Oxidative Stress and Apoptosis in Heart Failure Progression
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The syndrome of congestive heart failure (HF) is the most important cardiovascular disorder in the Western world from public health and health care resource utilization perspectives. Great strides have been made in treating patients with HF through the development of drugs that antagonize neurohormonal activation. Nevertheless, patients with HF experience clinically meaningful disease progression despite optimal current therapy.

Although the biological mechanisms for progression and ventricular remodeling have yet to be definitively explained, mounting evidence supports the theory that ventricular dysfunction worsens as a consequence of increased reactive oxygen species (ROS) formation, which in turn promotes myocyte apoptosis. Myocyte apoptosis is observed in numerous pathological situations including cardiomyopathy, ischemia, and transplant rejection and can be induced experimentally with neurohormonal agonists or direct generation of superoxide.

In this issue of Circulation Research, Cesselli et al have examined the linkage between pathways involved in mediating oxidative metabolism and apoptosis in dogs with pacing-induced dilated cardiomyopathy. Using both immunohistochemistry and immunoblotting techniques, the authors track changes in multiple apoptotic pathways including the caspases, mitochondrial cytochrome c release, and proteins involved in DNA damage (see Figure). Importantly, induction of these changes precedes the development of left ventricular (LV) dysfunction, providing additional strong support, but not definitive proof, that apoptosis participates in the progression of LV remodeling. In addition, a new signaling molecule, p66shc, linking oxidative stress and apoptosis is demonstrated to be upregulated with pacing-induced HF. p66shc is an oxidant stress–induced, proapoptotic protooncogene known to be activated by phosphorylation in response to stimuli such as H$_2$O$_2$, UV radiation, or epidermal growth factor. Transgenic disruption of p66shc or inactivation of its ability to be phosphorylated confers resistance to oxidative damage and prolongs life in mice. The observations made by Cesselli et al add further insight into the signaling pathways linking myocardial apoptosis with cellular ability to cope with oxidative stress. The major strength of the work is the comprehensive evaluation of multiple steps in proapoptotic signaling cascades, which demonstrates clearly that these pathways are activated as HF and LV dysfunction develop. Although this association is convincing, it does not prove that apoptosis is an essential feature of HF pathogenesis. This will remain an open question until interventions that inhibit apoptosis specifically are shown to affect the natural history of HF. Nevertheless, this work raises many interesting issues.

Whether mitochondria are initiators or secondary victims of apoptosis continues to be hotly debated. In either case, it is of great mechanistic interest that mitochondria are an important source of ROS in HF. Mitochondria generate ATP by a series of oxidation-reduction reactions mediated by respiratory complexes NADH-CoQ reductase (complex I), succinate-CoQ reductase (complex II), cytochrome c reductase (complex III), and cytochrome c oxidase (complex IV) (see Figure). Cytochrome c is a 13-kDa heme-containing protein that serves as an electron acceptor facilitating electron transfer from complex III to complex IV. The transfer of electrons allows the respiratory complexes to generate an electrochemical gradient by pumping protons (through complexes I, III, and IV; see Figure) from the mitochondrial matrix into the inner membrane, and this gradient (proton-motive force) provides the energy for ATP synthesis by F$_0$F$_1$ ATPase. Superoxide (O$_2^-$) generation in mitochondria occurs as a result of incomplete reduction of O$_2$ to H$_2$O. Whereas some O$_2^-$ formation occurs during physiological oxidative phosphorylation (and, to compensate, mitochondria contain superoxide dismutase and other antioxidant defenses), in HF, mitochondrial O$_2$ production is greatly augmented. The clear demonstration that mitochondria generate increased ROS in HF favors a central rather than bystander role for these organelles in apoptosis.

Mitochondria contribute to or initiate apoptosis through the release of cytochrome c, which in turn stimulates apoptosis activating factor (Apaf-1) and caspases 9 and 3. Atlante et al. in an in vitro model of neuronal toxicity, have shown that the formation of ROS may be the proximate cause of cytochrome c release from mitochondria, in a process that involves a pore opened by members of the BCL-2 family of proteins, Bax and Bak. Loss of cytochrome c likely disrupts the electron transport chain and may contribute to further O$_2^-$ production. The result is more oxidative stress, and a potential vicious cycle that further promotes apoptosis.

The central role of the mitochondrion in apoptosis and the fact that mitochondrial ATP synthesis is the major source of energy in cardiac myocytes suggest that disorders of apoptosis and energy metabolism may be linked pathologically. Although this linkage is speculative, there is strong evidence that oxidative stress may also impair energy metabolism in HF. This is of particular significance given that uncoupling of
Central role for ROS in myocardial apoptosis. Cellular sources of $O_2^-$ include mitochondria, XO, and NAD(P)H oxidase. Elevated $O_2^-$ production in heart failure contributes to the release of cytochrome c from mitochondria and the activation of p66<sup>shc</sup>, both of which participate in initiating or promoting apoptotic cascades. Thus, formation of ROS represents a central phenomenon for apoptosis in the failing heart. p53 and p21 are proapoptotic and antiapoptotic molecules, respectively, that are activated by p66<sup>shc</sup>. Bax and Bak are members of the BCL-2 protein family that participate in mitochondrial membrane pore-opening responsible for cytochrome c release into the cytoplasm. Fas is a cell surface receptor that activates apoptotic cascades when stimulated by its receptor.

Is the current totality of evidence sufficient to conclude definitively that oxidative stress–induced apoptosis is a final common pathway for progressive LV dysfunction? It is important to consider that apoptosis may not be the whole story behind net loss of myocytes in progressive LV dysfunction. As apoptosis is a basic mechanism important in embryogenesis and tissue repair, it may contribute to myocardial restoration after injury. This possibility is especially relevant given reports from the same group that myocytes can undergo mitosis and are therefore not terminally differentiated. Thus, disease progression in HF may reflect an imbalance between myocyte loss and replacement. In a setting where cells are being appropriately replaced, apoptosis may actually represent a favorable process whereby damaged cells are removed. Future work will need to examine the relative rates of myocyte loss and regeneration in HF models, as well as the role oxidative stress plays in stimulating or inhibiting myocyte mitosis.

The work by Cesselli et al<sup>9</sup> introduces the proto-oncogene p66<sup>shc</sup> into the increasingly complicated array of biochemical events that link oxidative stress with cardiac programmed cell death. To obtain a comprehensive view of how LV dysfunction progresses, future work will need to separate adaptive from nonadaptive consequences of apoptosis. In addition, it will be important to consider the broader spectrum of roles played by oxidant signaling in HF such as depression of myocardial energetics. Understanding these potentially reversible processes offers hope for novel treatment strategies for HF.

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