Séminaire

CONFÉRENCIER INVITÉ

Vendredi 29 juin 2018 à 11h

Salle des séminaires

Institut de biologie structurale - 71 avenue des Martyrs CS 10090 38044 Grenoble Cedex 9 - T.+33 (0)4 57 42 85 00

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Integral membrane pyrophosphatases as drug targets

Pyrophosphatases (PPases), found in all organisms, are essential enzymes, providing the thermodynamic "pull" for *eg* DNA synthesis by hydrolysing pyrophosphate. A key question in these – as in all enzymes – is their exact structural mechanism. This requires fleshing out static structures into a dynamic picture of enzyme motion. Membrane-bound pyrophosphatases (mPPases), which couple H^+/Na^+ transport to pyrophosphate synthesis/hydrolysis, are important in the infectivity of protozoan parasites. M-PPases have a unique structure with an alternate-access ion pumping mechanism.

I will describe the work that led to a thorough model for the mechansim of mPPases and how it differs from other inorganic pyrophosphatases. I will show how three new mPPase structures in different catalytic states indicate that closure of the substrate-binding pocket by helices 5-6 affects helix 13 in the dimer interface, which suggests a possible allosteric mechanism. The closure also leads to a downward motion of helix 12, which springs a "molecular mousetrap", repositioning a conserved aspartate and activating the nucleophilic water. Corkscrew motion at helices 6 and 16 rearranges the key ionic gate residues and leads to ion pumping. The structures, the implied position of the pumped ions in those structures, as well as electrometric data, allow us to propose a full catalytic "binding-change" model, where binding causes pumping, which in turn causes hydrolysis. This model has recently been validated and extended by molecular dynamics. Finally, I will discuss our efforts towards developing novel mPPase inhibitors that can kill protozoan parasites (unpubl.).

Hôte : Monika Spano (IBS/Groupe Synchrotron)

L'accès au campus EPN nécessite un avis de rendez-vous

Contactez O. Cavoret (au moins 48h à l'avance) - T. 04 57 42 87 04 - email : ibs.seminaires@ibs.fr