Autophagy represents an important biological process that contributes to cellular homeostasis. It is induced when the cell experiences stress, including nutrient and energy deprivation. For instance, the absence of nutrients and growth factors induces autophagy within minutes. Autophagy functions to protect cells against potential damage in association with exposure to stress, and thereby helps to defend cells and, subsequently, organs against dysfunction. There are multiple lines of evidence that autophagy has disease-preventing effects and, if disease still occurs, autophagy may limit disease severity. In addition, autophagy appears to play a key role in delaying the aging process.

How does autophagy mediate such disease-preventing and disease-limiting effects? For damage control, cells generate double-membrane vesicles, called autophagosomes, which sequester portions of the cytosol, including proteins and organelles. After fusion of an autophagosome with a lysosome, the sequestered cytosolic contents are degraded. This process allows cells to eliminate and recycle damaged proteins and organelles maintaining, at least temporarily, nutrient and energy homeostasis. The molecular details and regulation of autophagy are described in several recently published review articles.

There is accumulating evidence that autophagy plays a key role during cellular differentiation. The first observations in this area were made during terminal differentiation of reticulocytes into erythrocytes, a process that requires the elimination of mitochondria. Similarly, a critical role for autophagy has been demonstrated in B-cell, adipocyte, osteoclast, and keratinocyte differentiation processes, although not all studies used primary cells. It is assumed that whenever morphological and structural changes are required, autophagy is activated to perform the necessary remodeling process of the cell. Recently, autophagy was also shown to maintain adult stem cells, including hematopoietic, epidermal, and dermal stem cells. In hematopoietic stem cells, it was observed that defects in autophagy lead to increased intracellular levels of reactive oxygen species, which reduce the long-term self-renewal capacity. Moreover, several autophagy-regulating genes were shown to be critical for the maintenance of hematopoietic stem cells in vivo.

In this issue of Circulation Research, Zhang et al. provide support for the concept of autophagy-regulated differentiation by investigating molecular mechanisms by which fibroblast growth factor regulates cardiogenesis. They demonstrate that in the absence of fibroblast growth factor signaling, autophagy is increased in heart progenitor cells, a finding that is consistent with a growth factor withdrawal effect as discussed. Strikingly, however, induction of autophagy was followed by increased cardiomyocyte differentiation (Figure), suggesting that fibroblast growth factor prevents premature differentiation of cardiac progenitor cells, a process that leads to defective heart development during embryogenesis. Although it remains unclear whether the progenitor cells in this study represented adult stem cells or immature precursor cells, the data clearly show that autophagy is required for terminal cardiomyocyte differentiation. Because there is hope regarding the therapeutic application of stem cells in patients with ischemic and degenerative heart diseases, these findings are of great importance.

It should be noted that autophagy also plays a critical role in preventing heart disease beyond cardiomyocyte differentiation. For instance, defective autophagy is seen in some genetic causes of cardiomyopathy and skeletal myopathy. In these disorders, degeneration is linked to protein aggregation or muscle wasting. That autophagy is important for the protection of cardiomyocytes against proteotoxic stress has additionally been demonstrated in experimental mouse models of cardiac proteinopathy. Autophagy also plays a role in ischemic heart disease when ischemic stress induces autophagy in cardiomyocytes.
Taken together, autophagy is a key cellular catabolic pathway that serves to protect cells against stress, including a lack of nutrients or growth factors. Therefore, autophagy is induced under pathological conditions, including heart disease. However, autophagy also plays a homeostatic role under physiological conditions that prevent disease. In differentiation, autophagy is required for cellular remodeling. The fascinating studies of Zhang et al.20 extend this new concept to the heart, which requires autophagy control by fibroblast growth factor in heart progenitor cells for correct development.

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References


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