Research Week 2022

Molecular Pharmacology of $P2X_7$ Receptor Ligands Visualized by Cryo-EM

Adam Oken, Ipsita Krishnamurthy, Nic Lisi, Michael H. Godsey, and Steven E. Mansoor
Okena@ohsu.edu
Department of Chemical Physiology and Biochemistry, OHSU

Keywords

Structural Biology, Cryo-EM, Purinergic Receptors, P2XRs, P2X7, Ion Channels

Abstract

Extracellular ATP is a critical signaling molecule that is found in a wide range of concentrations across cellular environments. The family of nonselective cation channels that recognize extracellular ATP, termed P2X receptors (P2XRs), is composed of seven sub-types ($P2X_1$-$P2X_7$) that assemble as functional homo-trimeric and hetero-trimeric ion channels. Each P2XR is activated at distinct concentrations of extracellular ATP, spanning from low nanomolar to millimolar, and expressed in an array of cell types. Sensing concentrations of ATP that diverge from homeostasis, P2XRs are implicated in a variety of pathophysiological diseases corresponding to where they are expressed and activated in the body. The therapeutic potential of P2XRs is an emerging area of research, as overactive P2XRs have been shown to play pathophysiological roles in neuro-inflammation, vascular inflammation, and cell division. Although there are currently no FDA-approved drugs targeting P2XRs, structure-based drug design can provide unique and insightful details into the intricacies of each receptor to facilitate sub-type selective ligands. Here, we highlight potential therapeutically targetable sites in the P2XR family and how single-particle cryogenic electron microscopy (cryo-EM) can be used to advance drug discovery, focusing on two cryo-EM structures; the endogenous agonist ATP bound to $P2X_7$ and the noncompetitive antagonist JNJ-47965567 bound to $P2X_7$.