Study finds new pathway critical to heart arrhythmia

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University of Maryland School of Medicine researchers have uncovered a previously unknown molecular pathway that is critical to understanding cardiac arrhythmia and other heart muscle problems. Understanding the basic science of heart and muscle function could open the door to new treatments. The study, published recently in the journal *Cell*, examined the electrical impulses that coordinate contraction in heart and skeletal muscles, controlling heart rate, for example. Unraveling how the body regulates these impulses is key to understanding serious health conditions such as paralysis, muscle relaxation and heart arrhythmia.

Researchers in the *Cell* study examined ion channels — membrane proteins that allow the electrical charges to flow into and out of the cell. The number and location of channels on the cell's surface are critical to the heart's rhythm. The University of Maryland School of Medicine scientists found a new, previously unknown intracellular trafficking pathway that controls the number and location of the ion channels on the cell surface, affecting the passage of electrical charges and controlling the beat of the heart and other muscle activity.

Ion channels are proteins that form pores at the cell's surface. The pores open with careful regulation, allowing the passage of ions like potassium, sodium or chloride. These ions carry distinct electrical charges, and their regulated passage into and out of the cell stimulate and coordinate contractions such as the heart's rhythm.

"This study illuminates a new pathway for therapeutic intervention," says

Paul Welling, M.D., professor of physiology at the University of Maryland School of Medicine. "Drugs that interfere with or augment this signal may be used to control the number and location of ion channels in such a way to fight arrhythmia and other muscle disorders, potentially saving lives."

"Dr. Welling's research is an example of the world class basic science discoveries taking place at the School of Medicine, discoveries that we hope one day will lead to relief and new treatments for patients and their families," says E. Albert Reece, M.D., Ph.D., M.B.A. vice president for medical affairs for the University of Maryland, and John Z. and Akiko K. Bowers Distinguished Professor and dean of the University of Maryland School of Medicine.

Until recently, scientists have focused on the regulatory mechanisms that control the way that these ion channels open and close and how that action affects muscle contraction and heart rate. Years of research have shown that it is not simply the action of these ion channels that affects heart arrhythmia Scientists have found that the location and number of channels on the cell's surface are just as important to the heart's rhythm. The study in Cell describes a new intracellular trafficking pathway that controls the number and location of these ion channels on the cell surface.

"Previously, we were unsure how the ion channels get out to the surface of the cell," says Dr. Welling. "We found a new mechanism that operates like a molecular zip code, ensuring that the appropriate numbers of ion channels are sent to the correct cellular location, the cell surface. It also functions as a type of proofreading mechanism, making sure that only correctly made ion channels make it to the cell surface."

Dr. Welling and his colleagues examined the molecular pathology of the genetic condition Andersen-Tawil Syndrome, characterized by

uncoordinated muscle contractions, paralysis and disruptions in the normal heart rhythm. The syndrome is caused by mutations in the gene known as KCNJ2, which encodes a potassium channel in the heart and skeletal muscle known as Kir2.1.

The scientists examined how mutations in the potassium channel affects its passage through a key intracellular sorting station called the Golgi apparatus. The Golgi apparatus modifies, sorts and packages molecules for the cell's use. Dr. Welling's lab found that the Golgi apparatus selects the Kir2.1 channel to travel to the surface of the cell in an unusual, signal-dependent manner. The signal determines where the Golgi apparatus sends the potassium channel and how many it sends and verifies that the channels are of quality. In patients with Andersen-Tawil Syndrome, the signal is faulty and fails to properly regulate the ion channels and their path to the cell surface.

"Elucidating the mechanisms behind this rare disease provides insight into more prevalent forms of arrhythmia such as heart failure," says Dr. Welling. "There is great interest in understanding the mechanisms by which cardiac ion channels are regulated. This new pathway may be an excellent target for therapeutic intervention for both Andersen-Tawil syndrome and the far more common condition, like arrhythmias associated with heart failure."

The study has implications beyond the science of the heart, he added. The class of ion channels the researchers examined includes about 12 other ion channels that control various body processes from cognition to the salt balance in the kidneys. The next step for his lab, Dr. Welling says, is to study this pathway in relation to the kidneys. It is possible the same pathway affects the entire class of channels and helps regulate all the body processes associated with them.