Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MSc RESEARCH SCHOLARSHIP 2020-2021

RESEARCH INTERNSHIP PROPOSAL

Institute / Group

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Research Project Title

Enzymatic regulation of cell-surface glycanic landscape in human disease

Description of the project

Many pathological conditions have been associated with an alteration of cell-surface glycan structure and function. This is particularly relevant for Heparan sulfate (HS), a complex polysaccharide that play key regulatory roles in most biological processes, including cell proliferation and development, inflammation and immune response, angiogenesis, tissue repair or host-pathogen interaction and cancer.

HS elicits these activities through the binding and modulation of a wide array of proteins. These interactions depends on specific sulfations of the polysaccharide, which are tightly controlled during both its biosynthesis and post-synthetically, through the action of extracellular enzymes. The objective of the project is to study the patterning of HS for one type of sulfation (6-sulfation), which is critical in many physiopathological processes, including cancer. For this, we will carry out the structural and functional characterization of the enzymes involved in the remodelling of HS 6-sulfation. The project will thus include recombinant expression of proteins, enzymology, structural biology approaches (NMR, X-ray crystallography, SAXS), and functional studies (in vitro, in cellulo and in vivo, through our collaboration with the CEA IRIG-BCI lab). This study should provide significant insights into this major regulation system of HS activities, and for the design of new HS-based inhibitors and therapeutical approaches.

Keywords

heparan sulfate, interactions, enzymes, structure/function relationships, disease

Relevant publications of the team

A. Seffouh, R. El Masri, O. Makshakova, E. Gout, Z.el Oula Hassoun J.P. Andrieu, H. Lortat-Jacob and R.R. Vivès. “Expression and purification of recombinant extracellular sulfatase HSulf-2 allows deciphering of enzyme sub-domain coordinated role for the binding and 6-O-desulfation of heparan sulfate”. Cellular and Molecular Life Sciences, 76, 1807-1819 (2019).

K. Oshima, X. Han, Y. Ouyang, R. El Masri, Y. Yang, S.M. Haeger, S.A. McMurtry, T.C. Lane, P. Davizon-Castillo, F. Zhang, X. Yue, R.R. Vivès, R.J. Linhardt and E.P. Schmidt. “Loss of endothelial sulfatase-1 after experimental sepsis attenuates subsequent pulmonary inflammatory responses”. Am J Physiol Lung Cell Mol Physiol. 317, L667-L677 (2019).

C. Debarnot, Y.R. Monneau, V. Roig-Zamboni, V. Delauzun, C. Le Narvor, E. Richard, J. Henault, A. Goulet, F. Fadel, R.R Vivès, B. Priem, D. Bonnaffé, H. Lortat-Jacob and Y. Bourne. “Structural insights into substrate binding and catalytic mechanism of human heparan sulfate D-glucuronyl C5 epimerase”. PNAS, 116, 6760-6765 (2019).