Apoptosis as a therapeutic target in heart failure

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Heart failure, the ultimatum of various forms of myocardial disease, is associated with high mortality rate in this modern world (2). Multiple factors play important roles in the genesis of heart failure. The presence of left ventricular hypertrophy is a powerful predictor of the development of heart failure (3). It is believed that gradual deterioration of the hypertrophied left ventricle (LV), which ultimately participates in heart failure, is linked to progressive loss of cardiac myocytes (11, 18). The traditional explanation for myocyte loss was cell necrosis, but over the last decade there has been a surge of evidence affirming the role of apoptosis in the genesis of heart failure.

Cardiac hypertrophy is the consequence of an increase in cardiac myocyte size and/or mass. Since cardiac myocytes have no capacity for cellular proliferation, their only means of growth is by cellular enlargement. Given that cardiac failure is the most common result of insufficiency of myocardium, it is not surprising that cardiomyocyte hypertrophy is the dominant cellular response to virtually all forms of hemodynamic overload (4). Although it seems obvious that growing more myocardium could produce functional adaptation in a condition caused by myocardial insufficiency, specific hemodynamic benefits can be demonstrated through the application of the “Laplace principle” in the context of known biological conditions. According to the Laplace principle, wall stress = (Pr/2h), where P is intercavitary pressure, r is internal radius of the chamber, and h is thickness of the chamber wall. Thus, during hypertension, when increased pressure results in increased stress on the heart, an increase in wall thickness (h) can normalize wall stress and preserve systolic function (4, 6). This is the basic principle of compensatory hypertrophy. However, long-term adaptive/compensatory hypertrophy is associated with progressive ventricular dilatation. As a consequence of cardiac enlargement (r) and wall thinning (h), the ratio rh increases, and so does wall stress, despite constant intercavitytary pressure. This mathematical increase in wall stress generates its own hemodynamic stress on the heart, further stimulating overloaded hypertrophy signaling pathway and thereby altering the balance from cell growth response to cell death. Once these processes have progressed to this stage (decompensation, loss of cardiac myocytes), irreversible functional deterioration develops, which leads to heart failure and, ultimately, death (8, 13).

There are three clearly defined pathologically distinct modes of cell death: necrosis, apoptosis, and autophagy (9). There is clinico pathological evidence for all three forms of cell death in the end stage of cardiomyopathy (14). Although cardiac myocyte necrosis is the oldest postulated means of cell death in decompensating hypertrophy leading to cardiomyopathy, numerous examples are rapidly accumulating about the involvement of apoptosis during clinical cardiomyopathies and an experimental model of heart failure or decompensatory hypertrophy (1, 5). Generally, apoptosis is extremely rare in the normal myocardium. Only one apoptotic cell is visible per 10,000–100,000 cardiac myocytes (17). The ratio of apoptotic cardiac myocytes increases with the magnitude of heart disease, such as cardiomyopathy (11), hypertrophic heart disease (7), and right ventricular dysplasia (10), among others. There are two distinct apoptotic signaling pathways that can be induced during heart failure: 1) death receptor pathway and 2) mitochondrial pathway. In the case of death receptor pathway, Fas antigen (CD95), a major death receptor that belongs to the TNF superfamily of membrane receptors, is the first component of the pathway to receive a death signal. Fas is expressed in a variety of cell types, including thymocytes, activated B cells, T cells, monocytes, macrophages, and neutrophils, as well as a variety of nonimmune cells in the liver, lungs, and heart. When Fas binds to its ligand, FasL, it oligomerizes and forms a death signaling complex with FADD (Fas-associated death domain), which recruits caspase-8 and initiates the apoptotic cascade of caspase protease that culminates in systematic degradation of intracellular proteins and oligonucleosomal DNA cleavage. In contrast, in the case of mitochondrial pathway, outer mitochondrial membranes rupture or open mitochondrial permeability transition pores (MPTP) and release cytochrome c into the cytosol. This cytochrome c forms an apoptotic complex with Apaf-1, which recruits caspase-9 and initiates caspase cascade.

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Sharma et al. (15) show the initiation/activation of mitochondrial death pathway during the progression of a compensated hypertrophy to a decompensated heart failure in guinea pigs. The key finding of this study is the activation of mitochondrial death pathway, which includes lowering of mitochondrial membrane potential, cytochrome c release, and activation of caspase-3, leading to apoptosis during the transition to heart failure subsequent to chronic pressure overload.

Unlike necrosis, apoptosis is an ordered and regulated process and logically should be applicable to prevention if intervention occurs at the early stage. Many diseases of the modern societies can be attributed directly or indirectly to deregulation of programmed cell death or apoptosis. Disorders in which defective regulation of apoptosis contributes to disease pathogenesis involve either cell accumulation, in which cell eradication is impaired (e.g., cancer), or cell loss, in which the cell suicide program is inappropriately triggered (e.g., heart failure, neurodegenerative disease, inflammation, stroke). Obviously, heart failure would be classified as one of the clinical disorders in which apoptosis should be actively antagonized to limit cell loss. More information about the exact cell death pathway and their detailed mechanism and timing would be more helpful to prevent apoptotic disorder as well as heart failure. The importance of the above-mentioned research study in this area has risen our expectation even further.
The logical target to modulate cardiomyocyte apoptosis more directly in the failing heart would be executioner caspase. At this moment, broad-spectrum caspase inhibitors are already being evaluated in different clinical trials to determine their usefulness as a broad hepatoprotective drug in delaying or preventing the progression of hepatitis to cirrhosis. Indeed, much evidence points to the beneficial aspect of caspase inhibitors in acute ischemia-reperfusion-induced cardiac injury (19). Beside caspase, other cellular targets in the apoptotic pathway also hold promises as future therapeutic modalities in heart failure. Aurintricarboxylic acid (ATA) is an inhibitor that targets endonucleases, which are situated relatively downstream in the apoptotic pathways and provoke DNA strand break. ATA was recently shown to significantly reduce the number of apoptotic cell in the perinecrotic myocardium of an ischemia-reperfusion dog model (20). At the same time, Bcl-2 was found to be significantly increased, whereas Bax and activated caspase-3 were significantly reduced. A very recent publication reported that mitofusin-2 (Mfn-2), also called hyaluronan-binding protein, apoptosis and a potent therapeutic target of heart failure (16). Mfn-2 silencing inhibits oxidative stress-induced apoptosis, and overexpression of Mfn-2 triggers myocyte apoptosis through activation of caspase-9 and inhibition of AKT.

Recent investigations are disentangling the complex processes of apoptotic signaling pathways in the myocardium and developing novel approaches, aimed at counteringacting cardiomyocyte apoptosis in heart failure. Unfortunately, the cell death pathway contains very few conventional drug targets, such as enzymes and small-ligand receptors. To overcome this, a more thorough understanding of the molecular pathways that initiate and execute apoptosis is imperative in designing successful antiapoptotic therapies in heart failure.

REFERENCES