UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Press Release

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How Junctophilins organize electrically excitable cells

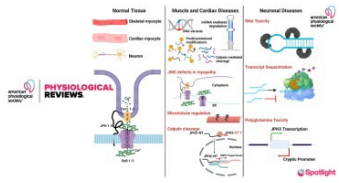
Experts from the University Medical Center Göttingen and the Baylor College of Medicine in Houston, Texas, summarize 20 years of Junctophilin research, new molecular analyses, and the role of Junctophilins in the development of human diseases in a comprehensive in-depth review article. Published with Spotlight Cover in the renowned journal Physiological Reviews.

(umg/mbexc) Junctophilins are a family of proteins found in presumably all electrically excitable cells of the brain and the nervous system and muscles. They play a central role in various important cellular functions in excitable cells of the striated skeletal and cardiac muscles, vascular smooth muscle and the nervous system. Junctophilins connect the plasma membrane of these cells with the membranes of the sarcoendoplasmic reticulum (SER), which, as an intracellular calcium store, plays a key role in activating muscle contraction. This shortens the information path between the cell surface and the SER organelle to approximately 15 nanometers. Voltage-dependent calcium channels in the cell membrane can thus be functionally coupled with intracellular SER calcium release channels (ryanodine receptors), thereby translating action potentials into a fast intracellular potassium signal chain.

Author Prof. Dr. Stephan E. Lehnart. RG Cellular Biophysics and Translational Cardiology. Photo: Colin Derks

The highlights from 20 years Junctophilin research, with a focus on the latest findings and models, have now been recently compiled by Prof. Dr. Stephan E. Lehnart from the Heart Research Center of the University Medical Center Göttingen, member of the Cluster of Excellence Multiscale Bioimaging: From Molecular Machines to Networks of Excitable Cells (MBExC), the Collaborative Research Center SFB 1190, and the German Center for Cardiovascular Research (DZHK) and Prof. Dr. Xander H.T. Wehrens from the American Baylor College of Medicine in Houston, Texas, USA. Their review article provides a comprehensive overview about the Junctophilin protein family and its evolutionary development, biogenesis, molecular binding partners and different functional roles in various electrically excitable cells. Moreover, the authors compile new insights into the molecular structure and pathogenetic role of human gene variants. They also consider research findings on the contribution of genetically defective or disease-related reduced JPH proteins in the development of a broad spectrum of human organ pathologies. The review was recently published in the renowned American journal Physiological Reviews and highlighted with a spotlight cover.

Author Prof. Dr. Xander H.T. Wehrens, Baylor College of Medicine, Houston, Texas, USA. Photo: XHT Wehrens.



Graphical illustration of the roles of junctophilin in normal tissues and molecular alterations in junctophilins associated with muscle, cardiac and neuronal diseases. Spotlight Cover, Physiol Rev.

Original publication: *The role of Junctophilin proteins in cellular function. Stephan E. Lehnart & Xander H.T. Wehrens, 2022, Physiol Rev 102: 1211 – 1261. https://doi.org/10.1152/physrev.00024.2021.*

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Junctophilins and their molecular function

Since their discovery in 2000, research on the junctophilin protein family revealed vastly different cellular roles in healthy and diseased tissues. Four variants of the JPH-protein (JPH1-4) are localized in the SER membrane of various muscle and neuronal cells. According to current publications, JPH1-3 in particular are crucial for the formation and molecular composition of cell-specific junctional membrane complexes. They thus contribute decisively to the local or-ganization of functional subunits, so-called calcium signaling nanodomains, of the cell interior. Their unique and evolutionary highly conserved protein structure is essential for their cell membrane-binding ability to spatially and temporally precisely control the activity of electrically excitable cells. Altered junctophilin expression or function affects intracellular calcium signaling and thus cellular excitability, which is essential for survival, and response to external influences, such as in the case of increased stress in the heart.

The role of Junctophilin variants in skeletal muscle, heart and neurological diseases

Dysfunction of incorrectly formed junctophilin proteins is associated with various heritable and acquired muscular, cardiac and neurological diseases. A heritable variant of the *JPH1* gene plays a role in a rare form of Charcot-Marie-Tooth disease in skeletal muscle. Here, nerve impulses from the brain no longer excite the affected muscles efficiently, causing muscle atrophy in the long term. Inherited mutations in the *JPH2* gene can cause various forms of cardiomyopathies, genetic disorders that are characterized by pathological enlargement of the left ventricle and an increased risk of cardiac arrhythmias. This is often associated with a disturbance of the intracellular calcium signaling causing an increased susceptibility for cardiac arrhythmias and contributing to a pathologic enlargement and other problems in cardiomyocytes. Variants of the JPH3 protein cause Huntington's disease-like 2 (HDL-2), a severe neurodegenerative disease characterized by movement, psychiatric and cognitive abnormalities.

On the other hand, patients with non-genetic, acquired forms of heart failure and cardiomyopathy frequently show significantly reduced JPH2 protein levels. Loss of JPH2 in humans and knockout mice results in a decrease in size, number, and function of junctional membrane complexes. This in turn impairs the excitation-contraction-coupling and leads to contractile dysfunction and arrhythmia susceptibility of the heart.

Further intensive research required

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“In view of the important roles of specific JPH isoforms in various electrically excitable cell types and the direct association of JPH dysfunction and human diseases, correcting JPH protein levels (e.g. in heart failure) or functionally defined defects have emerged as promising therapeutic targets for various skeletal muscle, cardiac muscle, and neuronal diseases”, says Prof. Lehnart. Research groups worldwide, including the MBExC and the SFB 1190, are intensively committed to study the role of Junctophilins in healthy and diseased muscle and neuronal cells and tissues. The review article provides a very comprehensive and in-depth overview of the current state of research including new data and JPH models. “Now, further investigations are required to determine whether two decades of basic and clinical research can be harnessed to translate these insights into new therapeutic options for patients.”, adds Lehnart.

*The **Göttingen Cluster of Excellence Multiscale Bioimaging: From Molecular Machines to Networks of Excitable Cells (MBExC)** is funded since January 2019 in the framework of the Excellence Strategy of the German Federal and State Governments. Applying a unique and multiscale approach, MBExC investigates the disease-relevant functional units of electrically active cells of heart and brain, from the molecular to the organ level. The MBExC unites numerous partners from the university and extra-university institutions in Göttingen. The overall goal: to understand the relationship between heart and brain diseases, to link basic and clinical research, and thus to develop new therapeutic and diagnostic approaches with social implications.*

*The **SFB 1190 Compartmental Gates and Contact Sites in Cells** is committed to addressing the role of compartmental gates and contact sites in cellular organization and physiology. We aim to understand how they achieve a selective distribution of molecules and thus functionally define and diversify cellular compartments.*

further information:
about MBExC: https://mbexc.de/
about the CRC 1190: https://www.sfb1190.de/index.php?id=833.
about the Lehnart Lab:
https://herzzentrum.umg.eu/forschung/arbeitsgruppen/zellulaere-biophysik-und-translationale-kardiologie/

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