Recent Advances in Cardiac Myocyte Biology and Function

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Cardiac myocyte dysfunction is the underlying cause of changes in cardiac contractility associated with several pathological conditions. Hence, the physiology of cardiac myocytes has been the subject of intense investigation and much attention has been paid to important questions such as the following: what maintains and regulates the structural and functional integrity of cardiac myocytes?; how do myocytes respond to stress?; what are the molecular changes that contribute to myocytes dysfunction in cardiac disease?; how can pathological changes in myocytes be prevented or attenuated?; what determines myocyte life and death?; and can adult myocytes be renewed or replenished? Recent advancements in the field continue to address these important issues.1–18

Cardiac myocyte hypertrophy has been an area of intense interest for a long time,19 because it is well-known that maladaptive cardiac myocyte hypertrophy and accompanying cardiac remodeling often lead to heart failure.20–21 Recent studies have uncovered new mechanisms of myocyte hypertrophy. For instance, Matsushima et al22 showed that increased nuclear oxidative stress caused by nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4) leads to oxidation and nuclear export of histone deacetylase 4 (a class II histone deacetylase), which is a repressor of transcription factors involved in hypertrophic response (eg, nuclear factor of activated T-cells); this suggest that inhibition of Nox4 can be another avenue for dampening maladaptive cardiac hypertrophy. G-protein–coupled receptor kinase-5 (GRK5) is another important regulator/kinase of a class II histone deacetylase, which is an important modulator of 2 major hypertrophic signaling pathways (ie, Ak strain thymoma/protein kinase B and extracellular signal-regulated kinase) and demonstrated that alteration of Pin1 activity in mouse hearts blunts myocyte and cardiac hypertrophy in response to pressure overload.26

Interrogation of the effects of genetic components or gene mutations on cardiac myocyte function and contractility is often challenging. A recent study reported on a successful generation of a new model system, neonatal mouse–derived engineered cardiac tissue with spontaneous contraction.27 The authors generated engineered cardiac tissues from both wild-type and myosin-binding protein C (Mybpc3)-null mouse hearts and demonstrated that adenovirus-mediated expression of human MYBPC3 in murine Mybpc3-null tissue rescued its contractile defect.27 Unlike rat-derived or chicken-derived counterparts, this murine system would allow access to many existing mouse models of cardiac disease and also permits direct in vitro genetic manipulation in cardiac myocytes in culture. Such in vitro approaches would aid in the dissection of molecular components governing myocyte biology and contractility. Also, advances in the induced pluripotent stem cell technology have clearly impacted on how we model genetic arrhythmia disorders (eg, long-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia). It is now possible to generate patient-derived cardiomyocytes that carry disease-causing gene mutations and, importantly, exhibit pathophysiological features in vitro.28–31 This can be accomplished by reprogramming easily accessible patient cells (eg, skin fibroblasts) to pluripotent embryonic stem cell–like cells (ie, induced pluripotent stem cells) and differentiating them into cardiomyocytes in vitro.39

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Undoubtedly, generation of genetically altered disease-specific cardiomyocytes will serve as a valuable tool not only in understanding the underlying molecular defects caused by disease-associated gene mutations but also in developing in vitro drug-screening systems. To generate new model systems, other investigators have used zebrafish to develop a novel system to address the need for a reliable, preclinical model for predicting cardiotoxicity of cancer therapeutics. The zebrafish model allows morphometric, cellular, and functional analyses of the heart after drug treatments with relative ease.

Myocardial infarction is characterized by rapid and massive loss of ventricular myocytes, and persistent myocyte deficiency and dysfunction underlie one of the leading causes of heart failure. Hence, myocardial regeneration has been a topic of heightened interest in recent years. Recent approaches involving directed differentiation or reprogramming of cells have provided a radically new alternative to replenish cardiomyocytes lost because of cardiac injury. Several studies have shown that nonmyocytes (e.g., cardiac fibroblasts) can be converted (or reprogrammed) into functional cardiomyocytes both in vitro and in vivo by introducing a set of transcription factors and microRNAs. Although poor reprogramming efficiency and the use of integrating viral vectors are potential problems associated with this approach, in vivo reprogramming of nonmyocytes to myocytes to regenerate damaged myocardium could potentially serve as a new paradigm for treating ischemic cardiomyopathies.

In heart failure research, most work has focused on myocyte contractile dysfunction, and relatively little attention has been given to the changes in tissue architecture and structural integrity. In this regard, the work of Genet et al offers new insights into the role of cardiac architecture in mediating contractile dysfunction. They reported that ephrin-B1 (Efnb1) is a component of the lateral membrane of the cardiac myocyte and is essential for cardiac tissue architecture cohesion by stabilizing their rod-shape morphology. Eph receptor tyrosine kinases and their ligands, ephrins, form an essential intracellular communication system in various contexts. These investigators reported that cardiomyocyte-specific ephrin-B1 (Efnb1) knockout mice developed cardiac tissue disorganization with loss of adult cardiomyocyte rod shape, which is often observed in end-stage heart failure in humans. Moreover, Efnb1 knockout mice exhibited hypersensitivity to mechanical stress. This suggests that cardiac tissue alterations that predispose to pathological responses may be mediated by deregulation of ephrin-B1. Proper maintenance of the integrity of intracellular structures within cardiac myocytes is also crucial for their functional competency. Previous reports indicated that human cardiomyopathy such as desminopathy and hypertrophic cardiomyopathy attributable to MYBPC3 mutations are associated with malfunction of the cardiac ubiquitin-proteasome system, subsequently leading to the accumulation of misfolded or damaged proteins. Spaich et al identified a novel myocyte-enriched E3 ubiquitin ligase component that plays an essential role in maintaining intracellular sarcomeric structure in cardiac myocytes. They reported that F-box and leucine-rich protein 22 (Fbxl22) is a component of a novel E3 ligase and that it targets 2 important sarcomeric proteins, α-actinin-2 and filamin C, for degradation. Knockdown of Fbxl22 in zebrafish was found to result in accumulation of α-actinin, severe contractile dysfunction, and cardiomyopathy, indicating that maintenance of normal sarcomeric structure and function is dependent on proper turnover of its structural components.

In recent years, a functional autophagic-lysosomal pathway has emerged as an important requirement for maintaining normal cardiac function and is, in fact, a vital survival mechanism under conditions of energy deprivation and proteotoxic stress. This notion has been further substantiated by recent studies investigating key factors that modulate autophagy in response to desmin-related cardiac proteinopathy. For instance, Zheng et al demonstrated that p62, a mediator of autophagy activation, is upregulated in cardiac myocytes using a mouse model of desmin-related cardiomyopathy and that it serves protective functions by promoting aggresome formation and increasing autophagic activation. In a related study, Pattison et al demonstrated that ectopic expression of Atg7, a mediator of autophagosomal biogenesis, can induce basal autophagy and rescues protein-misfolding–stressed neonatal rat cardiomyocytes by preventing the accumulation of misfolded proteins and aggregates while producing no detrimental effects on cell survival. These recent reports highlight the role of enhanced autophagic flux as an adaptive response to proteotoxic stress that promotes cardiomyocyte survival.

The protection afforded to cardiomyocytes under conditions of nutrient deprivation and energy stress through the activation of autophagy has brought significant attention to the identification of novel factors and pathways that may mediate its activation. For instance, Sciarretta et al recently reported that NADPH oxidase Nox4 effectively modulates autophagy-dependent survival in cardiomyocytes on glucose deprivation via production of reactive oxygen species in the endoplasmic reticulum and activation of the protein kinase RNA-activated-like endoplasmic reticulum kinase pathway. This phenomenon was recapitulated in vivo because both fasting and prolonged ischemia in mouse hearts resulted in Nox4 activation, thereby promoting autophagy and cardiac protection.

Recent work has uncovered novel players of cardiac hypertrophy that could be exploited for developing novel therapies in the future. New and innovative models of myocyte pathophysiology have emerged. Recent findings also emphasize the importance of relatively unappreciated aspects of cardiac myocyte biology, such as maintenance of structural integrity of cardiac myocytes and the flux of its molecular constituents, the deregulation of which leads to pathological changes. In addition, recent literature highlights stress-induced activation of autophagy as a physiologically important cytoprotective mechanism in cardiac myocytes. Identification of important mediators of myocyte autophagy will likely continue and open different avenues that lead to innovative therapeutic strategies to enhance survival of cardiac myocytes undergoing various insults.

Disclosures

None.
References


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