Offre de stage de Master / Master Internship offer

Internship supervisor and Host laboratory:

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Research project title:

Host-virus interplays governing envelopment and secretion of hepatitis C viral particles

Project description:

Hepatitis C virus (HCV) is a human pathogen that induces severe liver diseases. There has been little research on HCV secretion from hepatocytes; thus, exploring how this virus manipulates the cell secretory pathway to promote the production of viral particles is intriguing and, beyond gaining novel knowledge, it could also prove to be a resource for new therapeutic targets. Indeed, resistances to the new direct acting antiviral drugs (DAAs) are emerging and additional therapies to the existing treatments will be needed. This stimulates the unraveling of host-HCV interactions and, more particularly, the intersections of viral assembly and secretion with cellular membrane export processes.
Viroporins are small transmembrane viral proteins with ion channel activities modulating properties of intracellular membranes, which impacts several fundamental biological processes such as trafficking, ion fluxes as well as connections and exchanges between organelles. HCV encodes a viroporin, p7, exhibiting diverse proviral functions during assembly, envelopment and secretion of viral particles. HCV p7 is liberated by cleavage from the HCV polyprotein but also exists as an E2p7 precursor, of poorly defined properties. Our laboratory has shown that this retarded cleavage is a key regulation mechanism of E2 HCV surface glycoprotein and p7 viroporin functions associated to virion assembly and/or perturbation of cellular membrane processes. Specifically, we demonstrate that p7 liberation regulates the cell secretory pathway, which induces the intracellular retention of HCV glycoproteins and favors assembly of HCV particles, but which also modulates host proteins secretion. We also found that E2p7-regulated processing governs, *via* its unmasking, a novel determinant at p7 amino-terminus that drives a critical assembly function controlling the composition of different types of released viral particles. Overall, these recent results underscore an original post-translational control of assembly and secretion of HCV particles that dictates their specific infectivity.

The project in this internship is at the interface of cell biology and molecular virology. It aims at addressing the following questions:

- How does deregulation of the cell secretory pathway impact HCV-infected cell and liver functions, and HCV pathogenesis?
- What are the molecular mechanisms and host factors coopted and/or recruited by HCV p7 viroporin during the virion envelopment process?

The technologies and methods that will be used in this project are biochemistry, molecular biology, cell biology, imaging by confocal microscopy, and virology in P2 and P3 laboratories.

5 recent Lab publications:

DENOLLY S, C MIALON, T BOURLET, F AMIRACHE, F PENIN3, B LINDENBACH, B BOSON, & F-L COSSET. 2017. The amino-terminus of the hepatitis C virus (HCV) p7 viroporin and its cleavage from glycoprotein E2-p7 precursor determine composition and specific infectivity of HCV particles. In revision.

BOSON B, DENOLLY S, TURLURE F, CHAMOT C, DREUX M, & COSSET FL. Daclatasvir prevents hepatitis c virus infectivity by blocking transfer of the viral genome to assembly sites. Gastroenterology 2017;152:895-907 e14.

FUSIL F, CALATTINI S, AMIRACHE F, MANCIP J, COSTA C, ROBBINS JB, DOUAM F, LAVILLETTE D, LAW M, DEFRANCE T, VERHOEYEN E, & COSSET FL. A lentiviral vector allowing physiologically regulated membrane-anchored and secreted antibody expression depending on b-cell maturation status. Mol Ther 2015;23:1734-47.

CALATTINI S, FUSIL F, MANCIP J, DAO THI VL, GRANIER C, GADOT N, SCOAZEC JY, ZEISEL MB, BAUMERT TF, LAVILLETTE D, DREUX M, & COSSET FL. Functional and biochemical characterization of hepatitis c virus (hcv) particles produced in a humanized liver mouse model. J Biol Chem 2015;290:23173-87.

LEVY C, AERTS L, HAMELIN ME, GRANIER C, SZECSI J, LAVILLETTE D, BOIVIN G, & COSSET FL. Virus-like particle vaccine induces cross-protection against human metapneumovirus infections in mice. Vaccine 2013;31:2778-85.