Cryo-EM Illuminates the Mechanism of SGLT Inhibitors

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Sodium-glucose co-transporters (SGLT) harness the electrochemical gradient of sodium to transport glucose against their chemical gradients. In humans, SGLT1 and SGLT2 are crucial for glucose uptake and homeostasis and are important for human health. Their loss-of-function mutations lead to genetic disease in humans. These proteins are important drug targets. SGLT inhibitors are used for the treatment of diabetes and cardiovascular diseases. SGLTs are challenging targets for cryo-EM due to their small sizes (60-70kDa). We developed a "three-joint-tethering strategy" to increase the molecular weight of SGLTs and create a fiducial marker for image alignment [1]. Using this strategy, we determined the structures of human SGLT1 and SGLT2 with inhibitors bound [2, 3]. We found that SGLT inhibitors lock the transporter in the outward-open conformation to inhibit sugar transport.

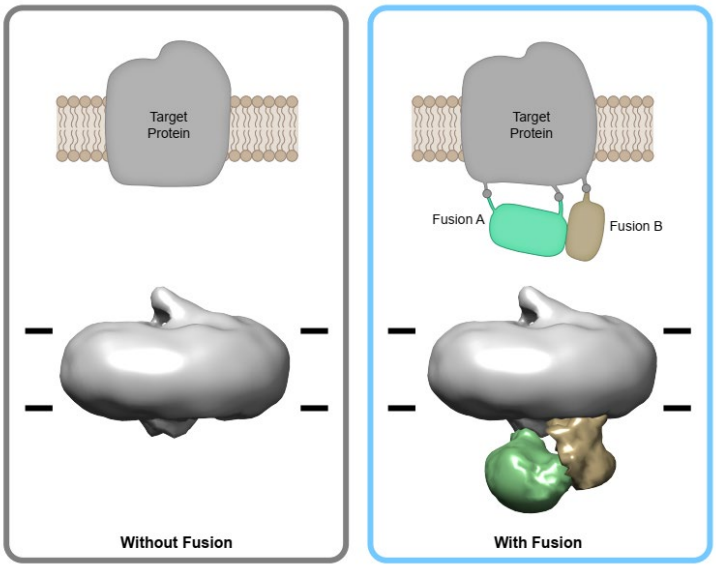

Figure 1. Three-joint-tethering strategy facilitates structure determination of SGLTs

References:

[1] Cui W, Niu Y, Chen L. The Protein Fusion Strategy Facilitates the Structure Determination of Small Membrane Proteins by Cryo-EM. Biochemistry (Mosc), 2022,

[2] Niu Y, Liu R, Guan C, Zhang Y, Chen Z, Hoerer S, Nar H, Chen L. Structural basis of inhibition of the human SGLT2-MAP17 glucose transporter. Nature, 2021, 601(280-284.

[3] Niu Y, Cui W, Liu R, Wang S, Ke H, Lei X, Chen L. Structural mechanism of SGLT1 inhibitors. Nat Commun, 2022, 13(1): 6440.