization of macrophages toward the pro-tumoral M2 phenotype while favoring M1 polarization. In contrast, PAI-1 overexpression reduced the expression of M1 markers in M1 macrophages. Additionally, PAI-1 silencing reduced angiogenic capacity, leading to decreased blood vessel formation.

In vivo, using a zebrafish model, PAI-1 knockdown or pharmacological inhibition significantly impaired ccRCC cell migration in the tail, further supporting its role in metastatic behavior.

Conclusion: Overall, our findings demonstrate that PAI-1 is a key driver of ccRCC aggressiveness and metastasis and highlight its potential as a promising therapeutic target for intervention.

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[P-19] Role of Estrogen Receptor (ER α) in the Lymphatic System

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Background: Lymphedema is a progressive condition characterized by impaired lymphatic return, swelling of extremities due to an accumulation fibrotic adipose tissue in the limb. It can be primary (genetic) or secondary following a filarial infection or breast cancer treatments. Lymphedema exhibits a higher prevalence in women compared to men, suggesting a role for sex hormones, particularly estrogens, in the development of the pathology. However, the underlying mechanisms remain poorly understood.

Hypothesis: To investigate the role of estrogen receptor alpha (ER α) in the lymphatic system, we developed an original mouse model with a specific deletion of ER α in lymphatic endothelium (ER α ^{LECKO} mice). Interestingly, these mice exhibit resistance to weight gain compared to control littermates, despite increased food intake. This phenotype was accelerated in high fat diet fed mice and was associated by a decrease in intestinal lymphatic lacteal lipid absorption.

Results: In vitro, the effect of 17 β -estradiol (E2) on lymphatic endothelial cells was investigated. We found that E2 increases trans-endothelial lipid transport. This was associated with an increase in fatty acid uptake by lymphatic endothelial cells. Our goal is now to determine whether ER α deficiency in lymphatic endothelial cells directly affects lipid transport or indirectly influences intestinal barrier function.

Conclusions: Overall, this study highlights a novel link between lymphatic estrogen signaling and lipid metabolism, providing new insights into the pathophysiology of lymphedema and its associated metabolic alterations.

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[P-20] Role of Nicotinamide N-methyltransferase (NNMT) in endothelial cell senescence: implications for vascular aging and chronic kidney disease

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Background. Aging profoundly disrupts vascular homeostasis by promoting arteriosclerosis and capillary rarefaction, ultimately impairing tissue perfusion and function. In the kidney, endothelial cell (EC) senescence has been associated with both renal aging and chronic kidney disease (CKD) development¹. Cellular senescence is accompanied by a decline in intracellular nicotinamide adenine dinucleotide (NAD⁺) levels, which has also emerged as a potential driver of renal and endothelial dysfunction in aging and disease². Targeting endothelial NAD⁺ metabolism may therefore represent a promising vasculoprotective and nephroprotective strategy. Recent studies have identified nicotinamide N-methyltransferase (NNMT) as a pro-fibrotic enzyme in the kidney that diverts nicotinamide (NAM) away from the NAD⁺ salvage pathway, the primary route of NAD⁺ regeneration in mammalian cells^{3,4}. Although NNMT has been linked to metabolic reprogramming and senescence in tubular epithelial cells in experimental models of CKD^{3,4}, its regulation and role in the (renal) endothelium remain largely unexplored.

Hypothesis. We hypothesized that NNMT is upregulated in renal ECs during aging and CKD, and promotes endothelial senescence by limiting NAD⁺ regeneration.

Results. To investigate the involvement of NNMT in renal ECs during aging and CKD, we analyzed in-house and publicly available single-cell RNA-sequencing datasets of renal cells from aging mice and CKD patients⁵. Glomerular and peritubular ECs showed upregulation of NNMT expression in aged animals, as well as in patients with hypertensive and diabetic kidney disease, as compared with young animals and control kidney donor tissues, respectively. Immunofluorescence analysis of kidney sections from the adenine-induced CKD mouse model confirmed NNMT expression in a subset of peritubular ECs under disease conditions, with minimal expression in controls. To investigate the role of NNMT in endothelial senescence, cultured HUVECs were exposed to doxorubicin (100 nM) for 24 h, followed by a 48-h recovery period to induce a senescence-like phenotype. Senescence induction was confirmed by increased senescence-associated β -galactosidase activity, upregulation of p21 (*CDKN1A*), *IL6*, and *VCAM1* expression, and reduced *LMNB1* expression. *NNMT* expression in response to doxorubicin varied across HUVEC donors, but consistently showing the same trend as *TP53* (p53) expression, supporting a coordinated regulation consistent with previous reports⁶. Importantly, pharmacological NNMT inhibition prevented doxorubicin-induced senescence and inflammatory marker expression in this model, supporting a functional role for NNMT in establishing or sustaining endothelial senescent phenotype.

Conclusions. These findings provide preliminary evidence implicating NNMT in endothelial senescence. NNMT may promote endothelial dysfunction by limiting NAD⁺ regeneration. These observations provide a rationale for exploring endothelial NNMT as a potential therapeutic target in aging and CKD.

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[P-21] Role of tumour-derived miR-155 in vascular remodeling associated with metastatic progression

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Background: The vascular endothelium and its underlying basement membrane (BM) form the structural and functional unit of the vascular wall, regulating permeability and maintaining vessel stability and integrity. We previously identified microRNA-155 (miR-155) as a potent inducer of podosome formation in microvascular endothelial cells. Podosomes are actin-based and MMP-enriched structures that function as organelles specialized in BM degradation. They are normally induced by VEGF, enabling endothelial cells to breach the BM and initiate sprouting angiogenesis. *In vivo*, intravitreal delivery of synthetic miR-155 in newborn mice induced podosomes in endothelial cells, disturbed developmental retinal angiogenesis and induced vascular remodeling. We now extend these findings by demonstrating that, in the adult retinal vasculature, miR-155 similarly compromises vascular homeostasis, leading to alterations in vascular architecture and increased vessel permeability.

Hypothesis: miR-155 is recognized as an oncomiR due to its involvement in various cancers. Given the well-established association of miR-155 with tumour progression, we hypothesized that tumour-derived miR-155 destabilizes the vascular wall by promoting endothelial BM degradation, thereby facilitating metastatic dissemination.

Results: Using complementary *in vivo* and *in vitro* approaches, we investigated the effects of melanoma-derived miR-155. A mouse model of lung metastasis was used to assess its contribution to metastatic dissemination, while mechanistic studies were conducted to characterize endothelial responses triggered by tumour-derived miR-155. Our results identify extracellular vesicle-associated miR-155 as a driver of vascular remodeling. By inducing podosome formation in endothelial cells and BM degradation, tumour-derived miR-155 weakens the vascular barrier, facilitates tumour cell extravasation, and ultimately promotes metastatic dissemination.

Conclusion: These findings uncover a previously unknown mechanism by which tumour-derived miR-155 remodels the vascular wall to promote metastasis. They identify the miR-155–podosome axis as a potential therapeutic target to preserve vascular integrity and limit metastatic progression.

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[P-22] Shifting from 2D co-cultures to 3D spheroid and vascularized models to mimic tumor endothelial cell-mediated immune reprogramming in thoracic cancers.

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Background: Responsible for an estimated 1.8 million deaths per year, lung cancer is one of the leading causes of cancer incidence and mortality worldwide, with non-small-cell lung cancers (NSCLC) accounting for 80-85% of cases. Over the past decade, immunotherapies have revolutionized patient outcome but only a small fraction of patients responds. The tumor microenvironment is an important parameter mediating such resistance with normal endothelial cells (NECs) educated into tumor endothelial cells (TECs), which display deregulated immunoregulatory features with therapeutical relevance.

Hypothesis: In this study we established various in vitro models to unravel how tumor cells could remodel NECs into TECs, and how their remodeling impacts the immune system.

Results: As such, we combined multi-omics approaches including single-cell RNA sequencing (scRNA-seq), meta-analysis and various functional assays to dissect the immunoregulatory functions of NECs/TECs.

We showed that coculturing ECs with various NSCLC cell lines induced profound alterations at the transcriptomic, proteomic and kinomic levels with the induction of pro-inflammatory pathways that reflect their activation state. Despite a limited impact of NSCLC-TECs on CD8 T lymphocyte proliferation and activation, we showed that CD4 T cells polarized into different subsets (Treg, Th22, Th1/Th2) when cocultured with NSCLC-TECs.

We also discovered that ECs could enhance the expression of pro-tumor markers on cocultured macrophages. In the seek to improve our 2D coculture system, we scrutinized at the single cell resolution, i) 3D multicellular tumor spheroids encompassing tumor cells, ECs, fibroblasts and monocyte-derived macrophages, and ii) vascularized tumor-on-chip with/without tumor cells. We showed that cell heterogeneity was much more complex than 2D cultures, with specific EC subclusters, peculiar cell-cell interactions and cell signaling that may have particular therapeutic importance.

Conclusion: Using various cocultures, spheroid and vascularized models we further refined the precise function of tumor ECs within the TME, and how they could modulate tumor immunity.

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[P-23] Telocyte-derived Netrin-1 targets endothelial UNC5B to drive vascular pruning during infantile hemangioma involution

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Background: Infantile hemangioma (IH) is the most common benign tumor in children, affecting close to 4-5% of newborns [1]. It follows a biphasic life cycle: an initial proliferative phase of ectopic angiogenesis and aberrant endothelial cell proliferation, leading to a hyperplastic vascular network, followed by a spontaneous involuting phase driven by vessel regression, leading to tumor disappearance between 5 and 7 years of age. Stromal telocytes (IH-TCs) [2] may contribute to this regression, as morphological changes in telocytes correlate with the decreasing number of vessels. We further demonstrated an anti-angiogenic effect of telocytes in vitro using a 3D sprouting angiogenesis assay [4].

Hypothesis: We hypothesized that telocyte-derived Netrin-1, a repulsive guidance molecule acting through the endothelial UNC5B receptor [3], mediates the anti-angiogenic and vascular pruning effect of IH telocytes during involution.

Results: A targeted transcriptional screen of 25 anti-angiogenic factors identified Netrin-1 as the most overexpressed, with a 12-fold increase in IH-TCs compared with control telocytes (Ctl-TCs) from foreskin. In coculture with primary endothelial cells (HUVECs), IH-TCs induced segregation of the two cell populations, an effect abolished by a Netrin-1-blocking mAb or genetic knockdown of Netrin-1 in IH-TCs, and absent with Ctl-TCs. Using a transendothelial transwell permeability assay, IH-TCs increased HUVEC monolayer permeability, compared with Ctl-TCs, through disruption of inter-endothelial VE-cadherin junctions, an effect counteracted by anti-Netrin-1. These anti-angiogenic and vascular pruning effects of IH-TC-derived Netrin-1 were further confirmed using an endothelial sprouting bead assay and a fibrin hydrogel pseudo-vessel network assay, with both genetic and antibody-based Netrin-1 inhibition.

Conclusion: Together, these data indicate that telocyte-derived Netrin-1 acts as an endothelial repulsive factor targeting UNC5B, driving the endothelial cell pruning that occurs during the involution phase of infantile hemangioma.

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[P-24] Uncovering glycosaminoglycan-rich blood vessels in the mediobasal hypothalamus, a key region for central metabolic control.

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Introduction: Periphery–brain cross-talk is essential for maintaining energy homeostasis. Central to this communication, orexigenic and anorexigenic neurons in the hypothalamic arcuate nucleus (ARH) integrate multiple blood-borne metabolic signals to trigger appropriate responses to fluctuating energy states. Crucially, access of circulating hormones to the ARH depends on vascular and extravascular structures with varying permeability, whose barrier properties change with energy state. Indeed, during fasting, structural rearrangements occur in this region, increasing blood vessel permeability and strengthening the extracellular matrix to enable more precise control of circulating molecule diffusion. Although extracellular matrix glycosaminoglycans, such as chondroitin sulfates, and their protein core (aggrecan) have been shown to regulate the distribution of blood-borne molecules in this brain region, their vascular functions remain poorly understood. In particular, heparan sulfate, a major component of the vascular glycocalyx, has not been characterized in the vasculature of the medio-basal hypothalamus (MBH).

Material & Method: Adult male wild-type mice, genetic mouse model of metabolic alteration (ob/ob and db/db mice) are used to characterize the distribution of N-sulfated heparan sulfate (N-HS) in the medio-basal hypothalamus.

Results: Immunofluorescence labelling for N-sulfated heparan sulfate (N-HS), CD31 and type IV Collagen in wild-type mice revealed a population of blood vessels in the ARH displaying strong N-sulfated heparan sulfate immunoreactivity. Strikingly, this N-HS-positive vessel subtype shows a spatially restricted distribution along the third ventricle, clearly distinct from the broader type IV collagen- and CD31-positive vascular network distributed throughout the MBH. This selective pattern identifies a previously uncharacterized blood vessel subtype at the ARH/third ventricle interface. Interestingly, the distinct distribution of N-HS does not mirror that of HS-bearing protein cores (e.g., perlecan), suggesting that glycosaminoglycan synthesis is independent of its protein core production. We are currently investigating the precise vascular localization of these polysaccharide chains, distinguishing between luminal and basal compartments. In parallel, we are characterizing the cellular sources responsible for their production, as well as the enzymes involved in their biosynthesis and maturation.

We will assess the plasticity of these glycosaminoglycans within this vascular subtype in response to metabolic status (fed versus fasted) and examine potential alterations in mouse models of obesity and diabetes (ob/ob and db/db). We will also investigate their functional roles using in vivo destabilization approaches targeting these polysaccharides.

Ultimately, our objective is to uncover a previously unrecognized vascular specialization within a region critical for peripheral–brain communication.

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[P-25] Unraveling the role of endothelial ZEB2 in the pathogenesis of idiopathic pulmonary fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is a rare but progressive lung disease with limited treatment options characterized by patchy fibrotic foci in the lung parenchyma. While historically considered as a disease initiated by alveolar epithelial injury, there is growing evidence that pulmonary endothelial cells (ECs) also actively contribute to IPF pathogenesis. One mechanism by which ECs promote fibrosis is (partial) endothelial-to-mesenchymal transition ((p)EndoMT), during which ECs transition into myofibroblasts, directly contributing to fibrosis. Transcription factor ZEB2 is a key driver of EndoMT, making it an attractive but thus far unexplored target in IPF.

Hypothesis: We hypothesize that EC-specific deficiency of ZEB2 attenuates IPF pathogenesis by reducing EndoMT.

Results: To induce IPF, we used the repetitive bleomycin-induced mouse model of pulmonary fibrosis, which closely resembles human IPF. To assess a dose-response relationship, 2 doses of bleomycin (3x 1 or 0.5 USP unit/kg) were administered via intratracheal instillations to EC-ZEB2 deficient mice and their wild-type littermates. At the high dose, EC-ZEB2 deficient mice showed higher survival than wild-type littermates 6 weeks after the first bleomycin instillation. Longitudinal analysis of *in vivo* microcomputed tomography (μ CT) scans showed an overall lower non-aerated lung volume in EC-ZEB2 deficient mice, and histology at (variable) time of death revealed that EC-ZEB2 deficient mice were largely protected against parenchymal damage. At the lower dose, all mice survived but mice developed a suboptimal pathological response on μ CT.

Conclusion: These findings suggest that endothelial ZEB2 deficiency is protective in IPF, potentially through modulation of EndoMT. An intermediate bleomycin dose (0.75 U/kg) may provide an optimal balance between survival and fibrosis formation to further assess the role of EC-ZEB2 in IPF pathogenesis.

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[P-26] Vasodilator-Induced Protection Against Oxaliplatin-Induced Peripheral Neuropathy in Tumor-Bearing Mice

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Background: Peripheral neuropathy is a major adverse effect of anticancer chemotherapy that can compromise treatment continuation, especially with oxaliplatin-based regimens prescribed for gastrointestinal cancer. Patients receiving oxaliplatin commonly develop sensory alterations affecting the extremities, which can progressively evolve toward more severe sensorimotor dysfunction as exposure accumulates. This condition remains a major clinical limitation due to the lack of effective preventive or curative treatments, largely linked to an incomplete understanding of its pathophysiology. Because oxaliplatin is administered intravenously, vascular mechanisms have been proposed to contribute to peripheral neuropathy development, potentially through alterations in intra-nervous perfusion and tissue homeostasis. We have identified that vasodilator could prevent oxaliplatin-induced peripheral neuropathy (OIPN) in acute mice models, and in a longer timeframe.

Hypothesis: We here want to provide a proof of concept for translational perspective that co-administration of oxaliplatin and vasodilators do not impair chemotherapeutic effect. To this end we are assessing that systemic administration of a vasodilator may attenuate OIPN in tumor-bearing mice without interfering with the antitumor treatment efficacy. We further developed an automated Catwalk gait analysis to provide a sensitive, non-invasive and operator-independent approach to detect functional locomotor alterations associated with chemotherapy-induced peripheral neuropathy (CIPN), complementing conventional Von Frey testing

Results: Following CT26 tumor cell implantation, mice were randomly assigned to three experimental groups: Sham, Oxaliplatin (Oxa), and Oxaliplatin combined to Tadalafil, a vasodilator (Oxa-Tada). Mechanical sensitivity was assessed using Von Frey test, while locomotor function was evaluated using the Catwalk automated gait analysis system.

Tumor burden was assessed using the peritoneal carcinomatosis index (PCI), confirming successful tumor establishment in all tumor-bearing groups. As expected, oxaliplatin treatment was associated with a reduction in PCI compared with the Sham group, consistent with its antitumor activity. Importantly, PCI values remained similarly reduced in the Oxa-Tada group, indicating that vasodilator co-administration did not interfere with oxaliplatin antitumor efficacy.

In parallel, oxaliplatin-treated mice developed mechanical hypersensitivity compared with Sham animals. In line with Von Frey results, tadalafil-treated mice exhibited reduced neuropathic symptoms compared with oxaliplatin alone. Catwalk analysis further showed a trend toward preservation of gait parameters in the Oxa-Tada group, suggesting attenuation of oxaliplatin-induced functional impairments.

Conclusion: These preliminary findings support a protective effect of vasodilator treatment in a tumor-bearing mouse model of OIPN. Moreover, automated Catwalk gait analysis provides an objective and non-invasive assessment of motor function that complements classical sensory testing and will be a strong added value for chronic model behavioral assessment of tumor-bearing mice. Conducted in close collaboration with clinicians, this translational approach may improve the assessment of CIPN and facilitate the preclinical development of vascular-targeted strategies aimed at preventing chemotherapy-induced neurotoxicity without compromising anticancer efficacy.

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