SCIENCE FOR THE BENEFIT OF HUMANITY

Nidhi Sabharwal, Ph.D.
Assistant Director
Office of Technology Transfer
(212) 327-7092
nsabharwal@rockefeller.edu

A Novel Target for Modulating the Kir Potassium Ion Channel: The Turret Domain

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Technology Summary

Many cells produce electrical impulses across their surface membrane to initiate physiological processes involved in human health, such as contraction of heart muscles or the firing of neurons in the brain. Ion channels are transmembrane protein molecules that allow ions to cross the membrane in a selective fashion, thus mediating the transmission of electrical impulses. This electrical signaling is how living cells transfer information over large distances rapidly. When this electrical activity is compromised, the body can suffer various conditions, such as heart arrhythmias, epilepsy, hypertension, etc. There is a need for methods to rapidly screen and identify chemical compounds that bind to and thus modulate the activity of ion channels.

The inward rectifier potassium (K+) channels, termed Kir channels, are involved in a number of essential physiological processes. Kir channels conduct potassium ions most efficiently in one direction, which is into the cell. Among their many functions Kir channel proteins control the pace of the heart, regulate secretion of hormones into the bloodstream, generate electrical impulses underlying information transfer in the nervous system and control airway and vascular smooth muscle tone. It is believed that various disease states are directly related to the function of Kir channel proteins. Hypertension, atrial fibrillation, and type 2 diabetes are related to Kir channel protein function and are serious conditions for which new therapies are needed. However, the Kir channel family of proteins are very similar to each other in both sequence and by inference, structure; thus, it has been very difficult to identify compounds that can specifically modulate one kind of Kir channel protein without cross-reacting with other types of Kir channel proteins.

Our researchers have solved the crystal structure of eukaryotic Kir channels at high resolution. Their work shows that the only site on the channel that could be targeted by inhibitor molecules with specificity from the outside is the extracellular turret domain. The turrent domain is a highly ordered structure with an amino acid sequence that is unique to each different Kir channel. It is therefore possible to use the turret domain as a target to identify therapeutic compounds that can selectively bind to different members of the Kir channel family of proteins.

Area of Application

- Identification of compounds for the treatment of pathologies associated with Kir channel dysfunction, such as hypertension, paralysis, atrial fibrillation and Type 2 diabetes.

Stage of Development

- Preclinical in vitro structure-function studies.

Lead Inventor

- Dr. Roderick MacKinnon

Patent Information

- U.S. patent application US 2013/0035475 is pending.

References

- Tao, et al. 2009. Crystal structure of the eukaryotic strong inward-rectifier K+ channel Kir2.2 at 3.1 A resolution. Science, 326:1668-74.