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

Supervisor(s):
Elisa Migliorini, elisa.migliorini@cea.fr

Host laboratory:
Biologie et Biotechnologie pour la Santé
https://biosante-lab.fr/en

Title of the M2 research internship:
Investigating the BMP-integrin crosstalk with biomimetic platforms

Project summary:
Bone morphogeneti protein 2 (BMP2) is a key molecule for normal bone development in vertebrates and induces osteoblastic differentiation of mesenchymal cells. We proved that integrins and BMP-SMAD signaling up-regulate each other (1, 2). To study that we designed two types of biomaterials which mimic the in vivo presentation of BMP2 via the extracellular matrix (ECM) (3) (i) polyelectrolytes layer-by-layer (LbL) films composed by Poly-L-lysine and Hyaluronic Acid with variable stiffness (4, 5) and (ii) streptavidin (SAv) platforms on which biotinylated components can be grafted (6, 7). These two biomaterials have complementary properties: the functionalization of SAv platforms is controlled with surface sensitive techniques (QCM-D and ellipsometry (8)), however it is not possible, so far, to modulate their stiffness. In particular we proved that surface immobilized BMP2 improved cellular adhesion on soft LbL films (1) and on SAv platforms presenting a low surface concentration of the adhesion peptide cRGD (2). Moreover, increasing the surface concentration cRGD, on SAv platforms, enhances SMAD 1/5/9 phosphorylation (2). The real mechanism behind this crosstalk is however not clear. Indeed, we have published and unpublished data showing that the same integrin can have opposite roles depending on the type of biomaterial used. It is therefore needed to uniform these readouts by comparing each physical and chemical property of our biomaterials. We aim to identify the “general” role of specific ECM components (such as cRGD and BMP2) and the corresponding cellular receptors (integrins and BMPRs) on BMP2 signaling ¬– that does not depend on the experimental condition. For that SAv platforms will be built on a soft polymer as polymethilsiloxane (PDMS) having similar mechanial properties as the LbL films. The platfoms will be characterised with surface sensitive techniques and the mechanical properties tested with AFM. Finally, cellular studies will be performed on the both biomaterials to compare the BMP-SMAD signaling.

Keywords:
bioinspired platforms, BMP2, substrate stiffness

Relevant publications of the team:
Fourel L, Valat A, Faurobert E, Guillot R, Bourrin-Reynard I, Ren K, et al. beta3 integrin-mediated spreading induced by matrix-bound BMP-2 controls Smad signaling in a stiffness-independent manner. The Journal of cell biology. 2016;212(6):693-706.

Sefkow-Werner J, Machillot P, Sales A, Castro-Ramirez E, Degardin M, Boturyn D, et al. Heparan sulfate co-immobilized with cRGD ligands and BMP2 on biomimetic platforms promotes BMP2-mediated osteogenic differentiation. Acta biomaterialia. 2020.

Migliorini E, Guevara-Garcia A, Albiges-Rizo C, Picart C. Learning from BMPs and their biophysical extracellular matrix microenvironment for biomaterial design. Bone. 2020;141:115540.

Crouzier T, Fourel L, Boudou T, Albiges-Rizo C, Picart C. Presentation of BMP-2 from a soft biopolymeric film unveils its activity on cell adhesion and migration. Advanced materials (Deerfield Beach, Fla). 2011;23(12):H111-8.

Crouzier T, Ren K, Nicolas C, Roy C, Picart C. Layer-by-layer films as a biomimetic reservoir for rhBMP-2 delivery: controlled differentiation of myoblasts to osteoblasts. Small (Weinheim an der Bergstrasse, Germany). 2009;5(5):598-608.

Migliorini E, Thakar D, Sadir R, Pleiner T, Baleux F, Lortat-Jacob H, et al. Well-defined biomimetic surfaces to characterize glycosaminoglycan-mediated interactions on the molecular, supramolecular and cellular levels. Biomaterials. 2014;35(32):8903-15.

Migliorini E, Horn P, Haraszti T, Wegner S, Hiepen C, Knaus P, et al. Enhanced biological activity of BMP-2 bound to surface-grafted heparan sulfate. Advanced Biosystems. 2017;1(4):1600041.

Migliorini E, Weidenhaupt M, Picart C. Practical guide to characterize biomolecule adsorption on solid surfaces (Review). Biointerphases. 2018;13(6):06d303.