Despite all efforts in its pharmaceutical treatment, heart failure is still a major cause of morbidity and mortality worldwide. Within the past decade, we have witnessed accumulating evidence that cardiomyocyte apoptosis is part of the phenotype of the failing myocardium. Most likely because of differences in the absolute number of cells affected, which have ranged by several orders of magnitude in various studies, the causal role of apoptosis in the pathogenesis of heart failure has been brought into question.

Programmed cell death (apoptosis) is an energy-requiring, active form of cell death. As such, it is a fundamental integral part of normal organ development in the first place. Additionally, in all organ systems, apoptosis represents the major mechanism to prevent uncontrolled tumor growth.

Apoptosis is executed by a family of ubiquitously expressed cysteine proteases termed caspases. Caspases are present in the cell as inactive pro-caspases that are cleaved and activated in response to apoptotic stimuli. Initial activation of caspases is brought about by at least 2 overlapping signaling pathways. One is characterized by the release of mitochondrial cytochrome c and subsequent activation of caspase-9, whereas the other involves the activation of caspase-8 caused by the transduction of a signal from membrane receptors belonging to the tumor necrosis factor receptor (TNF) family, such as Fas and its ligand FasL. Both the mitochondrial and the “death receptor” pathways have been shown to exist in the heart.

**Why Is Apoptosis So Detrimental to the Heart?**

Most of our knowledge of apoptotic cell death has come from the study of dividing or undifferentiated cells. The mechanisms of cell death in terminally differentiated, nondividing cells such as cardiomyocytes are less well defined. The adult myocardium is characterized by the loss of significant replicative potential of cardiomyocytes. Given the unprecedented low number of primary tumors in comparison to other organs, we have to concede that the suppression of the replicative potential in the heart is extremely effective. Apoptosis, however, can be easily reinduced in terminally differentiated cardiomyocytes, as many in vitro and in vivo studies have proven in the past. Therefore, in contrast to the embryonic heart, the adult myocardium is often unable to compensate for a decrease in contractile mass caused by cardiomyocyte apoptosis.

Thus, the combination of the robust suppression of cell cycle reactivation on one side and the propensity to undergo apoptosis to a variety of pathologic stimuli on the other side renders the heart particularly vulnerable to cell death.

**What Is the Role of Apoptosis in Heart Failure?**

Studies from the laboratory of Kitsis lend experimental support to the notion of a causal role of apoptosis in heart failure. Using a transgenic mouse model with cardiomyocyte restricted overexpression of a ligand-activated procaspase-8, this group was able to demonstrate that even low levels of cardiomyocyte apoptosis are able to convey a lethal dilated cardiomyopathy. This phenotype was preventable by caspase inhibition. Also, continuous subcutaneous administration of a polycaspase inhibitor ameliorated the development of heart failure and led to a significant improvement in survival rate in a 5/6 transgenic mouse model of peripartum cardiomyopathy.

It is evident that reduction in contractile mass attributable to ongoing loss of cardiomyocytes is detrimental to cardiac function. However, it is not only the mere loss of vital cardiac mass, to which apoptosis may contribute. The activation of apoptotic signaling cascades may also be an integral part of maladaptive growth responses. This view is corroborated by the fact that targeted inhibition of cyclin-dependent kinase activation, which is a prerequisite for even hypertrophic growth of postmitotic cardiomyocytes, has proven a powerful means for blocking cardiomyocyte apoptosis. Moreover, adaptive cardiac growth has been shown to be hampered when simultaneously anti-apoptotic factors have been deleted. Caspases have been shown to affect cardiac structures and functions independent of their modulation of apoptosis.

Finally, apoptosis of cardiac nonmyocytes may contribute significantly to the progressive nature of heart failure. Two recent studies from Fujiwara and coworkers have lent support to the hypothesis that apoptosis of granulation tissue cells are related to inverse cardiac remodeling after myocardial infarction. Therefore, initiation of pro-apoptotic signaling in cardiomyocytes, as well as noncardiomyocytes, could be a
crucial factor for the transition from compensated to decompensated maladaptive growth in heart failure.

**What Is the Role of the Fas/Fas Ligand System in Heart Failure?**

The role of Fas/TNF-receptor–dependent signaling in heart failure has been a matter of discussion for several years now. In this issue of *Circulation Research*, Li et al shed more light on this debate. Using a murine model of myocardial infarction (MI), they show that in post-MI tissue, Fas is expressed highly in the granulation tissue. They convincingly demonstrate that granulation tissue apoptosis is mediated via the Fas/FasL system and that inhibition of this system blocks maladaptive post-MI remodeling and leads to improvement in cardiac function and overall survival (see Figure).

This is an interesting study in several regards: (1) it provides a causal link between Fas/FasL-dependent signaling and heart failure; (2) it contributes significantly to our understanding of a causal role of apoptosis in heart failure; and (3) it supports the concept of a beneficial effect of specific anti-apoptotic interventions in heart failure.

However, some uncertainties remain. Li et al explicitly state that they could not detect cardiomyocyte apoptosis in their infarct model. How could this be reconciled with the plethora of studies unequivocally showing apoptotic cell death in different models of animal and human ischemic heart disease? This discrepancy most likely is attributable to the marked difference in the rate of apoptosis between postmitotic cardiomyocytes and proliferating granulation tissue cells. In their study, Li et al had to optimize tissue staining conditions for the high prevalence of apoptosis in the granulation tissue and, thus, may have missed the detection of low abundant cardiomyocyte apoptosis. Also, Li et al could not detect expression of Fas on cardiomyocytes. This is in contrast to several other studies clearly showing Fas expression on cardiomyocytes under basal, as well as different pathological conditions in animal and human tissue.

Although the evidence for Fas expression on cardiomyocytes is impressive, the study by Li et al supports the concept that Fas-dependent apoptosis of granulation tissue cells, rather than that of cardiomyocytes, is a critical event in post-MI heart failure. This hypothesis is corroborated by results from transgenic mice with cardiac-restricted overexpression of TNF-α. Although these animals develop a lethal dilated cardiomyopathy, apoptosis was observed primarily in the interstitial tissue, rather than in cardiomyocytes. Moreover, Wollert et al demonstrated that murine cardiomyocytes are resistant to apoptosis induced by an agonistic Fas antibody. This differential effect of the activation of the Fas/FasL system could be explained by the fact that in a variety of cells, which could include postmitotic cardiomyocytes, but not proliferating granulation tissue cells, Fas/TNF receptor-dependent signaling involves the simultaneous activation of pro- as well as anti-apoptotic pathways.

**Why Are Anti-apoptotic Interventions Such an Attractive Therapeutic Goal in Heart Failure Treatment?**

If we reconcile the data presented above, the perspective of therapeutic interference with pro-apoptotic stimuli in the context of heart failure should represent a very attractive platform for novel treatment options. It would allow us to specifically counteract ongoing loss of contractile mass and, in addition, would enable us to coax maladaptive growth pathways into a more compensatory growth response by reducing scar formation. Although caspase inhibition has proven effective in treatment of specific heart failure models, its lack of organ specificity may prove deleterious for long-term treatment. In this regard, identification and characterization of muscle-specific endogenous anti-apoptotic factors may represent a promising area of research. For example, ARC (apoptosis repressor with caspase recruitment domain) appears to be such an attractive target for molecular manipulation, because it is expressed exclusively in postmitotic cells. The fact that in cardiomyocytes ARC is constitutively activated by casein kinase II–dependent phosphorylation renders this molecule particularly appealing for therapeutic interventions. It is also notable that the therapeutic armamentarium already contains several orally active anti-apoptotic compounds, notably the cardioprotective agents diazoxide and nicorandil. Although these drugs have not yet been tested specifically in the heart failure population, the results of the article in this issue of *Circulation Research* provides excellent motivation for such clinical trials.

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**References**


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