MOLECUALR BASIS OF HUMAN AQUAPORINS INHIBITION

Aquaporins (AQPs) are a family of integral membrane proteins that function as selective channels for transport of water and small solutes across the membrane of cells[1]. This family includes thirteen isoforms (AQP0–AQP12), which differ in substrate selectivity, tissue distribution and physiological roles.

Our research mostly focuses on the aquaglyceroporins subfamily (AQP3, AQP7, AQP9), that also facilitates transport of glycerol, urea, and reactive oxygen species such as hydrogen peroxide (H_2O_2)[2,3]. Among the diverse physiological processes in which AQPs are implicated, roles in redox homeostasis, cellular metabolism, and signaling have emerged alongside their classical function in osmoregulation.

AQP3 is implicated in several pathological conditions, including T-cell acute lymphoblastic leukemia (T-ALL). Among its cellular functions, AQP3 facilitates the membrane transport of H_2O_2, thereby modulating intracellular redox homeostasis[3]. In the context of T-ALL, we hypothesize that selective inhibition of AQP3 activity disrupts this balance, leading to intracellular H_2O_2 accumulation and induction of cell death. Given its role in cancer cell survival, AQP3 represents a promising therapeutic target.

Here, we present the structural characterization of AQP3 in complex with small-molecule inhibitors using single-particle cryo-electron microscopy. These structures provide molecular-level insight into the inhibitor binding modes and the structural basis of pore occlusion upon AQP3 blockade. The activity of these molecules has been tested in cell-based assays using T-ALL cell line and resulted in the arrest of cellular proliferation. Based on these studies, structure-based drug design has been performed to develop a series of novel inhibitors. Together, these findings advance our understanding of AQP3 inhibition and support the development of AQP3-targeted therapies for T-ALL and other malignancies.

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