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 expression of multiple proapoptotic 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 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 complex V) 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 F0F1 ATPase. Superoxide (O2•−) generation in mitochondria occurs as a result of incomplete reduction of O2 to H2O. Whereas some O2•− formation occurs during physiological oxidative phosphorylation (and, to compensate, mitochondria contain superoxide dismutase and other antioxidant defenses), in HF, mitochondrial O2•− 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 O2•− 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
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.\(^3\) introduces the proto-oncogene p66\(^{shc}\) 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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**References**

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