Growing Old, Angiotensin II, Cardiac Hypertrophy, and Death
Making the Connection With p66Shc

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Hypertension and aging have similar effects on the structure and function of blood vessels and the heart. Both commonly result in decreased vascular compliance, endothelial dysfunction, and left ventricular (LV) hypertrophy and stiffness. Moreover, the risk of cardiovascular disease, including hypertension, increases exponentially with age in those >40 years of age. Therefore, one might surmise that hypertension and aging have some cause in common. The idea that angiotensin II (Ang II) might be the “missing link” was suggested by reports that renin-angiotensin system (RAS) inhibitors, in addition to being effective in treating cardiovascular and renal diseases, protect the cardiovascular system, kidney, and brain against the harmful effect of aging.1 Although findings based on angiotensin-converting enzyme inhibitors and the Ang II type 1 receptor blocker losartan should be interpreted with caution because of extra-RAS actions, evidence linking Ang II to increased collagen content and fibrosis of the aged heart is persuasive.2 Intriguingly, in light of the article by Graiani et al in this issue,3 the mitochondria from hearts of rats chronically treated with losartan were found to have increased NO synthase (NOS) activity and decreased hydrogen peroxide formation compared with controls, suggesting that blocking the action of Ang II could offset the deleterious effect of aging on cardiac mitochondrial function and integrity.4

But Ang II has never been a major interest of aging research, which has focused recently on the oxidative stress experienced by aging cells because of increased reactive oxygen species (ROS) formation.5 Mitochondria represent a major source for this increased ROS because their defense mechanisms are thought to become less effective with age in handling the superoxide and other ROS formed naturally during oxidative respiration. Although it was once thought that all of the harmful effects of ROS were from direct damage of cellular membranes and proteins, it is now known that ROS act more insidiously to cause cell death in the role of second messenger. For example, excessive respiratory chain superoxide may induce apoptosis by combining with NO from mitochondrial NOS to form peroxynitrite, a potent oxidant that promotes cytochrome C release from mitochondria, presumably by opening the mitochondrial permeability transition pore (mPTP).6

Another target of ROS as second messenger was shown recently to be the adaptor protein p66Shc, which, along with p46Shc and p52Shc, is encoded by the ShcA gene.5 p46Shc and p52Shc are derived from the same mRNA through alternative start sites and function prominently in Ras-related mitogenic/oncogenic signaling downstream of receptor tyrosine kinases. p66Shc, which is under control of a different promoter, does not couple to Ras activation, suggesting that this Shc isoform may function as a dominant-negative regulator of p46/p52Shc. Additionally, p66Shc is phosphorylated on Ser36 within its unique amino-terminal region in response to oxidative stress, an event that markedly sensitizes cells to apoptosis. One way p66Shc seems to enhance oxidative stress–induced apoptosis is by participating in the phosphorylation-induced repression of Forkhead transcription factors, which regulate expression of several antioxidant enzymes.5 Consistent with this, p66Shc knockout mice exhibit higher catalase activity.7 Another way is likely mediated by a mitochondrial pool of p66Shc because evidence suggests that activation of this pool leads to further ROS generation by inducing mPTP opening and cytochrome C release.8

Remarkably, p66Shc knockout mice not only show increased resistance to oxidative stress, but a 30% increase in life span.9 Graiani et al1 now report evidence that these mice may have a “better” heart as well. These investigators found that the hearts of p66−/− mice, which display normal systemic hemodynamics and LV wall thickness, were resistant to the deleterious remodeling effects of a subpressor dose of Ang II. Specifically, the pathological LV hypertrophy, as well as apoptosis of cardiomyocytes and endothelial cells, produced in wild-type mice by Ang II infusion was dramatically suppressed in p66−/− mice.

Obviously, one cannot draw any conclusion from the study of Graiani et al1 about the contribution of Ang II to the effects of aging on the heart; however, their study does identify a common mechanism between an agonist implicated in pathological LV hypertrophy and the aging process. Certainly, substantial evidence already exists implicating ROS formation in pathological LV hypertrophy, apoptosis, and heart failure in response to a variety of stimuli, including Ang II, but those studies have focused for the most part on NAD(P)H (and more recently) NOS3 as the source of ROS.10 Graiani et

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al3 have now formally introduced a new player that may better explain the progressive and insidious nature of pathological LV hypertrophy and its transition to heart failure. This is because p66Shc not only responds to ROS by forming more ROS, but protein levels of p66Shc are apparently increased by ROS through transcriptional and post-transcriptional means.11 Thus, if p66Shc were involved in hypertension-induced LV hypertrophy and heart failure, the harmful effects of mitochondrial ROS on cardiac myocytes would be predicted to occur over time, slowly at first but at an accelerating rate, much like what occurs in the aging process. Consistent with this, cardiac myocytes normally express little p66Shc, but its levels were shown to increase in dilated myopathy of the dog heart induced by ventricular pacing.12 A predominant role for p66Shc in hypertension-induced LV hypertrophy may seem unlikely given the fact that multiple intracellular signaling pathways linked to LV hypertrophy are known to be activated by pressure overload of the heart.13 However, the study by Graiani et al3 does demonstrate a prominent role for p66Shc in the amplification of a relatively weak hypertrophic signal (presumably by enhancing ROS formation). Moreover, the relative contribution of p66Shc to the hypertrophic process might increase as the magnitude of hypertrophy and oxidative stress increase, along with increased levels of p66Shc. Likewise, variability among individuals in the degree of LV hypertrophy may reflect differences in their expression levels of p66Shc.

The work of Graiani et al3 raises many other intriguing questions, such as whether Ang II activates p66Shc (assuming it does) indirectly via ROS derived from NAD(P)H oxidase activation or through a more direct route, whether p66Shc regulates NAD(P)H oxidase or xanthine oxidase, and the relative importance of endothelial versus cardiac myocyte p66Shc in cardiac remodeling. Given evidence suggesting that mPTP opening contributes to myocardial damage in ischemia-reperfusion,14 p66Shc is likely to play a role in myocardial infarction–induced damage to the heart as well. Evidence that preconditioning of human brain-derived SH-SY5Y cells by NOS1 activation blocked p66Shc expression and enhanced tolerance to oxidative stress lends support to this possibility.15 If p66Shc is bad for the heart, then why is this protein even expressed? The explanation offered by Graiani et al is that p66Shc may play a role in the normal apoptosis that occurs in the heart during development. In this context, increased p66Shc expression could be construed as another manifestation of the partial and futile return to a fetal phenotype observed in cardiac myocytes in response to stress. Reactivation of the local cardiac RAS, or at least of angiotensinogen expression, seems likely a part of this failed fetal reprogramming as well. In the developing heart, p66Shc and the local RAS might together help control cellular proliferation in part through apoptosis; however, re-expression of p66Shc and a local RAS would offer no such advantage in the mature heart populated mostly by terminally differentiated cardiac myocytes unable to re-enter the cell cycle but susceptible to apoptosis. The finding of a higher number of cycling cardiac myocytes in p66Shc−/− mice suggests that this protein may control proliferation by inducing terminal differentiation as well.

By linking Ang II–induced LV hypertrophy to a key aging-associated signaling mechanism, Graiani et al3 provide a possible explanation for the chronic and progressive nature of pathological cardiac remodeling and the transition to heart failure. However, as is true of any groundbreaking scientific work, the study of Graiani et al3 not only casts an old problem in a new light, but opens up a whole new world of possibilities. Targeting p66Shc may one day prove effective not only in treating LV hypertrophy and heart failure, but in keeping us truly young at heart.

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References

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