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Journal of Cell Signaling

Perspective

Mechanosensitive Ion Channels and Their Role in Cardiomyocyte Signaling Under Stress: A New Dimension in Cardiac Physiology

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DESCRIPTION

The heart, a continuously active mechanical pump, operates under varying physiological and pathological forces. Cardiomyocytes, the contractile cells of the heart, must constantly sense and adapt to mechanical stimuli such as pressure, stretch and shear stress. In recent years, MechanoSensitive Ion Channels (MSCs) have emerged as critical mediators of this mechanoelectrical feedback system. These channels, which respond to mechanical deformation of the cell membrane, play essential roles in transducing mechanical cues into biochemical signals, ultimately affecting cardiac electrophysiology, contractility, gene expression and remodeling under stress. Among the most studied mechanosensitive channels in cardiomyocytes are Piezo1, Piezo2, TRPV4 (transient receptor potential vanilloid 4), TREK-1 and KATP channels. These channels are activated by membrane tension or stretch and regulate the flow of ions such as calcium (Ca^{2+}), sodium (Na^{+}) and potassium (K^{+}). The influx or efflux of these ions alters intracellular signaling cascades, initiating both adaptive and maladaptive responses to mechanical stress.

Under normal physiological conditions, MSCs help maintain homeostasis. They regulate heart rate, ventricular filling and contractile force in response to changes in blood volume or pressure. However, in the setting of cardiac stress, such as hypertension, ischemia, or volume overload, the role of MSCs becomes more complex and consequential. Persistent activation of these channels can contribute to pathological remodeling, hypertrophy and even arrhythmogenesis. One of the most compelling discoveries in recent years has been the identification of Piezo1 as a primary mechanosensor in the heart. Expressed in both cardiomyocytes and endothelial cells, Piezo1 is activated by increased pressure and stretch. Upon activation, it allows Ca^{2+} influx, which can activate downstream pathways such as CaMKII (calcium/calmodulin-dependent protein kinase II) and MAPK/ERK signaling, both known to drive hypertrophic and fibrotic responses. In models of pressure overload, Piezo1 activation has been linked to increased expression of pro-hypertrophic genes and oxidative stress. Thus, Piezo1 is not just a passive responder but an active participant in the progression of heart failure.

In parallel, TRPV4 has also been shown to play a critical role in cardiomyocyte mechanotransduction. It responds to osmotic swelling and mechanical stretch, facilitating Ca^{2+} entry and activation of pro-inflammatory pathways. TRPV4 expression is upregulated in failing hearts and its inhibition in experimental models reduces cardiac fibrosis and preserves function. This makes TRPV4 a potential therapeutic target for conditions characterized by chronic mechanical stress. Another important class of mechanosensitive ion channels are the two-pore domain potassium (K2P) channels, such as TREK-1 and TASK-2, which are activated by stretch and modulate action potential duration and excitability. Their dysfunction has been implicated in atrial fibrillation and ventricular arrhythmias, particularly under conditions of acute mechanical overload or ischemia-reperfusion injury. These channels provide a direct mechanistic link between mechanical forces and electrophysiological instability, a hallmark of sudden cardiac death. Mechanosensitive channels also interact closely with cytoskeletal proteins and extracellular matrix components, forming a mechanotransduction complex that allows cardiomyocytes to integrate mechanical information with biochemical signals. Disruption of this complex-hrough genetic mutations or structural remodeling-can lead to altered mechanosensing, contributing to diseases such as dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.

From a therapeutic perspective, targeting MSCs represents a novel and underexplored approach in cardiology. While drugs that modulate these channels are not yet widely used clinically, preclinical studies have shown promising results. For example, Piezo1 inhibitors have been found to reduce hypertrophic responses in animal models and TRPV4 antagonists are being investigated for their anti-fibrotic effects. The challenge lies in achieving specificity, as many MSCs are expressed in multiple tissues and systemic inhibition could produce unintended side effects. Emerging technologies such as mechanogenetics and targeted nanoparticle delivery offer exciting opportunities to modulate MSCs with high spatial and temporal precision.

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Received: 02-Feb-2025, Manuscript No. JCS-25-38270; **Editor assigned:** 05-Feb-2025, PreQC No. JCS-25-38270 (PQ); **Reviewed:** 19-Feb-2025, QC No. JCS-25-38270; **Revised:** 26-Feb-2025, Manuscript No. JCS-25-38270 (R); **Published:** 03-Mar-2025, DOI: 10.35248/2576-1471.25.10.389.

Citation: Grant JM (2025). Mechanosensitive Ion Channels and Their Role in Cardiomyocyte Signaling Under Stress: A New Dimension in Cardiac Physiology. J Cell Signal.10:389.

Moreover, integrating single-cell transcriptomics and proteomics may help identify patient-specific mechanosensitive signaling profiles, paving the way for personalized mechanotherapy in heart disease.

CONCLUSION

Mechanosensitive ion channels represent a crucial but underappreciated aspect of cardiomyocyte biology, particularly in the context of mechanical stress. As sensors of stretch and pressure, they orchestrate a complex network of signals that govern cardiac adaptation and maladaptation. Their roles extend beyond simple ion conductance to influence gene expression, inflammation, remodeling and arrhythmogenesis. Given the central role of mechanical forces in virtually all forms of heart disease, understanding and targeting these channels offers a promising new direction in cardiovascular therapy. Future research must aim to decipher the specific contributions of individual MSCs under varying stress conditions and develop tools for precise modulation. As our insights deepen, mechanosensitive ion channels may become key therapeutic gateways in preventing and treating heart failure, hypertrophy and life-threatening arrhythmias.