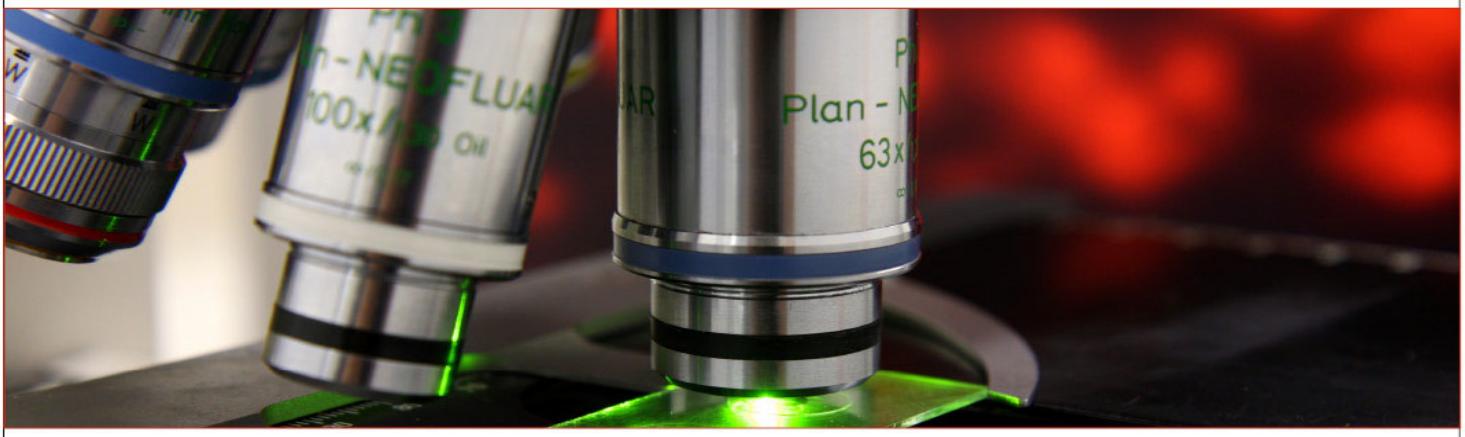
SÉMINAIRES ET CONFÉRENCES



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« Structure of the mammalian V-ATPase and its role in antiviral immunity »

The vesicular or vacuolar H+-ATPase (V-ATPase) is an ATP-dependent proton pump that acidifies endosomes, lysosomes, and the trans-Golgi network. This activity is essential for processes such as membrane trafficking, protein degradation, maturation of secreted proteins, and endosomemediated entry of viruses into cells. The V-ATPase also acidifies secretory vesicles to facilitate protoncoupled transport of small molecules such as neurotransmitters into the secretory vesicles. V-ATPase defects lead to numerous pathological conditions including cancer and neurological disorders. The VATPase is a multi-subunit complex composed of a soluble V1 region and a membrane-embedded VO region. ATP hydrolysis in the catalytic V1 region drives rotation of a central rotor subcomplex leading to proton translocation through the VO region. V-ATPase activity is regulated by reversible separation of the V1 and VO regions, with ATP hydrolysis inhibited in the isolated V1 complex and the VO complex becoming impermeable to protons. During viral infection, mammalian cells upregulate an antiviral protein called nuclear receptor coactivator 7 isoform B (NCOA7-B) that can interact with the V-ATPase and inhibit endocytosis of viruses such as Hepatitis C virus and Influenza A virus. We purified mammalian V-ATPase from rat brains using a novel purification protocol and performed structural analysis using electron cryomicroscopy (cryoEM), which allowed construction of an atomic model that for the first time revealed the composition and architecture of mammalian V-ATPase. The structure showed how two subunits within the VO region, ATP6AP1/Ac45 and ATP6AP2/PRR, enable assembly of the enzyme's catalytic and membrane regions, and also showed that RNAseK, a protein required for viral entry into cells, is an integral component of the VO region. We subsequently determined the structure of rat kidney V-ATPase with NCOA7-B. Structural and biochemical analysis suggests that NCOA7-B interferes with viral endocytosis by interacting with the V1 region and blocking V-ATPase activity. The knowledge gained from this work will improve our understanding of V-ATPase-mediated pathologies and provide a molecular blueprint for developing antivirals and other therapeutics.

Le lundi 19 avril 2021, 11h30

Invité de Pascale Legault

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