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EDITORIAL COMMENT

Autophagy and Myocardial Remodeling

Is it Autophagy or Autophagic Machinery and Signaling Pathways Regulating it?*

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Historically, the concept of autophagy started soon after the discovery of the lysosome in 1955 by Christian de Duve, who came up with the term "autophagy." Subsequent studies failed to yield any significant progress in our understanding of this process of degradation up until 1990s, when initial work in yeast led to the identification of autophagy-related genes (ATG) and their role in autophagosome membrane dynamics. Homologs of these ATG genes in yeast were found to be conserved in eukaryocytes, which indicated that autophagy is well conserved in higher species and mammalian cells. Over the last 10 years, investigators have made significant progress in understanding the molecular mechanisms of autophagy, as well as its physiological roles and relevance to human health and disease in multiple fields (e.g., cancer, microbial biogenesis, neurodegeneration, and the cardiovascular field). The papers by Ohsumi (1) and Klionsky (2) offer an in-depth overview of autophagy historical landmarks and the advances in our understanding of autophagy molecular biology.

Macroautophagy (hereafter referred as autophagy) is a vacuolar, self-digesting selective and nonselective process involved in the recycling of damaged organelles and aggregates of proteins or lipids by lysosomes (3). The efficiency of this process relies not only on autophagy induction, but also on a healthy, well-functioning lysosomal system. Therefore, an increase in the number of autophagosomes could potentially be explained by either autophagy induction and/or inefficient lysosomal degradation (**Figure 1**).

In the cardiovascular field, the role of autophagy has not been clearly defined: is it helpful or detrimental to the cardiomyocyte and to the heart as a whole? The initial concept was that too little or too much autophagy was considered maladaptive. However, conflicting evidence in recent literature suggests that this process can either be protective or maladaptive post-myocardial infarction (MI). For instance, the noncanonical activation of mitochondrial autophagy (mitophagy) by the autophagy receptor BNIP3 (4) has been shown to be maladaptive post-MI (5), whereas the canonical activation of autophagy has been shown to be protective (6,7). These differences between canonical and noncanonical autophagy activation could be explained by the fact that BNIP3, besides its role in mitophagy, promotes mitochondrial dysfunction, apoptosis, and myocardial remodeling via distinct mechanism(s), as previously shown (5,8–10). In this issue of the *Journal*, Sciarretta et al. (11) provide compelling evidence that trehalose, a natural disaccharide, reverses cardiac remodeling post-MI through the transcription factor EB (TFEB)–mediated activation of autophagy.

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As opposed to sucrose, another nonreducing disaccharide, trehalose reduced left ventricular (LV) dilatation, improved LV function, and attenuated apoptosis in mice with left anterior descending artery (LAD) ligation. This beneficial effect of trehalose was blunted when administered to beclin 1+/– heterozygous mice subjected to LAD ligation. The investigators concluded that the cardioprotective effect of trehalose occurred through the enhanced activation of autophagy post-MI, which led to enhanced mitochondrial quality control, an increase in

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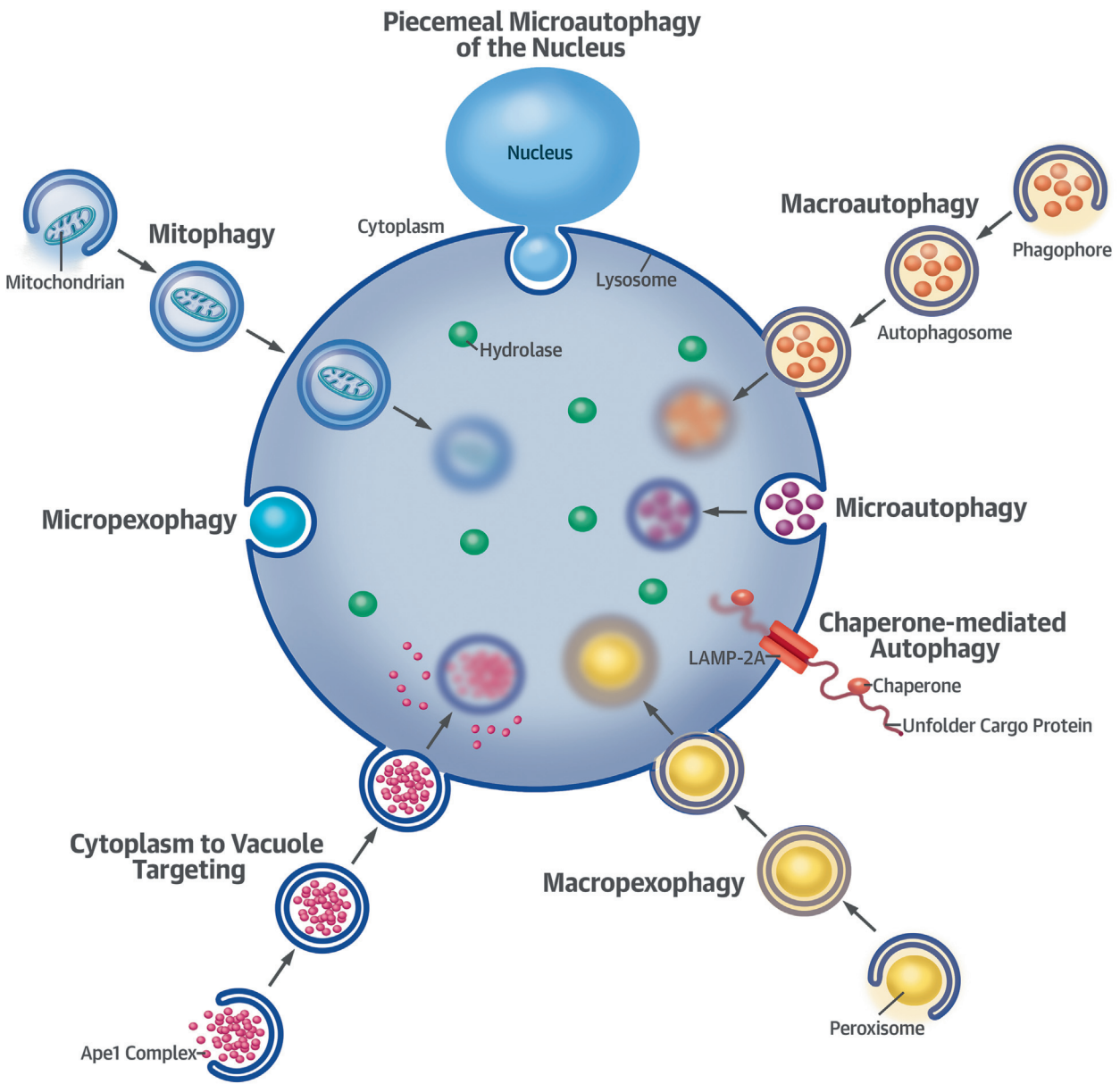
FIGURE 1 Selective and Nonselective Autophagy



Macroautophagy can be a selective or nonselective process depending on the cargo being selected for degradation. For instance, cytoplasmic protein aggregates are eliminated in a nonselective process through the formation of double-membrane autophagosomes via the canonical activation of autophagy in mammalian cells and the Cvt pathway in yeast, whereas mitochondrial autophagy (mitophagy) constitutes a selective form of macroautophagy. Atg32 in yeast (in concert with Atg8 and Atg11) and BNIP3 in mammalian cells (in concert with Atg8 and Parkin in cardiac myocytes) act as mitophagy-specific receptors and regulate selective degradation of mitochondria via the noncanonical activation of autophagy. Chaperone-mediated autophagy is another form of selective autophagy in which soluble unfolded proteins, carrying a specific motif, are tagged by chaperone proteins and targeted to the lysosome for degradation. Microautophagy is a nonselective form of autophagy that is not abundant in mammalian cells. Regardless of the form of autophagy, central to this process is the lysosome, which plays a fundamental role in this process of degradation. LAMP = lysosomal-associated membrane protein.

SERCA2a levels, and decreases in misfolded protein accumulation and apoptosis.

It was shown that TFEB up-regulates genes involved in lysosomal biogenesis (12). Trehalose enhanced lysosomal function, thereby adding further to its cardioprotective effect, which was attenuated with bafilomycin. This suggested a central role of the lysosomes in autophagy and cardioprotection. The