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Editorial commentary: Mitochondrial autophagy in cardiac aging is all fluxed up

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Functional decline towards cellular senescence presents a different set of problems in cardiomyocytes relative to proliferative cells. For example, senescence of proliferative cells serves an important tumor-suppressive role by promoting cell-cycle exit [1]. However, in non-proliferative and long-lived cardiomyocytes, senescence as a consequence of years of cumulative stress from aging may play a detrimental role and contribute to functional decline due to accumulation of damaged proteins, dysfunctional organelles, and DNA damage. As in most other tissues, cardiomyocyte senescence can be alleviated by enhancing removal of damaged components through upregulation of autophagy. Indeed, insufficiency of autophagy and lysosomal degradation is central to buildup of dysfunctional organelles and oxidative stress. The review by Shi et al. [2] presented in this issue of *Trends in Cardiovascular Medicine* examines the contribution of mitochondrial dysfunction to cardiomyocyte aging and the role of mitochondrial autophagy in maintaining cardiac function. As the field advances, cardiac aging appears inextricably tied to chronic autophagic insufficiency.

Mitophagy, the targeted removal of dysfunctional mitochondria by mitochondrial autophagy, occurs via multiple pathways. One mechanism discussed in detail by Shi et al. involves activation of the E3 ubiquitin ligase Parkin by the serine/threonine kinase PINK1, initiating ubiquitin-mediated targeting of mitochondria for autophagy. Given its reliance on mitochondria for oxidative metabolism, one might expect the heart to be highly reliant on this pathway for mitochondrial homeostasis, but mice with cardiomyocyte-specific deletion of Parkin have normal cardiac function [3]. The deleterious effects of Parkin deficiency only surface after severe injury, such as acute myocardial infarction [4]. Shi et al. discuss evidence that suggests involvement of the PINK1/Parkin pathway in delaying cardiomyocyte senescence. Recent data further support the role of Parkin in suppressing cardiac aging and provide a potential mechanism for Parkin deactivation in aging murine hearts. Parkin-mediated mitophagy undergoes an age-related decline in mouse hearts due to inhibition by p53, and cardiac aging is delayed by cardiomyocyte-specific overexpression of Parkin [5]. Although the significance of PINK1 and Parkin in normal maintenance of mitochondria appears minimal in murine hearts that live only a few short years, even a small impairment in this pathway may manifest as declining mitochondrial quality in patients after many

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years. What remains unclear is whether Parkin inhibition in aging heart can be compensated for by alternative mitophagy pathways discussed by Shi et al., and whether these findings have clinical relevance to elderly patients with heart failure.

In addition to the topic of mitochondrial targeting discussed by Shi et al., another facet of this field deserving of attention is how accumulation of damaged organelles may also result from defects in lysosome function. In considering mitochondrial maintenance by autophagy, one must always bear in mind the process as a whole—from formation of autophagosome and targeting of mitochondria, to lysosomal degradation. Flux through the autophagy pathway is the critical component, and inhibition at any point along the process is detrimental. Consequently, restoration of lysosome acidification in senescent fibroblasts has been shown to restore removal of dysfunctional mitochondria, resulting in metabolic reprogramming and alleviating senescence [6]. Another more standard approach, rapamycin inhibition of mTOR to stimulate autophagy, has widely been shown to delay senescence and promote longevity. Of note, rapamycin stimulates both formation of autophagosomes and lysosome maturation [7]—in essence enhancing overall flux. Improving targeting of mitochondria for autophagy in senescent cells is therefore only half of the solution. Enhancing lysosomal clearance is equally important, yet the interconnectedness of the two processes remains uncertain. Defects in lysosomal maturation may be an underappreciated cause of cardiomyocyte aging. Now that the foundations of understanding autophagosome and lysosome function have been established, future studies can begin to untangle the relative contributions of impaired mitochondrial targeting, inhibition of autophagosome formation, and defective lysosomal maturation in cardiac aging.

The challenge in designing therapeutics that target autophagy or mitophagy to delay cardiac aging or enhance resistance to injury is in finding a way to enhance the system without causing maladaptive effects. As discussed by Shi et al., over-activation of autophagy can be just as detrimental as insufficiency [2]. Although a magic bullet therapeutic that yields both not-too-much and not-too-little autophagy activation is unlikely, some promising results suggest that inhibition of upstream modulators of autophagy may provide just the right amount of fine tuning. For example, inhibition of histone deacetylases can either upregulate autophagy to protect the heart after acute myocardial infarction [8], or inhibit autophagy to prevent hypertrophy in response to pressure overload [9]. The differential effects on autophagy may be due to differences in duration or extent of stress, or may reflect the complexity of upstream sensors signaling changes in cellular energy and stress. Perhaps the best approach to designing therapeutics that alter autophagy is to try to more completely understand the intricacies controlling autophagy activation and lysosomal degradation, as well as the context of changes that occur to these processes with aging and environmental stressors. With a more comprehensive appreciation, novel therapeutic strategies to combat cardiac aging may be illuminated, and may allow for more individualized approaches to either augment autophagic flux or dampen maladaptive autophagy depending on the context and conditions.

A great deal of progress has been made over the last decade toward resolving the image of cardiac aging, and the central theme of insufficiency in autophagy and lysosome systems is coming in to focus. Although there is still much to learn, interest in the field is growing, and

the pace of new discoveries is accelerating. New technological advances and techniques discussed by Shi et al. allow for more in-depth analyses of autophagic flux, changes in cardiomyocyte metabolism, and the demands of an aging heart. Looking forward, the prospect of improving patient quality of life by delaying cardiomyocyte senescence through modulation of the autophagosomal clearance of dysfunctional cellular components still appears challenging, but is progressively becoming more attainable.

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