The tertiary structure of the human Xkr8–Basigin complex that scrambles phospholipids at plasma membranes

Xkr8–Basigin is a plasma membrane phospholipid scramblase activated by kinases or caspases. The research group of Takaharu Sakuragi and Shigekazu Nagata (Biochemistry & Immunology, IFReC) combined cryo-EM and X-ray crystallography to investigate its structure at an overall resolution of 3.8 Å. Its membrane-spanning region carrying 22 charged amino acids adopts a cuboid-like structure stabilized by salt bridges between hydrophilic residues in transmembrane helices. Phosphatidylcholine binding was observed in a hydrophobic cleft on the surface exposed to the outer leaflet of the plasma membrane. Six charged residues placed from top to bottom inside the molecule were essential for scrambling phospholipids in inward and outward directions, apparently providing a pathway for their translocation. A tryptophan residue was present between the head group of phosphatidylcholine and the extracellular end of the path. Its mutation to alanine made the Xkr8–Basigin complex constitutively active, indicating that it plays a vital role in regulating its scramblase activity. The structure of Xkr8–Basigin provides insights into the molecular mechanisms underlying phospholipid scrambling.

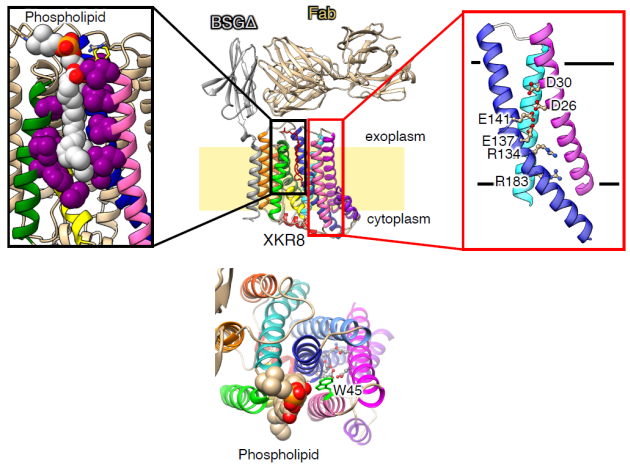

Figure: (L) Front view of the hXkr8–hBSGΔ complex. Hydrophobic residues surrounding PtdCho are in magenta spheres. PtdCho is in the silver sphere with the colored element. (R)Close-up side and top views of charged amino acids (Glu, Asp and Arg) in the α1, α4 and α5 helices. (Bottom) Extracellular view of the Xkr8 molecule. The Trp residues (green), which act as gatekeepers, are located at the boundary between phospholipids and the phospholipid transit region (pore).

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