Poster

The effect of R518W mutation on the function of NPC1 cholesterol transport: Molecular dynamics simulation study

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One of the key players of cholesterol trafficking in mammal is Niemann-Pick type C1 (NPC1) protein. The cholesterol transport from lysosomal by NPC1 is closely coupled with another protein called NPC2 and malfunction of any of these protein leads to a disease called the Niemann-Pick type C (NPC) disease. After the full-length NPC1 structure was determined by cryo-EM experiment, much of the details on the overall cholesterol trafficking process by NPC1 has been known. Nevertheless, many aspects of the mechanistic cholesterol transport process in atomic level needs to be elucidated. Interestingly, it is known that the NPC1 could act as one of the target proteins for the control of an infectious disease by acting as the virus entry point into the cells as well as for cancer treatment due to the inhibitory effect of tumor growth.

Many point mutations on NPC1 are reported. One of the point mutation on the NPC1 is R518W (or R518Q) and patients with this mutation shows the accumulation of lipids within the lysosomal lumen. In current study, we report the effect of corresponding mutation on the cholesterol transport process by the molecular dynamics simulation. The overall cholesterol transport proceeds in several stages, including transport of cholesterol from NPC2 to N-terminal domain (NTD) of NPC1, proper alignment of cholesterol containing NTD relative to the rest of the domains, and movement of cholesterol inside the NPC1 to the sterol sensing domain (SSD) within the NPC1. The current simulations show the point mutation affects the cholesterol transport process in different steps. The affected stages are the association step of NPC2 with the NPC1 transfer of the cholesterol step from NPC2 to NPC1-NTD and the passage within the NPC1 via a channel. The detailed analysis of the resulting simulation trajectory reveals the important structural features that are essential for the proper functioning of the NPC1 for the cholesterol transport, and it shows how the overall structure, which thereby include the function, can be affected by a single mutation.

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