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Therapeutic targeting of autophagy in cardiovascular disease

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ABSTRACT

Autophagy is an evolutionarily ancient process of intracellular catabolism necessary to preserve cellular homeostasis in response to a wide variety of stresses. In the case of post-mitotic cells, where cell replacement is not an option, finely tuned quality control of cytoplasmic constituents and organelles is especially critical. And due to the ubiquitous and critical role of autophagic flux in the maintenance of cell health, it comes as little surprise that perturbation of the autophagic process is observed in multiple disease processes. A large body of preclinical evidence suggests that autophagy is a double-edged sword in cardiovascular disease, acting in either beneficial or maladaptive ways, depending on the context. In light of this, the autophagic machinery in cardiomyocytes and other cardiovascular cell types has been proposed as a potential therapeutic target. Here, we summarize current knowledge regarding the dual functions of autophagy in cardiovascular disease. We go on to analyze recent evidence suggesting that titration of autophagic flux holds potential as a novel treatment strategy.

Contents

1. Introduction

Despite robust successes in recent decades to tame the acutely lethal manifestations of heart disease, it continues to grow as the number one cause of death worldwide. Identification of novel mechanisms of disease pathogenesis, exploitation of novel drug targets, advances in clinical

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care with new drugs, devices, and systems, together have culminated in a dramatic 75% decrease in age-adjusted mortality in the past 50 years [1]. Notably, these advances have not touched all patient groups [2]. Further, the scourge of heart disease continues to expand as it evolves in new directions. To cite one area of challenge, the worldwide pandemic of obesity, and consequent metabolic syndrome and diabetes, has emerged as one of the most vexing problems in cardiovascular medicine going forward.

One of the prominent features of the cardiovascular system is its ability to adapt to a wide range of environmental stresses. The myocardium itself manifests robust plasticity in the setting of both physiological and pathological stimuli [3]. A few of the intracellular signaling pathways active within the cardiomyocyte have been exploited already to accomplish therapeutic gains. Adrenergic signaling and the renin-angiotensin-aldosterone (RAAS) system are two prominent examples. Others are currently being explored, including the handling of intracellular Ca^{2+}, nitric oxide- and protein kinase G (PKG)-dependent events, ion channels, and epigenetic control of gene expression. Further, adaptations within the cardiomyocyte typically involve multiple responses that encompass virtually all intracellular organelles [4].

Post-mitotic cells, such as cardiomyocytes and neurons, rely critically on the housekeeping mechanisms of proteostasis – regulation of protein synthesis, processing, and elimination – owing to the limited ability of these cells to divide. These cells must survive for many years, and they cannot simply be discarded when they become ill or dysfunctional. Among the critical mechanisms of cardiomyocyte proteostasis are recycling events governed by lysosomes. For several decades now, the role of these events in heart disease has been recognized and acknowledged [5]. Initial studies centered on lysosomal processing, but more recent efforts have focused on pathways that identify and target proteins and dysfunctional organelles, sequester them, and then deliver them as cargo to the lysosome. This process, termed autophagy, is ubiquitous and highly dynamic. Presently, our understanding of molecular events governing autophagic flux has emerged to the point that one could envision it as a relevant therapeutic target. Indeed, we and others, have suggested that the ubiquitous intracellular process of autophagy could be manipulated – titrated up or down – for therapeutic gain [6–8].

2. Autophagy basics

Autophagy is a highly conserved process of protein and organelle catabolism and recycling. Proteins and mitochondria targeted for elimination are sequestered and delivered to lysosomes for degradation, and the resulting molecular components – amino acids, lipids, nucleic acids, carbohydrates – are released into the cell to support metabolic demand. Under basal conditions, when nutrient supply is ample, autophagy is maintained at low levels. Critically, those low but finite levels of autophagic flux are required for cell survival; if autophagic activity is suppressed to zero, cellular demise ensues rapidly [9,10].

Autophagic flux is rapidly activated by stress impinging on the cell. The exemplar of autophagy-activating cellular stress is nutrient deprivation. Starvation or growth factor deprivation triggers a robust activation of autophagic recycling of intracellular contents to sustain metabolic demand and support macromolecule biosynthesis.

With respect to the cardiomyocyte, many other forms of stress trigger changes in autophagic flux, including a number of cues relevant to heart disease. Pressure stress, such as that occurring in hypertension or aortic stenosis, triggers significant increases in cardiomyocyte autophagy, attaining a new, steady-state level of flux after the cell has responded with hypertrophic growth [11]. Ischemia triggers a transient increase in autophagic flux, as the cell responds to the "starved" state of ischemia. Some evidence suggests, however, that with time that increase in autophagic flux declines, falling below the normal steady state level of flux [12]. One possible explanation, which remains to be tested, is that autophagic flux, even when up-regulated by stress, is insufficient to sustain the ATP requirements of the continuously contracting myocyte all while providing ATP sufficient to support autophagic flux. As such, ATP levels decline and cardioprotective autophagic flux declines.

Three types of autophagy have been recognized in mammalian cells: chaperone-mediated autophagy, microautophagy and macroautophagy [13]. Chaperone-mediated autophagy is a selective degradation of cytosolic proteins harboring the amino acid motif KFERQ which is recognized by chaperones to facilitate protein transport into the lysosome through the lysosomal membrane protein LAMP2A. In microautophagy, substrate uptake occurs directly by means of invagination of the lysosomal membrane [14]. The specific roles in cardiovascular disease of these two forms of autophagy, chaperone-mediated autophagy and microautophagy, have not been elucidated to date, despite recent studies that reported a critical role for these types of autophagy in regulating the activity of certain metabolic enzymes [15–17].

Macroautophagy, by contrast, is the most prevalent and most extensively characterized form of autophagy. Macroautophagy (hereafter termed autophagy) involves a series of defined steps governed by multiple proteins encoded by autophagy-related genes (ATGs). Together, these proteins orchestrate the formation of a double-membrane vesicle, called an autophagosome, which fuses with a lysosome to deliver cytoplasmic cargo for acid hydrolase-dependent degradation. Finally, those degraded molecular elements are released into the cell as building blocks to support energy homeostasis and macromolecule biosynthesis.

2.1. Overview of the autophagic cascade

Our understanding of cellular and molecular mechanisms governing autophagy in mammals has expanded greatly over the past several years and will be presented here only in brief overview. Readers are referred to recent comprehensive reviews [18–20]. Autophagosome nucleation commences with the activation of several ATG proteins; class III phosphoinositide 3-kinase (PI3K) family members (vacuolar protein sorting 34 — Vps34) and Beclin 1 recruit membranes from intracellular sources (e.g. endoplasmic reticulum, mitochondria, Golgi apparatus, plasma membrane) or by de novo synthesis [21]. ATG8 and microtubule-associated protein 1 light-chain 3 (LC3; also known as MAP1LC3) protein play a crucial role during the ensuing autophagosome elongation step. In addition, they recruit adaptor proteins, such as ubiquitin-binding protein p62 (also called sequestosome 1) that facilitates cargo recognition and loading into the autophagosome. The last step, fusion of the autophagosome filled with cytoplasmic material with a lysosome, is regulated by soluble NSF attachment protein receptor (SNARE) proteins. The resulting autolysosome is the site where cytoplasmic material is degraded by lysosomal hydrolases [22].

A complex upstream signaling network regulates the activity of the autophagic process. Growth factors, nutrients, cellular energy status, and pathologic stresses impact autophagy and are integrated by the kinase activity of mechanistic target of rapamycin (mTOR). mTOR complex 1 (mTORC1) inhibition by nutrient deprivation or by pharmacological suppression (rapamycin, Torin 1) results in the induction of autophagy [13], activating the upstream signaling molecules involved in autophagosome formation (PI3K-III, Vps34, Beclin 1, ATG6 and ATG 14). The master role of mTOR in regulating autophagy has been confirmed in the cardiovascular system by genetic silencing of mTOR in cardiomyocytes [23,24]. At a transcriptional level, autophagy can be positively regulated by the forkhead box O (FoxO) family of transcription factors [25], which are known to play an important role in various forms of cardiovascular disease [26].

3. Autophagy in cardiovascular biology: friend or foe?

Existence of autophagic activity in the cardiovascular system has been recognized for some years [27–30]. More recently, insights have emerged regarding the role of this process in normal cellular