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EDITORIAL COMMENT

Autophagy Signaling and Oxidative Stress in Thoracic Aortic Aneurysms

Good, Bad, or Ugly?*

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Thoracic aortic aneurysms (TAA) are defined by a dilation of the aortic diameter. As the aortic diameter enlarges, so does the risk for dissection, a sequela that is often fatal if not treated emergently. Although the overall prevalence of TAA is quite low, there are select populations of patients who are significantly predisposed to this morbid and potentially lethal disease. Thoracic aneurysms exceeding 6 cm carry a yearly rupture rate of 7%, a growth rate of 0.1 cm/year, and a yearly mortality rate of 12% (1). Therefore, many patients with TAA are advised to undergo routine surveillance and elective surgical repair with an aortic diameter exceeding 5.5 cm (2).

Most TAA are thought of as a degenerative process and are typically associated with similar risk factors to that of atherosclerosis, including tobacco use, older age, male sex, family history, hypertension, hyperlipidemia, and diabetes. However, there is significant heterogeneity in the disease process with contribution from other risk factors such as the presence of a bicuspid aortic valve as well as connective tissue and syndromic diseases (eg, Marfan, Ehlers-Danlos, Loeys-Dietz, and Turner syndrome). Additionally, a subset of patients have isolated thoracic aneurysms that are either idiopathic or genetically inherited, often with variable penetrance. Overall, this heterogenous nature of TAA makes understanding the natural history and the decision of when to electively operate particularly challenging. The burden of this uncertainty is also shared by patients who are, too often, debilitated by the thoughts of an impending aortic repair surgery, which itself carries a 3%-5% mortality or with the risk of spontaneous aortic dissection and rupture. Therefore, a more complete understanding of the pathophysiology and mechanism is needed.

Aortic aneurysms are the result of the degeneration of vessel wall integrity in an otherwise high-pressure arterial system, which subsequently leads to vessel dilation and rupture. Vascular smooth muscle cells, which provide the structure and extracellular architecture to the tunica media and vessel wall, undergo apoptosis in the setting of a proinflammatory state. This involves oxidative stress, endothelial dysfunction, infiltration of macrophages and lymphocytes, and up-regulation of metalloproteinases resulting in extracellular matrix derangement (3). Although many of these features are shared between thoracic and abdominal aortic aneurysms, thoracic aneurysms have historically been more difficult to study because its disease pathogenesis is likely to involve multiple different pathways with 20% of thoracic aneurysms being attributable to genetic causes.

The current understanding of oxidative stress and autophagy has primarily been focused on abdominal aortic aneurysm. NADPH oxidase, a major source of reactive oxygen species, is up-regulated in patients' abdominal aortic aneurysms, and mice with loss of NADPH oxidase function have some element of protection from aneurysmal dilation (3). Similarly, vascular smooth muscle cell autophagy has primarily

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been studied in abdominal aneurysms. The genetic expression profile of patients' abdominal aortic aneurysms shows an increase in autophagy-related gene up-regulation. Furthermore, inhibition of autophagy in mice enhances aneurysmal growth, whereas activation of autophagy is protective (4).

In this issue of *JACC: Basic to Translational Science*, Irace et al (5) introduce autophagy and oxidative stress as potential mechanistic pathways in the development and progression of TAA. This observational study obtained tissue and serum samples from a total of 59 patients, 36 of which had TAA, and primarily examined biochemical and genetic expression markers of autophagy and oxidative stress. Notably, the investigators show elevated serum and tissue levels of Nox2 and hydrogen peroxide, which corresponded to reduced levels of nitric oxide. To investigate the role of autophagy, the investigators observed decreased levels of LC3, ATG5, and ATG7, strongly suggesting diminished autophagy activity in TAA. Interestingly, immunoblotting for LC3 showed reduction in both LC3-I and LC3-II, consistent with an upstream inhibitory regulator, either at the transcriptional or translational level. This may include master transcriptional regulations of autophagy such as TFEB or TFE3. Efforts were made to characterize the gene expression profile of several key autophagy players, but the investigators were limited by the difficulty in obtaining human samples large enough for effective comparison. Data were provided showing an increase in plasma levels of the autophagy chaperone p62/SQSTM1, which is suggestive of impaired autophagy because p62/SQSTM1 is also degraded in the autophagy-lysosome process. Future studies are needed to further understand these novel findings and to determine the mechanism of autophagy regulation, whether it be an upstream transcriptional mechanism or that of impaired autophagy flux.

The current study introduces new and important insights to the field and our understanding of thoracic aortic aneurysm pathogenesis. Importantly, it is the first study to our knowledge to show a decrease in autophagy in patients with nonsyndromic and nonruptured thoracic aneurysms. Although the study is largely observational, the findings are nonetheless thought-provoking and hypothesis-generating, which should lead to future studies focused on uncovering new mechanisms and possibly therapeutics. Although the pathophysiology of thoracic compared with abdominal aortic aneurysms is very different and more variable, we again see common shared pathways, including an overall down-regulation autophagy. In turn, this is also accompanied by increased oxidative stress, which may also act to promote autophagy as the investigators suggest. The mechanistic link between these pathways will need to be further investigated.

The exact role of autophagy, a process that removes and/or renews dysfunctional cellular components when working properly, in the pathophysiology of TAA and rupture is controversial—too much and it can induce cell death, too little and it is no longer protective, each of which can lead to pathology and cellular demise. What remains to be understood is the functional effects of autophagy in thoracic aneurysm formation. Furthermore, the role of autophagy is certainly not static. In contrast to the present study, Wang et al (6) observed increased expression of Beclin1 and LC3 in patients with thoracic aortic dissections and recapitulated these findings in mice with induced dissections. Results from the mouse experiments actually suggest that up-regulation in autophagy occurs just before the onset of aortic dissection. In this context, these data indicate the very dynamic nature of autophagy in the natural history of TAA progression, from a state of dilation to a state of dissections and rupture. The idea that autophagy signaling is dynamic and may phenotype switch at the time of or preceding the onset of dissection must be critically evaluated because it could serve as a surrogate biomarker of disease progression and may have substantial clinical implications in the prognosis, surveillance, and intervention of patients with TAA.

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