Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Host laboratory:
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Title of the M2 research internship:
Role of the catalytic activity of the dUSP36 deubiquitinase

Project summary:
Deubiquitinases (DUBs) are specific proteases which remove ubiquitin moieties from ubiquitinated proteins. DUBs regulate many biological functions including protein stability, cell signaling or endocytosis. Their dysregulation has been linked to many human pathologies, enlightening the importance of understanding how their functions are coordinated and regulated. Our team has been studying the DUB USP36 in the model organism Drosophila melanogaster for several years. dUSP36 is involved in several physiological processes including immunity, stem cell maintenance, autophagy. Moreover, we have recently shown that a nucleolar isoform of dUSP36 promotes cell growth and proliferation by regulating the Drosophila homolog of the MYC oncogenic protein. The MYC-USP36 complex, which also includes the E3 ligases AGO represents an evolutionary conserved regulatory node that tightly controls MYC ubiquitination levels and stability in both Drosophila and human cells. To further understand USP36 functions in vivo, we have generated a catalytically inactive version of the endogenous dUSP36 protein by mutating by CRISPR-Cas9 its catalytic cysteine to a serine residue. Compared to Drosophila Usp36 null mutants, which produce no dUSP36 protein and display strong cell growth defects leading to larval lethality, Usp36 catalytic dead mutants display very mild cell growth defects and survive to adulthood. This preliminary result unambiguously shows that the catalytic dead version of dUSP36 can fulfil some of the functions of the wild-type protein. This completely reshapes our understanding of the mechanisms by which USP36 regulates MYC stability. Genetic and biochemical experiments will be carried out to characterize MYC ubiquitination status and the activity of the E3 ligase AGO. Additionally, the requirement of USP36 catalytic activity in the other known phenotypes of Usp36 mutants (immunity, stem cell maintenance and autophagy) will be addressed using experimental procedures (RT q-PCR and immunofluorescence) which are routinely used in the team.

Keywords:
MYC-dependent cell growth, ubiquitin,

Relevant publications of the team:

Thevenon D, Seffouh I, Pillet C, Crespo-Yanez X, Fauvarque MO, Taillebourg E. A Nucleolar Isoform of the Drosophila Ubiquitin Specific Protease dUSP36 Regulates MYC-Dependent Cell Growth. Front Cell Dev Biol. 2020

Jacomin AC, Taillebourg E, Fauvarque MO. Deubiquitinating Enzymes Related to Autophagy: New Therapeutic Opportunities? Cells. 2018

Taillebourg E, Gregoire I, Viargues P, Jacomin AC, Thevenon D, Faure M, Fauvarque MO.The deubiquitinating enzyme USP36 controls selective autophagy activation by ubiquitinated proteins. Autophagy. 2012