High-resolution X-ray Crystallography of Membrane Proteins and Molecular Mechanisms of Membrane Transporters

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Cells are surrounded by lipid bilayer, which cannot easily permeate even a water molecule. Membrane channels and transporters embedded in the membrane mediate transport of the target solutes (ions, sugars, metabolites and xenobiotics) across the membrane, which is driven by chemical potential energy of the solutes themselves or partner ions, to maintain the intracellular circumstances. More than 30% of human genes encode membrane proteins, while more than 50% of drug targets are membrane proteins, which suggests membrane proteins are essential not only scientifically but also for medical application. Recently, high-resolution structures of membrane proteins have been getting more and more available, due to the advancement of cutting-edge technologies to improve crystallization of membrane proteins by lipidic cubic phase crystallization method, and to collect X-ray diffraction data from micro crystals using micro-focus beam in the synchrotron (BL32XU in Spring-8). These advancements allow us to fully understand the molecular mechanisms of membrane channels and transporters at an atomic resolution; how the transport is driven, how the channel or transporter exclusively selects its target solute and how the transport is regulated. Our recent structural and functional analyses of transporters indicate that bending of transmembrane helices at Pro or Gly residues facilitates the transition between outward-open, occluded and inward-open conformations in the transport cycle, which is triggered by binding of substrates or counter ions.