Structure of an ATP-sensitive potassium channel (K_{ATP})

Subject Code: C05

With the support by the National Natural Science Foundation of China, the collaborative research team led by Prof. Chen Lei (**陈雷**) at the State Key Laboratory of Membrane Biology, Institute of Molecular Medicine, Peking-Tsinghua Center for Life Sciences, Beijing Key Laboratory of Cardiometabolic Molecular Medicine, Peking University, Beijing, and Prof. Gao Ning (**高宁**) at the Ministry of Education Key Laboratory of Protein Sciences, Beijing Advanced Innovation Center for Structural Biology, School of Life Sciences, Tsinghua University, Beijing, recently reported the structure of an ATP-sensitive potassium channel (K_{ATP}) in *Cell* (2017, 168: 101—110).

K_{ATP} channels are fundamental to the energy homeostasis, and participate in a great many vital processes. The malfunction of K_{ATP} channels leads to various diseases such as as neonatal diabetes, hyperinsulinism, DEND syndrome and Cantú syndrome. K_{ATP} channels are important drug targets. K_{ATP} channel inhibitors such as sulfonylureas are widely used for treating type II diabetes, while K_{ATP} channel activators such as potassium channel openers are used for treatment of hyperinsulinism and have shown great promise for myoprotection. However, very limited information is known for the mechanism of K_{ATP} channels at atomic details, as well as for their regulation by inhibitors and activators. In fact, the only available structural data for the K_{ATP} channel complex is an 18 Å resolution structure published in 2005. For a variety of reasons, structural determination of K_{ATP} channels (a gigantic 880 kDa octameric membrane protein complexes) has been proven to be very challenging. The current work by the team shows how octameric K_{ATP} channel is assembled from Kir6 and SUR subunits in unprecedented details and reveals the structure and mechanism of TMD0-L0 fragment which is a key component in SUR that regulates Kir6. In addition, they have structurally located the putative binding site for sulfonylurea drugs and uncovered the mechanism of PIP_2 activation of Kir6 subunits. Taken together, their work provides the first major advance in studying the structure of K_{ATP} channels in the past decade and, more generally, provides a solid context in which to understand decades of research of K_{ATP} gating mechanism based on electrophysiology and other functional studies.

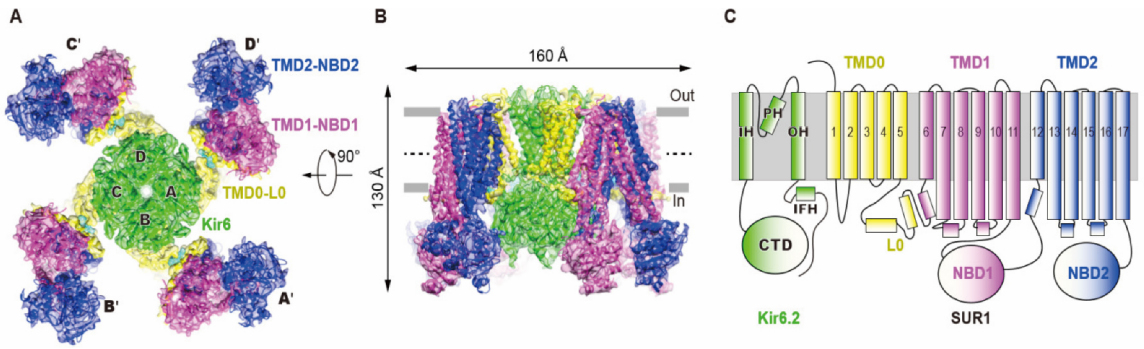

Figure Architecture of the K_{ATP} channel. Kir6.2, SUR1 TMD0-L0 (transmembrane domain 0-loop 0) fragment, TMD1-NBD1, TMD2-NBD2 and the putative glibenclamide (GBM) are shown in green, yellow, magenta, blue and cyan, respectively.