Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MSc RESEARCH SCHOLARSHIP 2020-2021

RESEARCH INTERNSHIP PROPOSAL

Institute / Group

IRIG / IBS – IRPAS

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Research Project Title

Do C1s mutations identified in diseases affect the function of this immune protease?

Description of the project

The highly controlled C1s protease is known as an innate immune trigger. It associates with a homologous protease (C1r) and a defense collagen (C1q) to form C1, the initiation complex of the complement cascade. Triggering of the cascade by C1 leads to the elimination of pathogens or self-debris via different biological effects. Due to its modular structural organization, C1s is a highly specialized serine protease, with only two main substrates, the complement cascade components C2 and C4. Recent observations have shown however the potential implication of C1s in pathological processes, raising the need to characterize further non-canonical functions and identify other potential targets for this protease. Heterozygous variants have recently been identified in the context of a severe periodontal Ehlers-Danlos syndrome, or discovered within renal tumors. In these cases, a gain of new catalytic functions independent of complement is a major hypothesis for their implication in the disease. The main goal of this M2 project will be to initiate the work on the molecular dissection of the effects of the mutations associated to renal cancer on C1s function. The student task will be to obtain the recombinant C1s variants using site-directed mutagenesis and to produce them in a mammalian expression system. C1s variants will then be tested for their impact on the structure and assembly of the C1 complex and for their enzymatic activity, as compared to the wild type C1s. The functional impact of the mutations on the cleavage of other new potential targets that could be linked to the disease will also be addressed. The student should have a strong background in biochemistry and an interest in immunology or biophysics and apply to one of the Masters in biology: Specialty Biochemistry and Structural Biology or Specialty Immunology, Microbiology, Infectiology.

Keywords

Cancer, protease, mutation, complement system, innate immunity

Relevant publications of the team

Two different missense C1S mutations, associated to periodontal Ehlers-Danlos syndrome, lead to identical molecular outcomes. I. Bally, F. Dalonneau, A. Chouquet, R. Gröbner, A. Amberger, … , N.M. Thielens, V. Rossi, C. Gaboriaud. In press. Frontiers in Immunology (2019) . doi: 10.3389/fimmu.2019.02962

Periodontal Ehlers-Danlos Syndrome Is Caused by Mutations in C1R and C1S, which Encode Subcomponents C1r and C1s of Complement. I. Kapferer-Seebacher, M. Pepin, R. Werner, T. Aitman, A. Nordgren, H. Stoiber, N. Thielens, C. Gaboriaud, …, P. Byers, J. Zschocke. Am J Hum Genet. (2016), 9:1005-1014.

Crystal structure of the catalytic domain of human complement C1s: a serine protease with a handle. C. Gaboriaud, V. Rossi, I. Bally, G.J. Arlaud, J.C. Fontecilla-Camps. EMBO J. (2000) 19:1755-65.