Université de Lyon – Project LYON6

Title: Effect of LSD1 overexpression on the extracellular matrix synthesis by human articular chondrocytes

Supervisor: Jérôme Lafont

Duration: 3 months

Project Context:
Within the cartilage, the deposition of matrix molecules is made by the chondrocytes, the unique resident cells. Understanding what regulates the synthesis of that matrix and the mechanisms of the articular cartilage homeostasis is crucial for cartilage repair purposes (1). Indeed, after trauma or with ageing, the cartilage matrix is progressively lost (2) without any chance to recover physiologically (and no pharmacological treatment is available). Our approach in the lab relies on the analysis of the cell response of the chondrocytes toward their stimulation by environmental factors (growth factors, low oxygen tension) (3,4). Although the genetic mechanisms have been studied for long, the epigenetics have been poorly investigated in the field of cartilage biology (5). This knowledge may help developing new strategies to promote the matrix deposition for cartilage repair (cell therapy) or may bring new targets to prevent the cartilage loss.

Project Objectives:
The project consists in studying the underlying mechanism of the chondrocyte gene regulation during their anabolic activity through the analysis of the role of the LSD1 chromatin modifying enzyme (6). RNA sequencing experiments in siRNA depleted cells performed in the lab allowed us identifying several putative target genes, which we want now to confirm using an overexpression strategy. Training will be given to the student for qPCR, and western blot technics for the analysis of specific gene expression. All the work will be based on primary culture experiments, thus students with cell culture basics is preferable although not compulsory. Since we demonstrated LSD1 interacts with SOX9 (submitted manuscript), which is a crucial transcription factor in controlling the gene expression of chondrocyte markers (7), we will also (ideally) test whether it can be a substrate of LSD1 using immunoprecipitation experiments. Altogether, the project will give the first insights into the new role of LSD1 in the SOX9-dependent gene regulation in chondrocytes.

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Bibliography

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3 - Hypoxia promotes the differentiated human articular chondrocyte phenotype through SOX9-dependent and -independent pathways. Lafont JE, Talma S, Hopfgarten C, Murphy CL. J Biol Chem. 2008 Feb 22;283(8):4778-86
6 - LSD1: biologic roles and therapeutic targeting - Alba Maiques-Diaz& Tim CP Somervaille Epigenomics (2016) 8(8), 1103–1116
7 - SOX9 is a potent activator of the chondrocyte-specific enhancer of the pro alpha1(II) collagen gene - Lefebvre, V; Huang, W; Harley, V R; Goodfellow, P N; de Crombrugghe, B. Molecular and cellular biology Mol Cell Biol. 1997 Apr;17(4):2336-46
Comments:
Our group has a well-recognized expertise in the field of cartilage biology and engineering with a specific focus on the control of the chondrocyte phenotype in vitro. Gene regulation studies are performed (basic research) to improve the in vitro cell manipulation and define appropriate cell culture of chondrocyte/stem cells for the clinics (translational research). The lab is equipped for tissue and cell characterization (histology and cell imaging platform) and animal models of cartilage repair have also been developed. Diverses culture conditions (3D matrices, soluble factors, bioreactor, hypoxic environment) are being tested in collaboration with various institutions (academic engineers, biotech companies etc...). The internship can be a starting point for a further collaboration through a joint project (grant application) with the University of Ottawa.