2018-2021

Doctoral thesis (I-MEP2) at LMGP Laboratory.

Engineered BiomimEtic platforms to analyse the molecular and cellular role of Heparan Sulfate on bone morphogenetic protein 2 (BeHSt)

Context

The industrial development of biomaterials for bone tissue regeneration is steadily increasing due to socio-economical need for bone repair therapies especially caused by the aging of the population and improvement of the quality of life. A boost of bone repair can be achieved using potent osteoinductive proteins, named bone morphogenetic proteins (BMPs). In Europe, the clinical use of BMP2 has been approved. However, its inappropriate delivery from collagen sponges and its supraphysiologic doses led to adverse clinical effects(1). Thus, there is a crucial need to engineer innovative carrier materials to optimize and better control the delivered dose of BMP2. Understanding which are the molecular regulators of BMP2 activity during bone repair and studying the BMP2 presentation *via* the bone extracellular matrix is therefore essential for a future **new generation of BMP2-delivering biomaterials**.

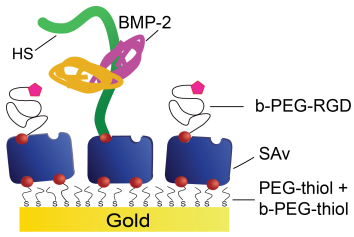

Figure 1: schematic representation of the biomimetic platforms that will be developed in this project.

In tissues, native BMP2 is presented via the extracellular matrix (**ECM**) **components**. The role of these ECM components on the bioactivity of BMP2 is still under debate.

Up to now important questions remain unanswered on (i) how can the presentation of BMP2 by ECM components affect bone differentiation? (ii) what is the role of each of these components in this context (iii) what are the underlying molecular mechanisms?

Project description

We design surfaces — **biomimetic platforms** — that present some selected components of the ECM. On the biomimetic platforms we will graft ECM components as the glycosaminoglycan heparan sulfate, which is known to bind BMP2 and adhesion peptides (cyclic RGD) to permit cells spreading *via* cellular adhesion receptors: integrins (**Fig 1**). The group has shown that the *bioactivity of BMP2 can be enhanced by integrins activation*(2). With quartz crystal microbalance with dissipation monitoring (**QCM-D**) and **spectroscopic ellipsometry**, we will characterize the binding of each ECM components on the streptavidin-coated platforms (**Fig 1**) (3, 4). After the characterization of the molecular assembling, we will use these platforms for studying **cellular adhesion and differentiation** with molecular biology methods as immunofluorescence and/or western blots. We will compare the effect of BMP2, presented *via* immobilized heparan sulfate or directly immobilized *via* biotin–streptavidin on BMP2-mediated osteogenic/chondrogenic differentiation.

Related Publications

1. Zara JN, Siu RK, Zhang X, Shen J, Ngo R, Lee M, et al. High Doses of Bone Morphogenetic Protein 2 Induce Structurally Abnormal Bone and Inflammation In Vivo. Tissue engineering Part A. 2011;17(9-10):1389-99.
2. 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.
3. 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.
4. 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.

Background and skills expected

Only master student (M2R), engineer diplomat or equivalent (minimum 5 years of university studies plus six months practical experience in a research environment) are eligible. We will select student motivated to work in a multidisciplinary environment, at the interfaces between physics, chemistry and biology. Expert in surface chemistry/ or biochemistry with basic expertise in cellular biology would be appreciated. The candidate should be interested to travel to accomplish two or three mission abroad to partner laboratories.

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Please send your CV, a motivation letter and a reference letter of your master thesis supervisor to the contact e-mail.