MS02-1-2 More than a single effect by a single point mutation: molecular dynamics simulation of NPC1 #MS02-1-2

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Abstract

The Niemann-Pick type C1 (NPC1) protein is one of the key players of cholesterol trafficking from the lysosome and its function is closely coupled with the Niemann-Pick type C2 (NPC2) protein. The dysfunction of one of these proteins can cause problems in the overall cholesterol homeostasis and leads to a disease, which is called the Niemann-Pick type C (NPC) disease. The parts of the cholesterol transport mechanism by NPC1 have begun to recently emerge, especially after the full-length NPC1 structure was determined from a cryo-EM study, so many details about the overall cholesterol trafficking process by NPC1 still remain to be elucidated. Notably, the NPC1 could act as one of the target proteins for the control of an infectious disease due to its role as the virus entry point into the cells as well as for cancer treatment due to the inhibitory effect of tumor growth. A mutation of NPC1 can leads to dysfunctions and understanding this process can provide valuable insights into the mechanisms of the corresponding protein and the therapeutic strategies against the disease that are caused by the mutation. It has been found that patients with the point mutation R518W (or R518Q) on the NPC1 shows the accumulation of lipids within the lysosomal lumen. In this paper, we report how the corresponding mutation can affect the cholesterol transport process by NPC1 in the different stages for a proper function by the molecular dynamics simulations. The simulation results show that the point mutation intervenes at least at three different steps during the cholesterol transport by NPC1 and NPC2 in combination, which includes 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.

References

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