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Relief from a heavy heart: redox-sensitive NF-κB as a therapeutic target in managing cardiac hypertrophy

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CARDIAC HYPERTROPHY is both an adaptive response to chronic pressure overload and a key risk factor in patients with hypertension (6). On one hand, cardiac hypertrophy may normalize wall tension, whereas on the other it may progress to a decompensated state causing overt heart failure, a common end stage of numerous cardiac disorders. Mechanisms of progression to heart failure include renal sodium and water retention, neurohumoral activation, and changes in cell signaling in the myocardial tissue (5, 18).

Fifteen years ago, Sen and associates (36) reported that mechanisms involved in the development or the regression of myocardial hypertrophy cannot be fully explained as responses to blood pressure control alone. They postulated that the development of hypertrophy is initiated by a mechanical or humoral signal to the myocardium, which in turn produces a soluble factor that triggers protein synthesis and initiates myocardial growth. Myotrophin was identified as a novel protein that was present in human, dog, and rat hypertrophied hearts. In neonatal cardiac myocytes, myotrophin increased cell surface area and caused myofibrils organization. Thus myotrophin emerged as a putative causative factor supporting cardiac hypertrophy (36). Later, Sen and associates (37) went on to identify myotrophin as a unique rel/nuclear factor (NF)-κB interacting protein in the rat heart. One of the ankyrin repeats of myotrophin was highly homologous specifically to those of IκBα/rel ankyrin repeats. Putative consensus phosphorylation sites for protein kinase C and casein kinase II, which were observed in IκBα proteins, were identified in myotrophin (37). It is now known that myotrophin stimulates protein synthesis and myocardial cell growth associated with increased levels of hypertrophy marker genes. A basal level of myotrophin exists in both the cytoplasm as well as the nucleus under normal conditions. In response to cyclic stretch, however, myotrophin levels elevate in the nucleus. Exposure of excised beating hearts to high pressure induces myotrophin gene expression. Soon myotrophin-κB DNA interaction emerged as an important step in initiating cardiac hypertrophy (11). Concurrent report by the same group demonstrating that the protein kinase C-IKK-NFκB pathway is involved in mediating myotrophin-induced hypertrophic response in cardiomyocytes represents a landmark progress identifying NF-κB as a molecular checkpoint regulating cardiac hypertrophy. NF-κB-dependent induction of the hypertrophic genes atrial natriuretic factor (ANF) and c-*myc* in cardiomyocytes marks a key mechanism underlying the hypertrophic effects of myotrophin (10).

As the evidence in support of the myotrophin-NF-κB paradigm mounted based on the study of rodent models, a clear need to develop the significance in a clinical heart failure setting arose. Plasma myotrophin levels were measured in 120 patients with heart failure and 130 age- and gender-matched normal controls (23). Whereas the results do not establish a causal relationship between myotrophin and heart failure, the observation reporting early activation of the myotrophin system in heart failure represents a significant confidence-building piece for the myotrophin-NF-κB paradigm in cardiac hypertrophy (23). Overexpression of heart-specific myotrophin in transgenic mice causes cardiac hypertrophy that progress to heart failure, similar to changes in human heart failure. Such hypertrophy is associated with increased expression of proto oncogenes, hypertrophy marker genes, growth factors, and cytokines, with symptoms that functionally and morphologically mimic those of human cardiomyopathy (27, 28).

The first direct evidence suggesting that NF-κB activation is required for the development of cardiac hypertrophy in vivo was obtained only recently. In an experimental model of aortic banding-induced cardiac hypertrophy, genetic and antioxidant strategies to arrest NF-κB activity attenuated banding-induced increase in heart-to-body weight ratio (17). Compared with pharmacological approaches, genetic tools to manipulate any given signaling pathway are more specific and thus more valuable in the laboratory. Once the hypothesis is tested and the principles unveiled, taking experimental findings to the bedside rely mostly on pharmacological approaches. Pharmacologically, inducible NF-κB activation may be repressed by strategies antagonizing oxidants (e.g., antioxidants), inhibiting IκB phosphorylation and degradation (e.g., sodium salicylate and acetylsalicylic acid or aspirin), or preventing binding of nuclear NF-κB protein to the κB site (e.g., aurine tricarboxylic acid). The antioxidant approach is effective in vivo (19, 20). In this issue of the *American Journal of Physiology-Heart and Circulatory Physiology*, Sen and associates demonstrate that the antioxidant pyrrolidine dithiocarbamate (PDTC) inhibits NF-κB activation in vivo and regressed cardiac hypertrophy in spontaneously hypertensive rats. The effect of PDTC was dependent on NF-κB and independent of hypertension (12). These findings underscore the potential of redox-active inhibitors of inducible NF-κB activity as therapeutic candidates in the management of cardiac hypertrophy.

During the last decade, as compelling evidence continued to accumulate supporting that reactive oxygen species (ROS) serve as cellular messenger molecules (3, 4, 26, 32), NF-κB has emerged as one of the most well-studied molecular checkpoints, the inducible activation of which may be reliably inhibited by redox-active agents (8, 14, 16, 29, 32, 34, 35). PDTC became a common experimental tool to inhibit inducible NF-κB activation. First synthesized in the mid-1800s, dithiocarbamates have found applications in the pharmaceutical industries because of their metal binding and antioxidant prop-

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erties (38, 39). Despite promising outcomes in the treatment of autoimmune deficiency syndrome (25) and cancer (7), dithiocarbamates do not seem to have found their way to clinical testing for more than a decade. Rationale for this cautious approach perhaps remain embedded in the historical background of dithiocarbamates as agricultural insecticides and fungicides (13). Dithiocarbamates, including PDTC, may undergo copper-catalyzed oxidation to form the corresponding thiuram disulfides, which are cytotoxic (2).

ROS function as second messengers signaling for the hypertrophy of cardiac myocytes (1, 43). TNF-α-induced myocyte hypertrophy is mediated through NF-κB activation via the generation of ROS (15). These observations rationally lead to the hypothesis that antioxidant-based therapies, dually targeting ROS and NF-κB, may help prevent cardiac hypertrophy. Among the thiol-based antioxidants that have proven ability to inhibit inducible NF-κB activity (29, 31–33), *N*-acetylcysteine (NAC) and α-lipoic acid (ALA) have a sound track record for safe and effective clinical use. Biochemical studies predict that based on the mechanisms of thiol regeneration, ALA is a more effective thiol antioxidant than NAC (24, 30). ALA defends against certain risk factors of cardiovascular disease (42). However, the insulin mimetic properties of ALA have made it a more suited candidate for the treatment of diabetes (24). Further studies are necessary to establish the benefits of ALA to patients suffering from cardiac disorders.

Oral and intravenous use of NAC has an extensive history of clinical studies addressing a wide range of disorders. In patients with unstable angina pectoris and a threat of infarct, the intravenous or oral administration of NAC in association with nitroglycerin effectively decreases the risk of worsening, mainly by preventing the occurrence of acute myocardial infarction (21). As an effective antioxidant in a clinical setting, NAC attenuates myocardial oxidative stress in the hearts of patients subjected to cardiopulmonary bypass and cardioplegic arrest (40). NAC improved bradycardic and tachycardic baroreflex responses in spontaneously hypertensive rats without modifying catecholamine responses (9). In addition to these favorable effects on the cardiovascular system, NAC has been tested in the laboratory for its effect on cardiac hypertrophy. NAC prevents cardiomyocytes hypertrophy in vitro (41). Angiotensin II-induced ANF expression in neonatal rat cardiac myocytes was also inhibited by NAC. Furthermore, NAC inhibited angiotensin II-induced cardiac hypertrophy in vivo (22). Taken together, the current state of knowledge warrants clinical testing of antioxidant therapies targeting inhibition of inducible NF-κB activation in the heart for the treatment of cardiac hypertrophy and related heart failure.

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