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The NPC1L1 sterol transporter: dynamics and interaction with natural compounds with inhibitory activity

The NPC1L1 sterol transporter: dynamics and interaction with natural compounds with inhibitory activity

Niemann-Pick C1-Like 1 (NPC1L1) is a transmembrane protein (*Figure 1*) essential for cholesterol uptake in cells, which starts with the binding to the extracellular N-terminal domain (NTD). The cholesterol molecule then passes through a tunnel connecting the luminal domains to the transmembrane sterol sensing domain (SSD), from which it is finally released into the membrane. Both the NTD and the SSD domains play crucial roles. Experimental tests have shown that the NTD deletion results in a significantly reduced cholesterol uptake [1]. On the other hand, the SSD associates with flotillins, proteins located in the cytosol that have been reported to be essential for efficient cholesterol uptake [2] and are likely involved in the endocytosis. Ezetimibe [3], an inhibitor of NPC1L1 activity, is believed to act in two ways, i.e. by blocking the tunnel for cholesterol transport and by inducing long-range conformational changes in the SSD, thus influencing its binding to the flotillins. Other NPC1L1 inhibitors include natural compounds such as polyphenols and sterols, which have been shown to decrease cholesterol uptake [4]. Overall, a clear and comprehensive picture of NPC1L1 mechanisms and inhibition is still not available. In this work, we first focused on 13 sterols extracted and characterized from Sorghum bicolor by colleagues of our university. Considering the similarity of plant sterols to the cholesterol, we hypothesized that they bind the NTD in a similar way. Molecular docking followed by MM/GBSA calculations showed that several plant sterols have a greater affinity for the NTD compared to cholesterol. *In vitro* assays will be performed to confirm our findings. Moreover, we are studying the dynamics of NPC1L1 by performing molecular dynamics (MD) simulations in a membrane model [5] for the apo, cholesterol-bound, and ezetimibe-bound structures. Principal component analysis on the MD trajectories showed that the motion of the NTD is linked to the motion of residues of the SSD, thus suggesting the existence of a concerted mechanism in which the two domains work together. These preliminary results provide new insights into NPC1L1 function and its interaction with sterols, and may contribute to a better understanding of cholesterol uptake inhibition.

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