Flippase and scramblase

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Researchmap https://researchmap.jp/Nagata0306

Abstract

Phospholipids are asymmetrically distributed between the inner and outer leaflets of plasma membranes with exclusive phosphatidylserine (PtdSer) localization in the inner leaflet. This asymmetrical distribution is maintained by ATP-dependent flippases, which specifically translocate PtdSer from outer to inner leaflets. When cells undergo apoptosis, the asymmetrical distribution of phospholipids is disrupted by a scramblase, leading to PtdSer-exposure. The PtdSer, thus exposed to the cell surface, works as an "eat me" signal for apoptotic cells. The PtdSer-exposure is also observed in other processes, such as activated platelets. We found that a patient with neurological deterioration carries a point mutation in a flippase, causing the flipping of phosphatidylcholine (PtdCho). We also determined the tertiary structure of the scramblase responsible for the apoptotic PtdSer exposure.

Background & Results

Two P4-type ATPases (ATP11A and 11C) are flippases at plasma membranes. A group at Tohoku University detected a de novo point mutation of ATP11A in a patient with neurological deterioration. This mutation caused an amino acid substitution (Q84E) in the first transmembrane segment of ATP11A, and the mutant ATP11A flipped PtdSer and PtdCho. Aberrant PtdCho flipping decreased PtdCho in the outer leaflet of plasma membranes and increased sphingomyelin (SM). This change altered cell characteristics, including cholesterol homeostasis and sensitivity to sphingomyelinase.

Two families of membrane proteins (TMEM16 and XKR) support the scrambling of phospholipids at plasma membranes. XKR8 forms a complex with Basigin and is cleaved by a caspase at the C-terminus to function as a scramblase. By applying cryo-EM analysis, we found that the XKR8-Basigin complex adopts a cuboid-like structure. A PtdCho molecule was present in a hydrophobic cleft on the surface. Six charged residues inside the molecule were essential for scrambling phospholipids in inward and outward directions, providing a path for the translocation of phospholipids.

Significance of the research and Future perspective

In this study, we have elucidated the etiology of a human patient with neurological deterioration. Our results will lead to how the patient should be treated. Our result also showed that the flippase should strictly follow substrate specificity and mislocalization of phospholipids causes severe human disease. Missense and nonsense mutations have been identified in the various P4-ATPase of human patients. Our results will give a hint to determine the etiology of these diseases.

Phospholipids have amphiphilic characteristics and are not easy to move between the lipid bilayer. The structure of the Xkr8-Basigin would provide insights into the molecular mechanisms underlying phospholipid scrambling. Since PtdSer-exposure occurs in various physiological and pathological settings, the design of the scramblase will help develop drugs that modulate this process.

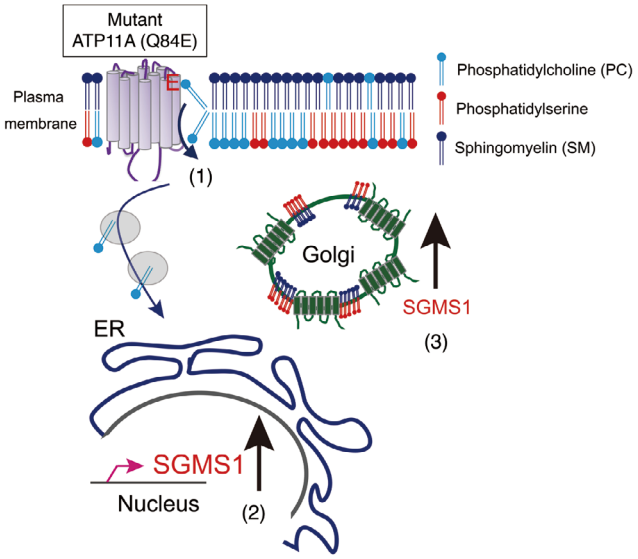

Figure 1. A point mutation (Q84E) in human ATP11A flippase that causes the intracellular transport of PtdCho(PC) (1), up-regulation of sphingomyelin synthase (SGMS1)(2), and the synthesis of SM (3).

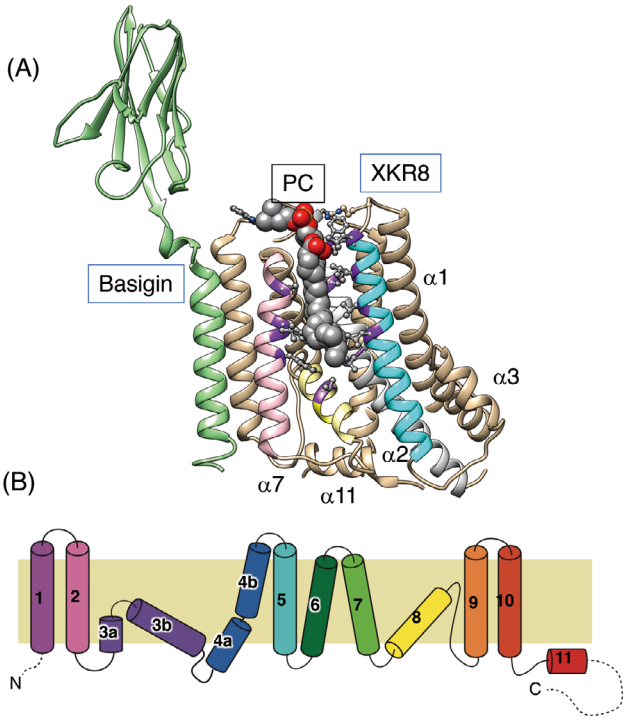

Figure 2. The tertiary structure of human XKR8-Basigin scramblase complex (A), and the transmembrane regions of XKR8 (B). The XKR8 on the upper periphery carries a hydrophobic cleft with a PtdCho(PC) molecule.

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Treatise Segawa, Katsumori; Kikuchi, Atsuo; Noji,Tomoyasu et al. A sublethal ATP11A mutation associated with neurological deterioration causes aberrant phosphatidylcholine flipping in plasma membranes. J. Clin. Invest. 2021, 131, e148005, doi: 10.1172/jci148005
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Keyword flippase, scramblase, phospholipid, phosphatidylserine