Séminaire

Institut de Biologie Structurale

CONFÉRENCIER INVITÉ

Vendredi 08 Novembre 2019 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

www.ibs.fr

par **Stephan Schenck**

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The TMEM175 Family of non-canonical K^+ Channels – Insights into Structure and Selectivity

The TMEM175 family constitutes recently discovered K^+ channels that are not related to classical K^+ channels. In animals they are expressed on the lysosome where they are important for autophagosome turnover and lysosomal pH regulation and are associated with the early onset of Parkinson Disease. They further appear in bacteria, archaea but are absent in plants and fungi. TMEM175 channels lack a P-loop selectivity filter, a hallmark of all known K+ channels, raising the question how selectivity is achieved. TMEM175 channels are also distinguished from canonical K^+ channels by their distinct pharmacological profile. They are not blocked by TEA or Ba^{2+} but conduct Cs^+. Like canonical K^+ channels the vertebrate TMEM175 channels are also blocked by 4-AP. We have crystallized a bacterial TMEM175 member in complex with macrobodies and solved the structure at a resolution of 2.4 Å revealing bound water and K^+ ions. Structural and electrophysiological analysis revealed that a highly conserved layer of threonine residues in the pore conveys a basal K^+ selectivity, challenging the idea that isoleucine residues (as recently proposed) form a hydrophobic selectivity filter in this protein family. Instead our findings suggest that large side chains occlude the pore, forming a physical gate, and that channel opening by iris-like motions simultaneously relocates the gate and exposes the otherwise concealed selectivity filter to the pore lumen.

In the seminar I will discuss the structure and function of TMEM175 channels. A focus will be the comparison to a previously reported X-ray structure with respect to the principle of selectivity. I will also discuss new insights into the K^+ selectivity of the human TMEM175 channel and present a model for opening and closing of these unusual ion-channels that is integrating the structural and functional analysis. In the last part of my presentation I will describe the macrobodies (nanobody-MBP fusion proteins) in more detail and show recent applications of these chaperones in cryo-EM.

Hôte : E. Pebay-Peyroula (IBS/groupe MEMBRANE)

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