Journal of Molecular and Cellular Cardiology 95 (2016) 31–41

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Nutrient-sensing mTORC1: Integration of metabolic and autophagic signals

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ARTICLE INFO

Article history:
Received 16 September 2015
Received in revised form 11 December 2015
Accepted 4 January 2016
Available online 7 January 2016

Keywords:
Autophagy
mTORC1
Amino acids
Glucose
Hypoxia
Metabolism

ABSTRACT

The ability of adult cardiomyocytes to regenerate is limited, and irreversible loss by cell death plays a crucial role in heart diseases. Autophagy is an evolutionarily conserved cellular catabolic process through which long-lived proteins and damaged organelles are targeted for lysosomal degradation. Autophagy is important in cardiac homeostasis and can serve as a protective mechanism by providing an energy source, especially in the face of sustained starvation. Cellular metabolism is closely associated with cell survival, and recent evidence suggests that metabolic and autophagic signaling pathways exhibit a high degree of crosstalk and are functionally interdependent. In this review, we discuss recent progress in our understanding of regulation of autophagy and its crosstalk with metabolic signaling, with a focus on the nutrient-sensing mTOR complex 1 (mTORC1) pathway.

Contents

Abbreviations: 2-DG, 2-deoxy-D-glucose; α KG, α-ketoglutarate; AMBRA1, autophagy/beclin 1 regulator 1; AMPK, AMP-activated protein kinase; Arf1, adenosine diphosphate ribosylation factor-1; Atg, autophagy-related; ATM, ataxia-telangiectasia mutated kinase; Bcl-2, B-cell lymphoma 2; Bnip3, BCL2/adenovirus E1B 19 kDa interacting protein 3; Bnip3L (NIX), BCL2/adenovirus E1B 19 kDa interacting protein 3-like; DAPK2, death-associated protein kinase 2; ERK, Extracellular signal-regulated kinase; FFAs, free fatty acids; G-6P, glucose-6-phosphate; GAP, GTPase-activating protein; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GDH, glutamate dehydrogenase; GEF, guanine nucleotide exchange factor; GLUT1, glucose transporter 1; GSK, glycogen synthesis kinase; HDAC, histone deacetylases; HEK, human embryonic kidney; HIF-1, hypoxia-inducible factor 1; HK, hexokinase; IGF, insulin-like growth factor; IKK, IkappaB kinase; I/R, ischemia/reperfusion; LKB1, liver kinase b1; LRS, leucyl-tRNA synthetase; MDM2, mouse double minute 2 homolog; MEFs, mouse embryonic fibroblasts; mitoHK, mitochondria associated hexokinase; mTOR, mechanistic (mammalian) target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; NF-κB, nuclear factor-κB; PI3K, phosphatidylinositol 3-kinase; Pkm2, pyruvate kinase muscle isozyme; PPARα, peroxisome proliferator-activated receptor-α; PRAS40, proline-rich Akt substrate 40 kDa; Rag, Ras-related small G-proteins; Raptor, regulatory-associated protein of mTOR; REDD1, regulated in DNA damage and development 1; Rheb, Ras homolog enriched in brain; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSK1, p90 ribosomal S6 kinase 1; siRNA, small interfering RNA; SLC38A9, number 9 of the solute carrier family 38; SQSTM1, sequestosome 1; TAK1, Transforming growth factor-β-activated kinase-1; TFEB, transcription factor EB; TG mice, transgenic mice; TXNIP, thioredoxin-interacting protein; TSC, tuberous sclerosis complex; ULK, unc51-like kinase; v-ATPase, vacuolar H^+-ATPase.

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http://dx.doi.org/10.1016/j.yjmcc.2016.01.005
0022-2828/

1. Introduction

The heart is a high-energy demanding organ as it is required to support the beat-to-beat contraction/relaxation cycle. Myocardial energy reserves are limited, just enough to fuel 10 heart beats. This is further decreased in the failing heart and thus, to meet high energy demand, the heart needs to constantly generate ATP by using free fatty acids (FFAs), glucose, lactate, ketone bodies and amino acids. Although the heart derives energy primarily from the oxidation of FFAs, the heart alters its energy substrate use to adapt to changes in nutrient availability. For example, glucose utilization is increased in response to feeding or hypoxia and the use of ketone bodies and amino acids is increased under starvation, providing metabolic flexibility to ensure cardiac energy homeostasis [1–3]. In response to ischemia, cellular uptake of metabolic substrates such as fatty acids, glucose and oxygen is diminished and sustained ischemia causes energy depletion and eventual cell death [4,5]. Since adult cardiomyocytes have limited ability to regenerate, cardiomyocyte death is a major cause of heart disease. High calorie diet induces metabolic syndrome in which hyperglycemia and hyperlipidemia mediate cardiotoxicity and heart dysfunction [1–3].

Macroautophagy (hereafter referred to as autophagy) is an intracellular recycling system whereby cytoplasmic components and damaged organelles undergo lysosomal degradation. Autophagy is activated in response to stresses including low nutrient availability, to provide an energy source [6–10]. Autophagy, which means "self-eating" in Greek, was first described by Christian De Duve [11], when he observed the sequestration of cytoplasmic components and organelles into newly emerging double-membrane vesicles called autophagosomes. Autophagy consists of several sequential steps — membrane nucleation, elongation, autophagosome formation, fusion with lysosomes and autophagolysosome formation [6–10,12]. Autophagy is a highly conserved process from yeast to humans, and is governed by a series of autophagy-related (Atg) proteins [12,13]. This self-digestion process was initially considered as a cell death mechanism (type II programmed cell death) and indeed excessive autophagy contributes to cardiovascular diseases including ischemia/reperfusion injury, although the functional role of autophagy in I/R injury is still under debate [14–20]. It has been shown that autophagy and autophagic flux are increased by I/R, mainly due to oxidative stress, and that excessive activation of autophagy induced by I/R exerts detrimental effects [14,21–23]. On the contrary, it has been demonstrated that autophagy induced by I/R plays a protective role in cardiomyocytes [15,22]. Furthermore, Ma et al. reported that autophagic flux is impaired during reperfusion in part by oxidative stress and this contributes to cardiomyocyte death in I/R injury [16] and it has been shown that enhanced autophagic flux mediates HDAC inhibitor-induced protective effects against I/R [17]. Thus further studies will be required to determine the regulation of autophagy by I/R and its functional role during reperfusion.

Nonetheless it has been established that autophagy plays an important role in cellular homeostasis under basal conditions as well as serves as a protective mechanism against ischemia and starvation. For instance, induction of autophagy plays a critical role in neonatal survival [24]. In the heart, deletion of Atg5, a protein required for autophagosome elongation and maturation, leads to cardiac hypertrophy, left ventricular dilation and contractile dysfunction indicating that autophagy in the heart under baseline conditions is a homeostatic mechanism [25,26]. Autophagy is rapidly induced in response to nutrient starvation or cellular stress, digesting cellular contents to produce amino acids and fatty acids to synthesize proteins or to produce ATP for cell survival [14,25,27–33]. It has been shown that inhibition of autophagy increases myocardial infarction induced by chronic ischemia while induction of autophagy is protective [14,31,33–37]. Removal of damaged mitochondria by autophagy (mitophagy) also provides cardioprotection by preventing mitochondria death pathways [38–42]. Autophagy is a highly regulated cellular process and it is important to develop a comprehensive understanding of the autophagic signaling complexity involved in maintaining the fine balance between adaptive and maladaptive autophagy. Induction of autophagy in response to nutrient starvation is established to be regulated by several protein kinases including AMPK, mTOR and ULK1. This review summarizes recent progress in our understanding of nutrient-sensing mechanisms that regulate mTOR complex 1 (mTORC1) and the initiation of autophagy.

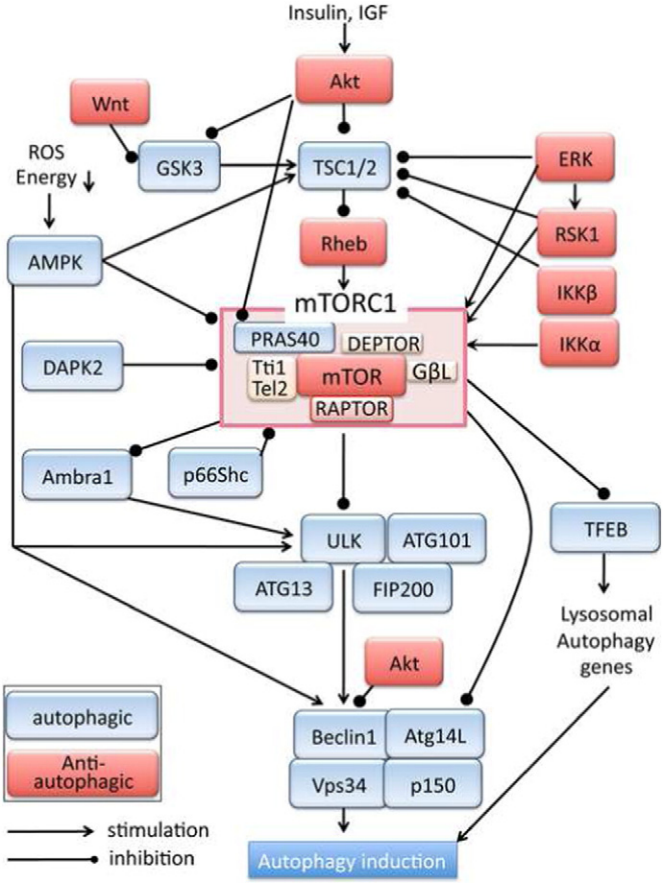

Fig. 1. mTORC1 pathway and autophagy.