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Host laboratory:
Lab : BIOSANTE

Host group/team:
BMP in Angiogenesis & lymphangiogenesis (BAL)

Title of the M2 research internship:
Role of the ALK1-BMP pathway in the stabilization of the blood brain barrier in the central nervous system

Project summary:
In the central nervous system (CNS), endothelial cells are particularly tight, forming a barrier called the blood-brain barrier (BBB). This barrier is crucial for maintaining neuronal integrity by shielding neurons from harmful substances. However, BBB integrity declines with aging and is further compromised in numerous neurodegenerative diseases, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), multiple sclerosis, and Huntington's disease. Conversely, the extreme tightness of the BBB poses a significant challenge for therapeutic interventions, as it prevents 98% of potential therapeutic molecules from crossing into the CNS. Therefore, understanding the molecular mechanisms that govern the formation and maintenance of the BBB is essential for developing tools that enable controlled, "on-demand" modulation of its permeability.
ALK1, a serine-threonine kinase endothelial receptor, is essential for vascular development and maintenance in adulthood. However, its specific role in vascular stabilization within the CNS remains poorly understood. Preliminary findings from our team suggest that the BMP9/10-ALK1 signaling pathway is critical for regulating vascular permeability, particularly in preserving the unique tightness of CNS blood vessels. Notably, using fluorescent tracers and MRI contrast agents, we have observed vascular integrity defects in the brain and retina of KO mouse models lacking the ALK1 receptor or its ligands, BMP9 and BMP10.
This project aims to elucidate the molecular mechanisms by which ALK1 maintains BBB integrity, with the ultimate goal of leveraging this pathway as a therapeutic target for BBB-related diseases.

To achieve this, endothelial cells isolated from ALK1 knockout (KO) mice or subjected to siRNA-mediated ALK1 knockdown will be assessed for barrier integrity by measuring transendothelial electrical resistance (TEER). The structure of intercellular junctions—tight junctions (Claudin-5, ZO-1) and adherens junctions (VE-cadherin)—will be characterized using confocal microscopy. Additionally, the phosphorylation/expression status of junctional proteins and key signaling molecules (Wnt pathway, β-catenin) will be analyzed. Finally, specific attention will be given to the organization of the glycocalyx through transmission electron microscopy studies, as a recent publication (Nature, 2025) has demonstrated a direct involvement of mucin-O glycosylation in the maintenance of BBB integrity. By dissecting the molecular mechanisms through which ALK1 regulates BBB maintenance, this project aims to establish a foundation for utilizing this pathway as a therapeutic strategy in diseases involving BBB dysfunction.

Keywords:
Endothelial cells, blood brain barrier, vascular permeability, cell signaling,

Relevant publications of the team:
1. Desroches-Castan A. *, Tillet E. *,. Bouvard C., Bailly S. BMP9 and BMP10: two close vascular quiescence partners that stand out. Dev Dyn. 2021 Jul 9. doi: 10.1002/dvdy.395. Review
2. Ricard N, Bailly S, Guignabert C, Simons M. Nat Rev Cardiol. 2021 Feb 24:1-16.The quiescent endothelium: signalling pathways regulating organ-specific endothelial normalcy.

3. Tabosh T, Liu H, Koça D, Al Tarrass M, Tu L, Giraud S, Delagrange L, Beaudoin M, Rivière S, Grobost V, Rondeau-Lutz M, Dupuis O, Ricard N, Tillet E, Machillot P, Salomon A, Picart C, Battail C, Dupuis-Girod S, Guignabert C, Desroches-Castan A, Bailly S. Impact of heterozygous ALK1 mutations on the transcriptomic response to BMP9 and BMP10 in endothelial cells from hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension donors Angiogeneis 2024, 27; DOI: 10.1007/s10456-023-09902-8
4. Desroches-Castan A, Koca D, Liu H, Roelants C, Resmini L, Ricard N, Bouvard C, Chaumontel N, Tharaux PL, Tillet E, Battail C, Lenoir O, Bailly S. BMP9 is a key player in endothelial identity and its loss is sufficient to induce arteriovenous malformations 2024, Cardiovasc. Res 29; DOI: 10.1093/cvr/cvae052
5. Bouvard C., Tu L., Rossi M., Ouarne M., Helfer E., Perret P., DaubonT., Desroches-Castan A., Roelants C., Chaumontel N., Humbert M., Mallet C., Bikfalvi A., Saval L., Tillet E., Guignabert C., Bailly S. (2021) Different cardiopulmonary phenotypes for single- and double-knock-out mice deficient in BMP9 and BMP10.
Cardiovasc. Res, 2021 Jun 4:cvab187. doi: 10.1093/cvr/cvab187
6. Al Tabosh, T. et al. Hereditary hemorrhagic telangiectasia: from signaling insights to therapeutic advances. J Clin Invest 134, e176379 (2024).