Breaking down the barriers in cryo-EM analysis of membrane proteins

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Membrane proteins (MPs) used to be the most difficult targets for X-ray crystallography. With the revolution of single-particle cryo-EM, rapid progress has been made for structural elucidation of isolated MPs. However, various barriers, including the size of target, lack of electrochemical gradients and membrane curvature, are still limiting a broader investigation of MPs in near-physiological condition. For a comprehensive structural elucidation of MPs that rely on these chemical and physical properties for their biological functions, we developed a series of approaches in sample optimization, cryo-sample preparation and image processing to represent the near-atomic structure for small MPs and MPs in liposomes. Our approach, which can be widely applied to cryo-EM analysis of MPs with distinctive soluble domains, lays out the foundation for structural analysis of integral or peripheral MPs whose functions are affected by transmembrane electrochemical gradients or/and membrane curvatures.