Poster Presentation

MS010.P09

Membrane proteins involved in bacterial phospholipid biosynthesis as drug targets?

Margarida Archer Frazao[1], Przemyslaw Nogly[1], Ivan Gushchin[2], Alina Remeeva[2], Ana M. Esteves[1], Pikyee Ma[1], Nuno Borges[1], Isabel Moraes[3], Helena Santos[1], Valentin Gordeliy[2]

[1]Itqb Nova, Oeiras, Portugal, [2]IBS, Grenoble, France, [3]MPL, DLS, Oxfordshire, United Kingdom

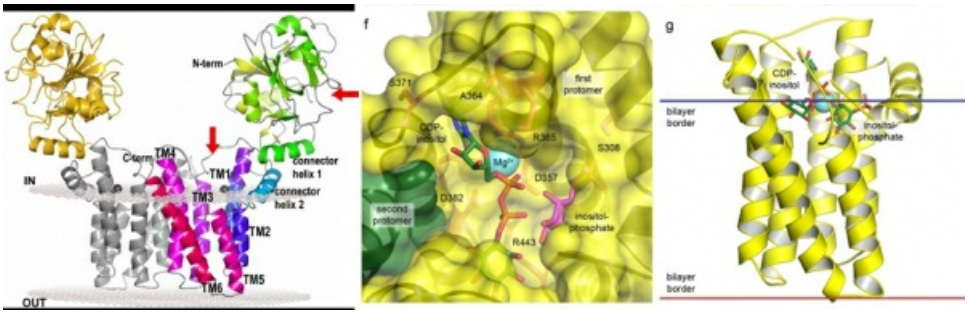
E-mail: archer@itqb.unl.pt

Phospholipids are not only major structural components of biological membranes but they also play key roles in cell physiology, regulation, and maturation of numerous cellular processes. Disruption of phospholipid homeostasis is associated with several human diseases and plays a crucial role in pathogen invasion, infectivity, and virulence [1]. A better understanding of their metabolic pathways and regulation should help development of chemotherapeutic drugs against cancer and various infectious diseases. To shed light into de novo biosynthesis of phospholipids, we have determined the first three-dimensional structure of a representative of the CDP-alcohol phosphatidyltransferase (CDP-AP) family. Members of this family are integral membrane proteins that catalyze the transfer of a substituted phosphate group from a CDP-linked donor to an alcohol-acceptor, an essential reaction for phospholipid biosynthesis across all domains of life. This novel X-ray structure of an archaeal bifunctional enzyme comprises a membrane CDP-AP domain (DIPPS) coupled with a cytoplasmic nucleotidyltransferase domain at 2.65 Å resolution [2]. It elucidated the overall fold of DIPPS, a dimeric arrangement of 12 transmembrane α-helices, the architecture of the active site comprising highly conserved amino acid residues and a divalent ion along with its location at the membrane interface. Substrates were docked into identified pockets and validated by mutagenesis studies. A structure-based catalytic mechanism is proposed [2] and a comparative analysis is performed with [3]. This structure also paves the way for homology modeling of other CDP-APs, namely those with biomedical interest.

1- Heath, R.J., White, S.W. & Rock,C.O. (2001). Prog Lipid Res 40, 467-497

2- Nogly, P., et al. (2014) Nat Commun 5, 4169. DOI: 10.1038/ncomms5169I: 10.1038/ncomms5169

3- Sciara, G., et al. (2014) Nat Commun 5, 4068. doi: 10.1038/ncomms5068.



Keywords: Membrane proteins, phospholipid biosynthesis, CDP-OH phosphotransferases