Molecular Mechanisms Underlying the Transition of Cardiac Hypertrophy to Heart Failure

Toru Oka, MD; Issei Komuro, MD

Heart failure is a condition in which the heart cannot supply enough blood to the body's organs, and is a final common consequence of various heart diseases. In the past 2 decades, much progress has been made in understanding the molecular and cellular processes that contribute to cardiac hypertrophy and heart failure, leading to the development of effective therapies. However, heart failure remains a leading cause of mortality worldwide and the precise molecular mechanisms that mediate the transition of cardiac hypertrophy to heart failure are largely undefined. This review discusses the potential mechanisms of heart failure progression focusing on (1) cardiac myocyte loss, (2) abnormalities of calcium handling, and (3) myocardial ischemia and hypoxia. These factors are closely related, and are considered to contribute to the pathogenesis of contractile dysfunction and heart failure in a cooperative manner. Elucidation of the molecular mechanisms underlying the transition of cardiac hypertrophy to heart failure will lead to the development of novel therapeutic strategies for heart diseases.

Key Words: Angiogenesis; Ca²⁺ handling; Cell death; Heart failure; Hypertrophy

Heart failure is a complex disorder that leads to disturbance of the normal pumping of blood to the peripheral organs to meet the metabolic demands of the body. Heart failure is the result of long-standing cardiovascular diseases such as hypertension, ischemic heart disease, myocarditis, valvular insufficiency, or cardiomyopathy. When the ventricle is stressed, cardiac performance is initially maintained by acute adaptive (compensatory) mechanisms, including hypertrophy, retention of salt and water, stimulation by neurohumoral factors, and activation of intracellular signaling pathways in the heart and vasculature. However, when the hemodynamic overload is severe and prolonged, myocardial contractility becomes depressed. The animal model of pressure overload hypertrophy suggests that depression of myocardial contractility is caused not only by insufficient hypertrophy causing afterload mismatch, but also by depression of the myocardium's intrinsic contractility.

Myocardial remodeling and the transition from compensated hypertrophy to failure of the myocardium involve a complex of events at the molecular and cellular levels: (1) myocyte growth or hypertrophy; (2) changes in myocyte phenotype resulting from re-expression of fetal gene programs and decreased expression of adult gene programs; (3) alterations in the expression or function, or both, of proteins involved in excitation–contraction (E-C) coupling and contraction; (4) myocyte death caused by necrosis or apoptosis; (5) changes in the extracellular matrix; and (6) abnormalities in energetics. Together, these events result in changes in myocardial structure (eg, increased myocardial mass, chamber dilation, greater sphericity) and function (eg, impaired systolic or diastolic function, or both) that often lead to further pump dysfunction and hemodynamic overload. Stimuli for these changes include mechanical strain on the myocyte, neurohormones (eg, norepinephrine, angiotensin II), inflammatory cytokines (eg, tumor necrosis factor (TNF)-α), other peptides and growth factors (eg, endothelin), and reactive oxygen species (eg, superoxide, nitric oxide). These stimuli occur both systemically and in the myocardium in response to circulatory failure and hemodynamic overload. They serve as an important link between pathological factors in the environment and the inter- and intracellular signaling pathways that mediate changes in the structure and function of the cellular elements of the myocardium.

In this review, we focus on the transition of cardiac hypertrophy to heart failure, and discuss recent advances in the understanding of the molecular mechanisms underlying heart failure initiation medicated by myocyte loss, abnormalities of Ca²⁺ handling, and myocardial ischemia/hypoxia.

Cardiac Myocyte Loss: Apoptosis, Autophagy, and Necrosis

Cardiac myocyte death occurs in a number of pathological conditions, such as ischemic or dilated cardiomyopathy, hypertensive heart disease, and aging? Although a decline in pumping capacity initiated by cardiac cell death is supported as inducing ventricular remodeling and finally resulting in symptomatic heart failure, there still remains controversy over the pathologic role of cell death in the progression of heart failure. In the failing heart, an imbalance between the signaling pathways that promote cell survival and those that promote cell death results in a decrease in the number of cardiomyocytes. Cell death is divided into 3 types based on the differences in the ultrastructural morphological fea-
Autophagy involves the turnover of intracellular organelles and long-lived proteins, excessive amounts have been proposed as causing apoptosis, autophagic death, and necrosis.

Apoptosis is characterized by cyttoplasmic condensation, nuclear pyknosis, chromatin condensation, DNA fragmentation, cell rounding, membrane blebbing, cytoskeletal collapse, and the formation of membrane-bound apoptotic bodies. Cell death during embryonic development is essential for successful organogenesis and the crafting of multicellular tissues. Pro-apoptotic signaling is divided into extrinsic and intrinsic pathways. Extrinsic death signaling is activated by the Fas ligand or TNF-α, whereas intrinsic apoptotic pathway is activated by DNA damage or oxidative stress and mediated by the mitochondria and endoplasmic reticulum (ER). Pro-apoptotic signaling mediated by the death receptor, mitochondria or ER finally activates caspase (a family of calcium-dependent cysteine proteases central to apoptosis), inducing apoptosis. Apoptosis in the myocardium can be initiated by multiple pathways, including those triggered by ROS, angiotensin II, sympathetic stimulation and cytokines, and a low, but significantly abnormal, rate of cardiomyocyte apoptosis seems to contribute to the phenotype of heart failure. Pro-survival pathways that counter cardiomyocyte apoptosis seems to contribute to the phenotype of heart failure. In the failing heart, autophagy has been demonstrated as another form of heart failure.

Autophagic Cell Death

Autophagic death is characterized by the appearance of numerous cytoplasmic autophagic vacuoles of lysosomal origin, followed by mitochondrial dilatation and enlargement of the ER and Golgi apparatus. Autophagy can be induced by cellular starvation and is characterized by the recycling of proteins within the organelles. Although autophagy plays an important role in cellular homeostasis (ie, in the turnover of intracellular organelles and long-lived proteins), excessive amounts have been proposed as causing cellular destruction and degenerative diseases. In the human failing heart, autophagy has been demonstrated as another type of myocardial cell death. Akazawa et al generated transgenic mice overexpressing human diphtheria toxin receptor in the heart under the control of a-MHC promoter. Administration of diphtheria toxin induced autophagic cardiac cell death with subsequent heart failure, suggesting that autophagy in the heart has a causal role in the pathogenesis of heart failure. Furthermore, genetic manipulation of autophagy-associated genes, such as beclin 1 and ATG5, has revealed they are involved in cardiac remodeling and dilated cardiomyopathy, suggesting the importance of autophagic myocyte death in heart diseases.

Necrosis also contributes to heart failure, and a recent report found that augmenting Ca²⁺ entry through the L-type Ca²⁺ channel (LTCC) triggered the opening of mitochondrial permeability transition pores by activating cyclophilin D (also known as PPID), thereby inducing necrosis. Thus, mitochondrial- and necrosis-dependent heart failure may be a pleiotropic disorder that involves not only apoptosis, but also necrotic loss of myocytes in association with dysregulated Ca²⁺ handling.

Ca²⁺ Handling Abnormality During Heart Failure Progression

Ca²⁺ is the central regulator of E-C coupling, and intracellular Ca²⁺ movements critically regulate subsequent mechanical contractions in the normal heart. A small amount of Ca²⁺ first enters through the LTCC during membrane depolarization. This Ca²⁺ influx triggers a large-scale Ca²⁺ release through the Ca²⁺ release channel of the sarcoplasmic reticulum (SR), referred to as the ryanodine receptor (RyR). RyR is a Ca²⁺ release channel existing as a huge homotetramer traversing the SR membrane. RyR is also a scaffolding protein to which numerous key regulatory proteins are bound, forming the junctional complex. RyR is associated with the FK506-binding protein (FKBP), calmodulin, protein kinase A (PKA), and protein phosphatase 2A. The released Ca²⁺ binds to troponin C within the myofilaments, which induces their activation and a consequent muscle contraction. Relaxation is initiated by dissociation of Ca²⁺ from troponin C, followed by its reuptake into the SR through phospholamban (PLN)-regulated Ca²⁺-ATPase (SERCA2a) and subsequent trans-sarcolemmal Ca²⁺ removal through the Na⁺/Ca²⁺ exchanger operating in its forward mode. The whole process of Ca²⁺ movement is characterized by a transient increase in intracellular [Ca²⁺] from 100 nmol/L to approximately 1 μmol/L.

In the human failing heart, although the density of the LTCCs seems to be unchanged or reduced, the overall activity of the channels is likely increased, contributing to a greater profile of Ca²⁺ handling dysfunction. In the failing heart, Ca²⁺ uptake into the SR is impaired, and Ca²⁺ concentration in the SR is therefore decreased. These defects have been ascribed to a decline in SERCA2a production, reduced levels of PLN phosphorylation, and depletion of SR Ca²⁺ through leaky RyR2 channels. For RyR channel stabilization, an accessory protein, FKBP12, also known as calstabin 2), plays an important role. Marx et al showed that the phosphorylation of RyR2 by PKA leads to dissociation of FKBP12, and this dissociation is proposed as increasing the leakage of Ca²⁺ from the SR. It has been reported that physiological hypertrophy is associated with a normal or increased number of myocardial

Hypoxic Response and Angiogenesis in the Failing Heart

It has been reported that physiological hypertrophy is associated with a normal or increased number of myocardial
capillaries, whereas pathological hypertrophy is correlated with a reduction in capillary density; suggesting that coronary angiogenesis occurs during physiological hypertrophy and that vascular rarefaction in the setting of pathological hypertrophy may cause myocardial hypoxia and lead to contractile dysfunction. Indeed, in a mouse model of Akt-induced cardiac hypertrophy, it was shown that hypertrophic stimuli induced the expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and angioptietin 2 in the adaptive phase of hypertrophy, and that blockade of VEGF signaling resulted in a reduction in capillary density and an early transition to heart failure.26 Pressure overload, a potent stimulus of pathological cardiac hypertrophy, increases myocardial oxygen demand while decreasing coronary perfusion pressure and increasing extrinsic compressive forces on coronary microvasculature. Greater demand for perfusion, concomitant with increased coronary resistance, contributes to a mismatch between myocardial oxygen demand and supply, and induces relative ischemia/hypoxia in hypertrophy. Pressure overload-induced hypertrophy in VEGF-deficient mice lead to a reduction in myocardial capillary density and accelerated the transition from compensatory hypertrophy to failure.29 On the other hand, supplementation of VEGF during prolonged pressure overload preserves contractile function.29,31 Mechanistically, it has been shown that downregulation of hypoxia-inducible factor-1 (Hif-1) by the p53 tumor suppressor protein, which is induced in the myocardium in the late stage of pressure overload-induced hypertrophy, contributes to the reduced expression of angiogenic growth factors.31 These results suggest that, in compensatory or physiological hypertrophy, growth-promoting signals simultaneously induce hypertrophy and angiogenic growth factor expression in myocytes and thus maintain the balance between myocyte hypertrophy and coronary angiogenesis. These studies also suggest that impaired expression of myocardial angiogenic growth factors in the pathological phase of pressure overload-induced cardiac hypertrophy results in vascular reduction and has a causative role in the transition of cardiac hypertrophy to heart failure. Thus the balance between cardiac growth and angiogenesis in the heart is one of the determinants of whether the hypertrophy is physiological/compensate or pathological/decompensate, and impaired angiogenesis during sustained growth stimuli is critical for the progression from adaptive to maladaptive hypertrophy.

The cardiac transcription factor, GATA4, has an important stimulatory role in angiogenesis and thus helps to maintain the balance between muscle growth (hypertrophy) and nutrient supply (capillary density).32 GATA4 is a zinc-finger transcription factor that is abundantly expressed in cardiomyocytes from early embryonic stages to adulthood and regulates cardiac-specific gene expression.33 Deletion of the gene encoding GATA4 in the adult heart reveals its important role in cardiac hypertrophy, stress-compensation and cardiac myocyte viability.34 As a mechanism of this, Heineke et al showed that transgenic overexpression of GATA4 in the adult heart enhanced coronary angiogenesis, whereas myocyte-specific deletion of GATA4 resulted in a reduction in capillary density.32 Furthermore, they demonstrated that myocytes overexpressing GATA4 can induce in vitro angiogenesis in a paracrine fashion through the secretion of VEGF-A, and that GATA4 binds to and transactivates the VEGF-A gene promoter.32 Endogenous GATA4 levels are increased in murine hypertrophic myocardium induced by pressure overload associated with greater capillary density; however, over extended periods, GATA4 levels are reduced parallel with reduced capillary density in the decompensate failing heart. Therefore, GATA4 can directly regulate the angiogenic program regulating VEGF-A expression in the heart through a hypoxia-independent mechanism. These results highlight a novel mechanism whereby Hif-1 or GATA4 promote cardiac adaptation following pathologic stimulation, suggesting a possible novel therapeutic approach to inducing the angiogenic program.

References
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