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Master Internship offer

Title of the project: "Deciphering the role of the cytoskeleton in the activation of the Pyrin inflammasome and characterization of *PSTPIP1* variants".

Institution, Director of the institut: CIRI (https://ciri.ens-lyon.fr), François-Loïc Cosset

Host laboratory, Head of the team: « Inflammasome, infections bactériennes et autoinflammation

(I2BA) », Thomas Henry (https://ciri.ens-lyon.fr/teams/I2BA)

Scientist in charge of the project: Flora Magnotti, flora.magnotti@inserm.fr

Internship project:
The Pyrin inflammasome is an innate immune signaling platform, deregulated in several auto-inflammatory diseases (AIDs), a group of heritable disorders characterized by recurrent inflammatory flares. Familial Mediterranean fever (FMF) is the most common AID and is due to mutations in the *MEFV* gene, the gene encoding Pyrin. AIDs indirectly linked to Pyrin have also been identified, including the PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome) which is due to mutations in *PSTPIP1*, a gene encoding a protein involved in cytoskeletal organization.
The mechanism of Pyrin activation and its link with PSTPIP1 are still poorly understood but are controlled by the cytoskeleton.
The purpose of this stage is to better elucidate the role of PSTPIP1, in the Pyrin inflammasome activation mechanism, using a model of human monocytes expressing wild-type or mutated proteins. In addition, a protocol to characterize *PSTPIP1* variants will be developed to classify the variants in terms of pathogenicity. The student will use cell culture (including of primary human macrophages), CRISPR/Cas9 technology, molecular biology and lentivirus transduction to invalidate the genes of interest and evaluate the impact of different *PSTPIP1* variants. He/She will monitor the inflammasome activation by measuring pyroptosis (an inflammatory cell death), by quantifying cytokines release and measuring specific parameters by flow-cytometry. He/She will study the formation and the localisation of the Pyrin inflammasome using confocal microscopy.
This study should enhance our fundamental knowledge on the pyrin inflammasome and help the genetic diagnosis of PAPA syndrome. On the long term, it may lead to the development of selective treatments for AIDs.

Keywords : Inflammasome, Pyrin, PSTPIP1, cytoskeleton, Autoinflammatory diseases.

3 Relevant publications :

- Magnotti, *et al.* Cell Rep, 2022 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9626387)
- Shoham, *et al*. PNAS, 2003. (www.pnas.org/doi/epdf/10.1073/pnas.2135380100)
- Standing, *et al*. J Exp Med, 2017 (https://pubmed.ncbi.nlm.nih.gov/27994071/)