Poster Presentation

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Understanding of cholesterol binding protein structure with molecular dynamics

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NPC1L1 (Niemann-Pick type C1 like 1), a polytopic transmembrane protein of 1332 amino acids, plays important role on the dietary cholesterol absorption in intestine and it shares sequence homology with NPC1 (Niemann-Pick type C1). Like its homolog, NPC1L1 was predicted to have a typical signal peptide and 13 membrane-spanning domains, which is in consistent with recent experimental data. The X-ray crystallography structure of this domain without cholesterol (PDB id: 3QNT) shows it has a conserved N-terminal "NPC1" domain, and extensive N-linked glycosylation sites. Since its discovery, several studies demonstrated the importance of NPC1L1 as one of it the key players in both dietary cholesterol absorption and biliary cholesterol re-absorption. On the other hands, NPC1 and NPC2 are main players of cholesterol control in lysosome and it is known that mutation of one of these proteins leads to disease, called Niemann-Pick disease type C (NPC) disease. The crystal structures of N-terminal domain (NTD) of NPC1 were determined with and without cholesterol (PDB id: 3GKI and 3GKH). Also the structure of whole NPC1 (PDB id: 3JD8) was reported very recently.

The structure of NPC1L1 in complex with cholesterol can provides insights into the mechanism of the cholesterol mediation by NPC1L1 and we attempted to compare the cholesterol complex of NPC1L1 and NPC1 with molecular docking followed by molecular dynamics study. The NTD molecular dynamics simulation of NPC1 and NPC1L1 in combination with cholesterol shows noticeable difference in structural fluctuation on several loop regions, suggesting possible difference in cholesterol internalization mechanism between NPC1 and NPC1L1. For molecular dynamics simulation, we obtained the starting structure with docking study based on the X-ray crystal structure. We will propose the structure and dynamics fluctuations of NPC1L1 and NPC1 in complex with cholesterol, trying provide insights into bulk cholesterol endocytosis of enterocyte membrane. We believe the current study can contribute the development of cholesterol absorption inhibitor for hypercholesterolemic patient ultimately.

[1] Kwon, H.J. et al. Cell (2013), 137, 1213-1224

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