Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

Supervisor(s):
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Host laboratory:
BioSanté biosante-lab.fr/

Host group/team:
BMP

Title of the M2 research internship:
Intercellular communication alterations in lungs and liver following ALK1 deletion in mice

Project summary:
ALK1 is a receptor expressed by endothelial cells, the cells forming the inner layer of blood vessels, and binds circulating Bone Morphogenetic Proteins (BMPs)-9/10. Loss of function mutations in ALK1 are associated with a rare vascular disease called hereditary hemorrhagic telangiectasia (HHT). HHT symptoms include dilated arteriovenous malformations that alter hemodynamics and are prone to rupture leading to bleeding. Symptoms worsen with age, with a total penetrance at around 60-year-old. We hypothesized that ALK1 is crucial for the homeostasis of the adult endothelium. In order to identify the roles of ALK1 in this adult endothelium, we used tamoxifen-inducible endothelial ALK1 knockout mice. We performed single cell RNA sequencing on liver and lungs from these mice and identified cell-cell communications that are affected following the loss of ALK1. The internship will consist in validating disrupted signaling pathways using a large panel of techniques, including state-of-the-art in situ hybridization (RNAscope technology), ligand quantification by ELISA and receptors expression by qPCR. The activation of corresponding signaling pathways will be assessed by western blot on tissue lysates. Rescue of phenotypes will be tested using neutralizing antibodies against overexpressed ligands or recombinant proteins for downregulated ligands. Vascular phenotype is assessed on tissue sections followed by immunofluorescence /confocal microscopy and blood vessel permeability can be studied by the use of fluorescent tracers in adult mice. Altogether, the project includes various techniques from mRNA and protein expression (RNAscope, qPCR, ELISA, western blot), to mouse tissue imaging. The intern will not directly handle mice but should not disagree with animal experimentation.

Keywords:
physiopathology of vascular disease, signaling pathway, mouse models

Relevant publications of the team:

- 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

- Desroches-Castan A, Tillet E, Ricard N, Ouarné M, Mallet C, Belmudes L, Couté Y, Boillot O, Scoazec JY, Bailly S, Feige JJ. Bone Morphogenetic Protein 9 Is a Paracrine Factor Controlling Liver Sinusoidal Endothelial Cell Fenestration and Protecting Against Hepatic Fibrosis. Hepatology. 2019 Apr 9. doi:10.1002/hep.30655

- Al Tabosh T., Al Tarrass M., Tourvieilhe L., Guilhem A., Dupuis-Girod S., Bailly S. Hereditary hemorrhagic telangiectasia: from signaling insights to therapeutic advances. J Clin Invest. 2024 Feb 15;134(4):e176379. doi: 10.1172/JCI176379.

- Al 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. Angiogenesis. 2024 Jan 31. doi: 10.1007/s10456-023-09902-8.

- Bouvard C., Tu L., Rossi M., Ouarne M., Helfer E., Perret P., Daubon T., 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 1 double-knock-out mice deficient in BMP9 and BMP10.