MBG FOCUS TALK

hosted by MBG - Structural Biology

Tuesday 18th August 2020 from 15:00-15:45

Online Zoom Seminar (#881 133 5521)

By Postdoctoral researcher Ching-Shin Huang

Amgen Inc. - SSF, California

Occluding cholesterol delivery - Mechanism of action of the blockbuster drug Ezetimibe

The intestinal absorption of cholesterol is mediated by a multi-pass membrane protein, Neimann-Pick C1-Like 1 (NPC1L1), the molecular target of a cholesterol lowering therapy ezetimibe. While ezetimibe gained FDA approval in 2002, its mechanism of action has remained unclear. Here we present two cryo-EM structures of NPC1L1, one in its apo-form and the other complexed with ezetimibe. The apo-form represents an open state in which the N-terminal domain (NTD) packs loosely to the rest of NPC1L1, allowing the NTD central cavity accessible for cholesterol loading. The ezetimibe-bound form signifies a closed state in which the NTD rotates ~60 degrees, creating a continuous tunnel enabling cholesterol movement into the plasma membrane. Remarkably, ezetimibe blocks cholesterol transport by occluding the tunnel instead of competing with cholesterol binding. These findings provide insights into the molecular mechanisms of NPC1L1 mediated cholesterol transport and ezetimibe inhibition.

Hosted by Associate Prof. Bjørn P. Pedersen, Dept. of Molecular Biology and Genetics, AU

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