Structural features involved in Heparan sulfate binding and processing by Sulf extracellular sulfatases

Laboratory/Institute : IBS, Grenoble, France / Industrial partner

Phd supervisor: Romain Vivès

Scientific Context and objectives

Heparan Sulfate (HS) polysaccharides bind a very large array of signaling proteins, thereby modulating their availability, stability, structure and reactivity. These interactions occur through saccharide domains (termed S-domains) of specific sulfation pattern, present within the polysaccharide. Assembly of such functional domains is orchestrated by a complex biosynthesis machinery and their structure is further regulated at the cell surface by post-synthetic modifying enzymes, including extracellular sulfatases of the Sulf family. Sulfs catalyze the selective removal of 6-*O*-sulfate groups, which are required for the recognition of many proteins, and specifically target HS S-domains. Although structurally subtle, these modifications have great functional consequences, and Sulfs have emerged as critical regulators of HS activity, in physiological processes such as embryogenesis and tissue regeneration, and in diseases such as cancer. However, despite increasing interest, these enzyme mechanisms remain poorly characterized. In this context, we propose to perform an integrated structural and functional study of the Sulfs, to clarify the structural basis of Sulf/HS recognition process, substrate specificities and catalytic mechanism.

This multi-disciplinary project relies on the close collaboration and complementary expertise of an academic team and an industrial partner. The PhD candidate will work in close interactions with both partners and will be in charge of the production of recombinant protein (in eukaryotic and prokaryotic expression systems), the development of dedicated isotopic labelling techniques suitable for NMR studies, the preparation and screening of oligosaccharide substrate libraries using functional assay (SPR, enzyme assays…) and the structural analysis of Sulf enzyme using combined approaches of NMR and X-ray crystallography.

Location

The PhD project will take place in the SAGAG group at the Institute for Structural Biology (IBS, http://www.ibs.fr/research/research-groups/structure-and-activity-of-glycosaminoglycans-group/), within the European Synchrotron campus and will benefit from the complementary expertise of the project partners in biochemistry, NMR and X-ray crystallography, as well as privileged access to the Partnership for Structural Biology (PSB) state of the art platforms (protein expression, high-throughput crystallization, NMR spectrometers).

The selected candidate will work in a stimulating international environment, and will graduate from UGA, one of the top French university. Grenoble is a highly dynamic city located in the heart of the

French Alps, ranked as the 5th most innovative city in the world (FORBES 2013). It is very easily accessible (3h from Paris by train, 1h from Lyon international airport).

Candidate profile

The PhD candidate should hold (or be about to obtain) a Master's degree (or equivalent) with honor (top rank > 25%), in biochemistry and structural biology (NMR, X-ray crystallography…) and show high interest in working at the interface of biochemistry and biophysics. Previous successful laboratory internship experience, notably in the production of isotopically-labelled protein and NMR analysis, will be an indisputable advantage for the candidate selection. A demonstrated ability to perform independent work and communication/writing skills are also considered as important criteria.

Position

Doctoral contract co-funded by an industrial partner and the UGA-IDEX Glyco@Alps program.

Application

Please send a CV (including reference for possible recommendation), to romain.vives@ibs.fr

Deadline: 25th of May 2018