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Nutrient-sensing mTORC1: integration of metabolic and autophagic signals

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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 evolutionary 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 complex1 (mTORC1) pathway.

Keywords

autophagy; mTORC1; amino acids; glucose; hypoxia; metabolism

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

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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 mediates 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, 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 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.

2. Biology of the mTOR pathway

2.1. mTORC1 negatively regulates autophagy

Mechanistic (mammalian) target of rapamycin (mTOR), a serine/threonine kinase, plays a major role in regulating cellular growth and metabolism. mTOR forms two distinct signaling complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [10, 43-45]. mTORC1 constitutes of mTOR, Raptor (regulatory-associated protein of mTOR), GβL/mLST8, Tti1/Tel2, DEPTOR (DEP domain-containing mTOR-interacting protein) and PRAS40 (proline-rich Akt substrate 40 kDa)(figure 1) [46-50]. Raptor is the defining component of mTORC1, acting as an essential scaffold for mTORC1-mediated phosphorylation of downstream target molecules such as 4E-BP1 and p70S6K [48, 51, 52]. PRAS40 is an inhibitory binding protein of mTORC1 [46, 47, 53, 54]. Under nutrient-rich growth conditions, mTORC1 supports cellular growth and suppresses autophagy. On the contrary, in response to nutrient starvation, mTORC1 is inhibited and autophagy is induced to provide energy source. Genetic or pharmacological inhibition of mTORC1 activity has been shown to increase autophagy and provide cardioprotection against stress [14, 31, 33-37, 54]. mTORC1 inhibits the autophagy-initiating molecular complex composed of ULK (Atg1), Atg13, Atg101 and FIP200 through phosphorylation of ULK (figure 1) [55-59]. In addition, ULK stability and activity is also inhibited by phosphorylation and inhibition of AMBRA1 (autophagy/beclin 1 regulator 1) mediated by mTORC1 [60]. ULK1 positively regulates activity of Vps34, a class III phosphatidylinositol 3-kinase (PI3K), which forms molecular complexes with several components of the autophagy machinery including Beclin1 and Atg14L and plays a critical role in vesicle nucleation in autophagy[61]. It has been shown that ULK1 phosphorylates Beclin1 to activate Vps34 activity, thus mTORC1-mediated inhibition of ULK1 results in inhibition of Vps34 activity and autophagy[62, 63]. Further, mTORC1 phosphorylates Atg14L and inhibits the lipid kinase activity of Vps34 [64]. mTORC1-induced inhibition of the Vps34 complex therefore serves as a brake on initiation of autophagy. In addition to directly acting on key components of the autophagic pathway, mTORC1 also transcriptionally inhibits autophagy by phosphorylating and inhibiting TFEB (transcription factor EB), a key regulator of lysosomal and autophagy genes [65, 66].

2.2. Upstream kinases of the mTORC1 pathway

2.2.1. Activation of mTORC1

2.2.1.1 Akt dependent: Growth factors such as IGF and insulin bind their receptors leading to activation of PI3K/Akt signaling. The mTORC1 pathway is one of the most established downstream targets of Akt. Akt phosphorylates and inhibits TSC (tuberous sclerosis)1/2 complex, a GTPase-activating protein (GAP) for the small G-protein Rheb (Ras homolog enriched in brain) [67-69]. Inhibition of TSC1/2 leads to an increase in GTP-bound active Rheb which is a direct activator of mTORC1 (figure 1). In cardiac-specific Rheb transgenic (TG) mice, mTORC1 activity is increased and autophagy induction is suppressed under ischemic conditions, and the hearts are susceptible to ischemic injury [35]. A study using

Rheb-deficient mice also suggest that the Rheb-mTORC1 pathway is indispensable for cardiac hypertrophic growth after early postnatal period [70]. Akt also phosphorylates PRAS40, an inhibitory binding protein of mTORC1, and dissociates PRAS40 from Raptor, leading to activation of mTORC1 [46, 47, 54]. Akt also phosphorylates and inhibits glycogen synthesis kinase (GSK) 3α/β, an inhibitor of mTORC1 activation, relieving the inhibitory effects of GSK3s on mTORC1 [71, 72]. Wnt has also been demonstrated to inhibit GSK3-dependent phosphorylation of TSC2, independent of the canonical β-catenin dependent regulation, and thereby stimulate the mTORC1 pathway [72]. In addition, Akt directly inhibits activity of pro-autophagic Vps34 complex through phosphorylation of Beclin1 [73]. Thus Akt plays a major role in activation of mTORC1 to inhibit autophagy. All three known Akt family members, Akt1, Akt2 and Akt3, are expressed in the heart, although Akt1 and Akt2 are the predominant isoforms [74, 75]. It has been suggested that Akt2 regulates cardiac metabolism and Akt1 regulates cardiac growth, but both confer cardioprotection [74-78]. mTORC1 activity is upregulated and autophagy is suppressed in the hearts of high-fat diet-induced obesity mice [35, 79]. Interestingly, Akt2, but not Akt1 nor Akt3 is upregulated by high-fat diet and plays a critical role in activation of mTORC1 as well as in regulation of autophagy flux [80], while caloric restriction compromises mTORC1 activity and increases autophagy in the heart [81, 82].

2.2.1.2. Akt independent: Independent of PI3K/Akt pathway, ERK (Extracellular signal-regulated kinase) activation is reported to inhibit TSC1/2 as well as activate Raptor [83, 84] resulting in mTORC1 activation. Downstream of ERK, p90 ribosomal S6 kinase 1 (RSK1) also inhibits TSC1/2 and activates Raptor to promote mTORC1 activity [86, 87]. ERK and RSK1 activation has been suggested to contribute to phenylephrine induced mTORC1 activation and protein synthesis in adult rat ventricular cardiomyocytes [85]. IKKβ, an upstream kinase of NF-κB signaling pathway, is also found to phosphorylate and inhibit TSC1 activating mTORC1 pathway in non-cardiomyocytes [86]. Importantly, IKKβ dependent mTORC1 activation is also reported in cardiomyocytes [87]. IKKα is also reported to be involved in activation of mTORC1 [88]. These results suggest the close interaction between mTORC1 and NF-κB signaling pathways [87].

2.2.2. Inhibition of mTORC1

2.2.2.1. AMPK dependent: AMP-activated protein kinase (AMPK) is a sensor for metabolic suppression. It is activated by reduction in cellular ATP levels (increase in AMP/ATP ratio) caused by glucose deprivation, or decrease in mitochondrial oxidative phosphorylation during metabolic suppression. A previous study demonstrated that induction of autophagy by *in vivo* ischemia is attenuated in AMPK dominant-negative TG mouse hearts [14]. AMPK negatively regulates the mTORC1 pathway at multiple steps [29, 58, 59, 89-91]. It phosphorylates and enhances TSC1/2 activity, and also phosphorylates Raptor inducing its binding to 14-3-3, both resulting in inhibition of mTORC1 activation [90, 91]. In addition, AMPK directly phosphorylates and inhibits ULK1 and Beclin1 to induce autophagy [59, 60, 95, 98]. Previous studies have demonstrated a central role for AMPK in the regulation of cardiac metabolism and autophagy. AMPK is activated in the hearts of caloric restriction mice and AMPK inhibition reverses mTORC1 inactivation and diminishes autophagy induction [92]. In high-fat diet induced obesity mice, cardiac AMPK

activity is decreased, resulting in activation of mTORC1 and inhibition of autophagy [79], suggesting the central role of AMPK in the regulation of cardiac metabolism and autophagy.

2.2.2.2. AMPK independent: Glycogen synthesis kinase (GSK) 3α/β was originally identified as a negative regulator of glycogen synthesis, but it is now recognized that GSK3 regulates many other cellular functions including apoptosis [93]. GSK3 is a constitutively active kinase and its activity is inhibited by Akt mediated phosphorylation, as mentioned in the previous section. GSK3 inhibits the mTOR pathway by phosphorylating TSC2 [72]. A study in the heart demonstrated that inhibition of GSK3β stimulated mTOR signaling and inhibited autophagy, resulting in increased cardiac damage after prolonged ischemia [94]. Chronic inhibition of GSK3α and resultant overactivation of mTORC1 induces suppression of autophagy, and this contributes to age-related pathologies including cardiac hypertrophy and contractile dysfunction [95]. Death-associated protein kinase 2 (DAPK2) is a calcium/calmodulin (CaM)-regulated serine/threonine kinase and is abundantly expressed in heart, lung, and skeletal muscle [96]. DAPK2 inhibits mTORC1 through phosphorylation of Raptor, and it has been shown to enhance autophagy induced by amino acid deprivation or increase in intracellular calcium by thapsigargin [97]. p66Shc is one of the *SHC1* gene encoding proteins and is known as an adaptor molecule. p66Shc has been shown to increase mitochondrial oxidative stress in different cells including cardiac myocytes [104-108] and p66Shc upregulation is also suggested to be associated with type 2 diabetes and obesity [98-101]. Recent studies demonstrate that p66Shc inhibits mTORC1 activity induced by serum or insulin, and thereby limits glucose uptake and metabolism [113] and that p66Shc positively regulates autophagy in human lung adenocarcinoma [102]. Although these studies have linked p66Shc to the regulation of mTORC1, energy metabolism and autophagy, the mechanism by which p66Shc inhibits mTORC1 has not been fully determined nor has it been examined whether mitochondrial distribution and resultant oxidative effect of p66Shc is involved in mTORC1 inhibition. It would be of interest to test the role of p66Shc in metabolism and autophagy in the heart.

3. Nutrient sensing regulation of mTORC1

3.1. Amino-acid dependent regulation of TORC1

3.1.1 mTORC1 activation at the lysosome—In 1977, Mortimore and Schworer demonstrated for the first time that amino acid depletion directly induces formation of autophagosomes in the perfused liver [103]. mTORC1 is a key component in amino acid deprivation-induced autophagy. Withdrawal of amino acids from culture media was shown to rapidly inactivate mTORC1 signaling in mammalian cell lines [104]. The amino acids, leucine, arginine and glutamine, demonstrate particular potency in mTORC1 activation [116-119]. It has not been fully determined whether and how amino acids regulate mTORC1 activity in the heart but many insights into amino acid-dependent regulation of mTORC1 have been derived from studies in non-cardiac cells. Interestingly, the amino acid-dependent regulation of mTORC1 is independent of PI3K/Akt and TSC pathway [104-106], suggesting the existing of alternative amino acid sensing mechanism.

Identification of the Rag subfamily of Ras-related small G-proteins (Rag GTPase) has led to improve understanding of amino acid-dependent regulation of mTORC1 (figure 2) [107, 108]. The Rag family proteins are comprised of four members (RagA, B, C and D) and form heterodimers, RagA/B and RagC/D. Rag proteins play a crucial role in the heart, as loss of RagA/B in cardiomyocytes results in hypertrophic cardiomyopathy [109]. While the Rag complexes do not directly activate mTORC1 kinase activity, they mediate mTORC1 translocation to the lysosome in response to amino acid stimulation [110]. Binding of the Rag complexes to the lysosomal membrane is aided by Ragulator (LAMPTOR1-3 complex) which resides on the lysosome. Ragulator functions as a guanine nucleotide exchange factor (GEF) to activate Rag GTPases leading to enhanced binding of the Rag complexes to mTORC1[111]. Thus the Ragulator-Rag complex serves as a docking site for mTORC1 at lysosomes in response to amino acids (figure 2).

p62, also called sequestosome 1(SQSTM1), is an adaptor protein involved in the regulation of diverse cellular functions through its multi-domain structure. p62 has been reported to regulate mTORC1 activity in response to amino acids, but not to insulin [127]. p62 binds the Rag GTPases and Raptor and this binding is independent of Ragulator, providing an alternative docking site at the lysosome (figure 2) [127]. Rheb, a direct activator of mTORC1, is reported to localize on multiple endomembrane compartments including the lysosome [108, 112]. Thus the recruitment of mTORC1 to the lysosome brings it into proximity with Rheb, resulting in mTORC1 activation [108, 112]. On the contrary, upon amino acid removal, mTORC1 is released from the lysosome, causing it to become cytoplasmic and inactive[129, 130]. This dissociation and inactivation of mTORC1 is positively regulated by the TSC complex translocation to the lysosome induced by amino acid removal. [129, 130].

3.1.2 Amino acid sensing mechanisms—A limited RNAi screen for lysosomal proteins required for mTORC1 activation by amino acids identified vacuolar H^+-ATPase (v-ATPase) as a potential amino acid sensing protein [113]. In this paper, it is shown that v-ATPase interacts with and activates Ragulator in response to accumulation of amino acids in the lysosomal lumen, and is needed for the activation of the Rag GTPases and subsequent mTORC1 recruitment to the lysosome. ATP hydrolysis and associated rotation of the v-ATPase, but not the lysosomal proton gradient, appear to be essential for activation of the Ragulator mediated by the v-ATPase. Two recent independent studies have further identified SLC38A9 (number 9 of the solute carrier family 38) as a novel physical and functional component of the lysosomal machinery that controls mTORC1 activity in response to amino acid [114, 115]. SLC38A9 transports amino acids across the lysosomal membrane and binds the Ragulator-Rag GTPases complex in an amino acid-sensitive manner to stimulate mTORC1 activity [114, 115]. These studies also demonstrated the differential regulation of mTORC1 by specific amino acids. Wang et al., showed that SLC38A9 is an arginine transporter and responsible for arginine- but not leucine-induced mTORC1 activation[114]. Rebsamen et al., demonstrated that SLC38A9 has an ability to transport glutamine as well as arginine [115]. Leucyl-tRNA synthetase (LRS), which catalyzes the attachment of leucine to its tRNA, has been shown to directly bind to and regulate RagD, stimulating mTORC1

activity [116]. This non-canonical role of LRS might provide a novel mechanism for leucine-selective mTORC1 regulation.

Although deletion of RagA and RagB in cardiomyocytes results in hypertrophic cardiomyopathy, mTORC1 activity was not substantially impaired in the heart [109], implying the existence of Rag GTPase-independent mechanism for mTORC1 activation. Indeed, a mechanism for amino acid-dependent but Rag-Ragulator-independent mTORC1 activation at the lysosome has recently been discovered [117]. In RagA/B-deficient cells, leucine failed to activate mTORC1, but the ability of glutamine to activate mTORC1 was preserved, suggesting that RagA/B is required for mTORC1 activation by leucine but not glutamine. The study further demonstrated that glutamine-induced mTORC1 recruitment to the lysosome and subsequent activation required v-ATPase and adenosine diphosphate ribosylation factor-1 (Arf1), a key regulator of intracellular vesicle trafficking [117]. These studies show that mTORC1 is differentially regulated by specificamino acids, but there might be an interplay between amino acids. Glutaminolysis, the process by which glutamine is metabolized to glutamate and subsequently to α-ketoglutarate (αKG), is shown to be sufficient to activate mTORC1 signaling through αKG-dependent activation of RagGTPase [118, 119]. The conversion of glutamate to αKG is activated by glutamate dehydrogenase (GDH). Leucine is an allosteric activator of GDH [120], providing a mechanistic link between leucine and glutamine in glutaminolysis-dependent regulation of mTORC1 activation.

3.2. Glucose-dependent regulation of mTORC1

3.2.1. AMPK dependent and independent mechanism—Glucose is an essential energy source and glucose deprivation induces autophagy in many different cell types, which is accompanied with decreased activity of mTORC1. AMPK, activated by reduction of cellular ATP levels, is established to inhibit mTORC1 and induce autophagy in the absence of glucose. Accumulating evidence, however, has revealed that AMPK-independent pathways also regulate mTORC1 activity in the absence of glucose. mTORC1 activity is decreased in response to glucose deprivation in AMPK-α1 and -α2 double knockout MEFs [24, 121]. Similarly mTORC1 is inhibited in TSC1 or TSC2 knockout MEFs subjected to glucose deprivation [119, 138, 139]. These results suggest that mTORC1 inhibition induced by glucose deprivation can take place in an AMPK and TSC1/2 independent manner. It has recently become clear that cells directly sense intracellular glucose levels to regulate the mTORC1 pathway (figure 3). As mentioned above, lysosomes are recognized as an mTORC1 activation site, and it has been shown that glucose deprivation causes mTORC1 to be diffusely distributed in the cytosol in HEK-293T cells [24]. Conversely when mTORC1 is tethered at the lysosome through constitutive activation of RagA expression, glucose deprivation fails to decrease mTORC1 activity even though AMPK is activated [24]. These recent findings suggest that RagGTPases, in addition to their established role in amino acid sensing, participates in the direct sensing of glucose availability to recruit mTORC1 to the lysosome to be activated.

3.2.2. Glucose-sensing mechanisms—mTOR activation induced by insulin has been shown to require glucose in the heart, suggesting that glucose metabolism has a regulatory

role in mTORC1 activation [122, 123]. Glucose-dependent mTORC1 activation is independent of the hexosamine biosynthetic pathway, AMPK, and the pentose phosphate pathway suggesting the contribution of glycolysis to this response. An increase in work load is associated with glucose-6-phosphate (G-6P) accumulation and mTORC1 activation in the heart [122, 123]. The first step of glycolysis is mediated by hexokinases (HKs), which phosphorylate glucose to produce G-6P [124, 125]. Hexokinase-2 (HK2) is the predominant isoform in insulin-sensitive tissues such as skeletal muscle, adipose tissues and heart. HK2 is also upregulated in many types of tumors, associated with the Warburg effect, enhanced aerobic glycolysis[124-126]. In addition to the established role of HK2 in glucose metabolism, HK2 also confers cellular protection. Overexpression of HK2 provides cellular protection against oxidative stress in cardiomyocytes[127-129] and also prevents maladaptive hypertrophy o the heart *in vivo* [127]. Conversely, heterozygotic HK2 knockout hearts are more susceptible to ischemia/reperfusion injury as well as pressure overload[130, 131]. Studies in the 1960s identified that a significant fraction of total cellular HK2 in the heart is associated with mitochondria via its N-terminal region[132-135]. Mitochondria-associated HKs (mitoHKs) can exert protective effects on mitochondria to prevent mitochondrial death pathways[124, 128, 136-139]. We previously demonstrated that mitoHK2 binding is enhanced by Akt-mediated phosphorylation of HK2 at Thr473, contributing Akt-mediated mitochondria protection [128, 138, 140].

We recently reported that HK2 functions as a molecular switch from glycolysis to autophagy through regulation of mTORC1 (figure 3) [141]. Studying the protective effect of HK2 in cardiomyocytes, we observed that 2-deoxy-D-glucose (2-DG), a glucose analogue that is phosphorylated by HKs but not metabolized further, attenuates decrease in mTORC1 activity, inhibits induction of autophagy, and increases cell death induced by glucose deprivation. This suggests a regulatory role of HK2 in mTORC1 inhibition and protective autophagy in the absence of glucose. HK2 knockdown by siRNA-mediated gene silencing also attenuates mTORC1 suppression and inhibits induction of autophagy while HK2 overexpression potentiates the responses in the absence of glucose [141]. These observations suggest that HK2 acts to suppress mTORC1 and thereby stimulates autophagy in response to its substrate (glucose) withdrawal. We demonstrated that HK2 binds to mTORC1 through Raptor and this binding is largely increased by glucose withdrawal in the heart. We identified that HK2 (but not HK1, which is ubiquitously expressed) contains a TOS (mTOR signaling) motif, which is present in p70S6K and 4E-BP1 (mTORC1 substrates), and through which these substrates bind to Raptor and subsequently undergo phosphorylation by mTOR [52, 142]. A TOS motif-deficient mutant of HK2 fails to bind and inhibit mTORC1. Thus HK2 interacts with mTORC1 via binding to Raptor through its TOS motif, functioning as a decoy substrate. Interestingly, the switch between the glycolytic and autophagic effects of HK2 appears to be regulated by G-6P, a product of HK2 activity [141]. Therefore, under low glucose conditions, decreased levels of G-6P induces HK2 interaction with mTORC1 to facilitate autophagy, while under glucose-rich conditions, HK2 produces G-6P which in turn inhibits HK2 binding to mTORC1 to support cellular metabolism and growth (figure 3). It would be of interest to determine whether HK2 binding to mTORC1 prevents localization of mTORC1 to the lysosome and its subsequent activation.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) catalyzes the conversion of glyceraldehyde 3-phosphate (GAP) to D-glycerate 1,3-bisphosphate, the sixth step of glycolysis. GAPDH has also been implicated in several non-glycolytic cellular functions including roles in the nucleus [143]. The role of GAPDH in regulation of autophagy was first described as a potential mechanism by which GAPDH expression confers cell survival against caspase-independent cell death [144]. A later study in the brain identified GAPDH as a Rheb binding protein [145]. The binding of GAPDH to Rheb is increased by decreasing glucose concentration, leading to dissociation of mTORC1 from Rheb and thus inhibition of mTORC1. This inhibitory binding is preserved in TSC1 KO and AMPK silenced cells, but prevented by binding of GAP to GAPDH (ie., substrate binding)(figure 3). This inhibitory binding of GAPDH to Rheb is also suggested to contribute to GLUT1 upregulation-induced activation of mTORC1 [146]. Interestingly, GAPDH is also implicated in regulation of mitochondria specific autophagy in cardiomyocytes [147].

Taken together these findings suggest that glycolytic flux regulates mTORC1 activity to coordinate cellular metabolic status with autophagy development. Conversely, mTORC1 positively regulates glycolysis. For instance, an unbiased genomic, metabolic and bioinformatic study in TSC1/2 deficient cells reveals that mTORC1 signaling activates the genes encoding nearly every step of glycolysis [148]. This is also supported by other studies using TSC1/2 deficient cells demonstrating that mTORC1 activation is sufficient to upregulate GLUT1, HK2, GAPDH, pyruvate kinase muscle isozyme (Pkm2) and lactate gene expression [149, 150]. A muscle-specific mTOR conditional knockout mouse also showed significantly decreased expressions of GLUT4, HK2 and Pkm2 in the heart [151] (figure3). Thus mTORC1 activation enhances glycolysis to support cell growth under nutrient rich conditions, while it is negatively regulated by glycolytic molecules under starvation to ensure cellular energy homeostasis through autophagy, suggesting the intrinsic connection between glycolytic and mTORC1/autophagy pathways.

Alternations in cardiac energy metabolism has been suggested to contribute to cardiac disease. In diabetes, there is a shift in cardiac metabolism away from glucose metabolism towards fatty acid metabolism, which is opposite to the changes observed in heart failure induced by pressure overload [152-155]. The metabolic shift in diabetes, especially in type-1 diabetes (insulin-sensitive diabetes), is associated with significant decrease in HK2 [156-159] and insulin treatment restores HK2 levels supporting the role of Akt/mTORC1 pathway in expression of HK2 [156-158, 160]. Hyperglycemia is also reported to decrease GAPDH expression in endothelial cells [161]. In general, autophagy is decreased in type-1 diabetes thus it would be of interest to determine whether these decreases in HK2 and GAPDH expression are causally related to suppression of autophagy.

3.3. Oxygen dependent regulation of mTORC1

3.3.1. HIF-1—Autophagy regulation mediated by oxygen-sensing signaling pathways has also been reported (figure 4). Hypoxia-inducible factor 1 (HIF-1) is a transcriptional factor, and at low levels of oxygen, degradation of the α-subunit of HIF-1 (HIF-1 α) is inhibited, leading to the activation of a transcriptional program to metabolically adapt to the lack of oxygen [162]. Expression of Bnip3, a mitochondrial pro-apoptotic Bcl-2 protein, is induced

by hypoxia through HIF-1, contributing to cardiac damage induced by ischemic stress [163-167]. It has been demonstrated that Bnip3 regulates not only cardiac apoptosis but also mitophagy [168, 169]. Interestingly, Bnip3 negatively regulates mTORC1 pathway. A yeast two-hybrid assay identified Bnip3 as a Rheb-binding protein and the binding decreases GTP-bound Rheb levels, playing an important role in hypoxia-induced mTOR inhibition [170]. It has yet to be determined if Bnip3 inhibits the mTOR pathway to regulate autophagy in the heart. In addition to regulation of mTORC1, Bnip3 and Bnip3L (NIX) have been described to inhibit binding of Bcl-2 to Beclin1, releasing the Bcl-2 dependent inhibition of Beclin1, to drive autophagy [171]. Thus Bnip3 may regulate autophagy at multiple steps.

REDD1 (regulated in DNA damage and development 1, also known as RTP801, DDIT4 and Dig2) is a 25 kDa protein which is ubiquitously expressed in various tissues, and is highly induced by hypoxia. The expression of REDD1 is regulated by several transcription factors including HIF-1 and ATF4 (a regulator of ER stress responses), as well as by post-translational regulation (through ubiquitin-proteasome system) [172, 173]. Previous studies demonstrated that REDD1 is rapidly induced by stress and subsequently inhibits mTORC1 activation [174-176]. REDD1 inhibits the interaction of TSC2 with 14-3-3, resulting in greater TSC2 dependent inhibition of mTORC1 [177]. Although the role of REDD1 in the heart has not been fully examined, REDD1 knockdown impairs autophagy in hypertrophied cardiomyocytes [178]. In addition to mTORC1 regulation, a recent study discovered that REDD1 forms a complex with TXNIP, a pro-oxidant protein, and induces ROS, suppresses ATG4B activity and activates autophagy [179].

3.3.2. p53—Another intriguing regulatory mechanism of mTORC1 pathway was obtained from studies of p53, a key tumor suppressor protein. Under physiological conditions, p53 expression is inhibited by MDM2-dependent proteasomal degradation while its expression is increased in response to stress including hypoxia. In addition to the established role of p53 in cell death, it is becoming increasingly recognized that basal or low levels of p53 expression plays an important role in the maintenance of redox state as well as energy homeostasis [180-186]. p53 transcriptionally regulates expression of various molecules which inhibit mTORC1 activity, including AMPK, TSC2 as well as sestrins [187-190]. Sestrin1 and sestrin2 inhibit mTORC1 through activation of AMPK and are involved in the induction of autophagy in tumor cells [188-190]. Intriguingly sestrin2 is expressed in the heart and the expression is increased in response to *in vivo* ischemia [191]. Furthermore, sestrin2 KO hearts show impaired activation of AMPK and increased cardiac damage induced by ischemia/reperfusion [191]. Thus sestin2 may provide cardioprotection through inhibition of mTORC1 and activation of autophagy.

3.3.3. Oxidative stress dependent mechanism—Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed by the incomplete reduction of oxygen. It has been demonstrated that the levels of ROS/RNS are increased by starvation or hypoxia, and play a regulatory role in the induction of autophagy [192-194]. For example, ROS, specifically hydrogen peroxide (H_2O_2), directly activate autophagy during nutrient starvation by oxidization and inhibition of ATG4 and subsequent increase in LC3 lipidation [192]. Activation of AMPK by H_2O_2, superoxide anion (O_2^-) or peroxynitrite ($ONOO^-$) has been

demonstrated in non-cardiac [195-198] and cardiac cells [199, 200], suggesting a redox dependent regulation of AMPK (figure 4). Mitochondria are an important source of ROS (H_2O_2 and O_2^-) which can interact with NO to generate $ONOO^-$ and it has been demonstrated that mitochondria-derived ROS are critical in AMPK activation and autophagy under stress conditions [195, 197, 201-203]. ROS and RNS positively regulate AMPK activity through direct and indirect mechanisms. H_2O_2 results in oxidative modification of AMPKα subunit to increase its catalytic activity [198, 204], and $ONOO^-$ induces activation of liver kinase B1 (LKB1), an upstream kinase of AMPK [200, 205]. Recent studies in non-cardiac cells also suggest that ataxia-telangiectasia mutated (ATM) kinase, best known for its role in nuclear DNA damage, functions as a redox sensor in the cytosol to activate AMPK through LKB1, stimulating autophagy [206, 207]. In the heart, ATM has been shown to play a regulatory role in cardiac remodeling [208]. However, the role of ATM in regulating AMPK, mTORC1 and autophagy in the heart has yet to be determined.

3.4. Fatty acid and mTORC1/autophagy

FFAs are the major fuel for the heart. However FFAs-sensing mechanisms in direct regulation of mTORC1 and autophagy in the heart has not been demonstrated. FFAs are transported into cardiomyocytes and esterified to fatty acyl CoA by fatty acyl CoA synthase. Fatty acyl CoA is then transported to mitochondria for beta-oxidation to produce ATP or converted to triglycerides (TGs) and stored in lipid droplets. In pancreatic β-cells, high concentration of palmitic acid activates mTOR, decreases autophagic flux and induces cell death, suggesting the involvement of impaired autophagy in lipotoxicity [209]. In the heart, loss of long-chain acyl-CoA synthase isoform 1 reduces FFA oxidation by >90% and increases glucose usage 8-fold to compensate, which in turn activates mTORC1 and suppresses autophagy [210]. The observations support the reciprocal relationship between FFAs and glucose oxidation (Randle Cycle) [211] as well as the glucose-sensing autophagy inhibition described above. During starvation, FFAs are released from TGs by the process of lipolysis. mTORC1-autophagy pathway is shown to be involved in lipid breakdown by degradation of lipid droplets in hepatocytes [212]. A recent study in liver also showed that TAK1-dependent AMPK activation induced by starvation inactivates mTORC1 resulting in induction of autophagy, as well as activation of PPARα, a key transcription factor in regulation of FFA oxidation, facilitating lipid breakdown [213]. A critical role of autophagy in lipolysis is supported by a study in adipocytes demonstrating that ULK1 and ULK2 enhance lipid breakdown by inducing autophagy[214]. Interestingly, ULK1 and ULK2 have distinct non-autophagic functions in regulation of lipid metabolism; ULK1 stimulates FFA oxidation and inhibits FFA uptake while ULK2 has opposing effects [214]. A recent seminal study in mouse embryonic fibroblasts provides new insight into the role of autophagy in regulation of FFAs trafficking to mitochondria during starvation. Rambold et al., demonstrated that autophagy breaks down cellular membranes to supply FFAs to lipid droplets from where FFAs generated by lipolysis are further transferred into mitochondria to produce ATP. This study also demonstrated that mitochondrial fusion and resultant continuous mitochondrial network are required to distribute and efficiently oxidize transferred FFAs [215]. These recent findings indicate that autophagy plays a crucial role in lipid metabolism and FFAs utilization under nutrient starvation to preserve cellular energy

homeostasis and thus it would be of interest to determine if these mechanisms operate in the heart.

Conclusion remark

We have described some recent advances in our understanding of nutrient sensing mechanisms in the regulation of mTORC1 and autophagy. Autophagy is a key cellular catabolic process in which mTORC1 serves as a convergent point in nutrient-sensing pathways. However, the physiological and pathophysiological role and significance of the nutrient-sensing regulation of mTORC1 signaling pathways in the heart need to be further investigated.

Although direct inhibition of mTORC1 facilitates autophagy which could confer cardiac protection, mTORC1 also regulates a myriad of cellular functions in other organs. For example, mTORC1 deficiency leads to skeletal muscle dystrophy in mice [216]. From a whole-body metabolic perspective, mTORC1 positively regulates β cell size and proliferation and insulin secretion in the pancreas, and inhibits ketogenesis and PPARα activity in the liver [217, 218]. Thus global inhibition of mTORC1 may result in widespread systemic disturbances and have a detrimental outcome. It will be important to identify the regulatory molecules, particularly heart-specific molecules, that selectively modulate the mTORC1 pathway to confer cardioprotective autophagy as these would provide potential therapeutic targets that can be explored in the treatment of cardiovascular diseases.

It is intriguing that autophagy is activated in response to nutrient deprivation to provide metabolic defense, and this is tightly regulated by diverse metabolic molecules. Alternation in energy resources and metabolism is an important factor in the progression of cardiac disease. Understanding the complexity of the crosstalk between autophagic and metabolic pathways during the progression of cardiac disease will aid in the development of therapeutic strategies to prevent or treat heart failure.

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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 19kDa Interacting Protein 3
Bnip3L (NIX)	BCL2/Adenovirus E1B 19kDa 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

Highlights

- Autophagy is important for maintaining cardiac homeostasis.
- mTORC1 plays a major role in regulating cellular growth and metabolism and inhibits autophagy
- mTORC1 serves as a convergent point in nutrient-sensing pathways.

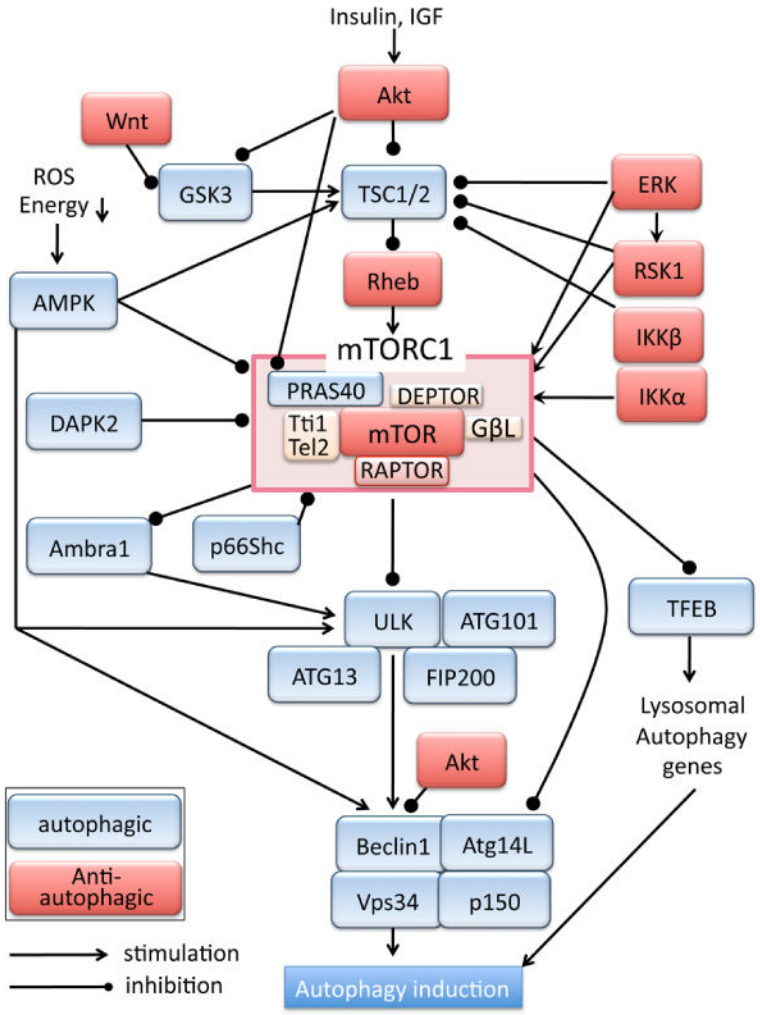

Figure 1. mTORC1 pathway and autophagy

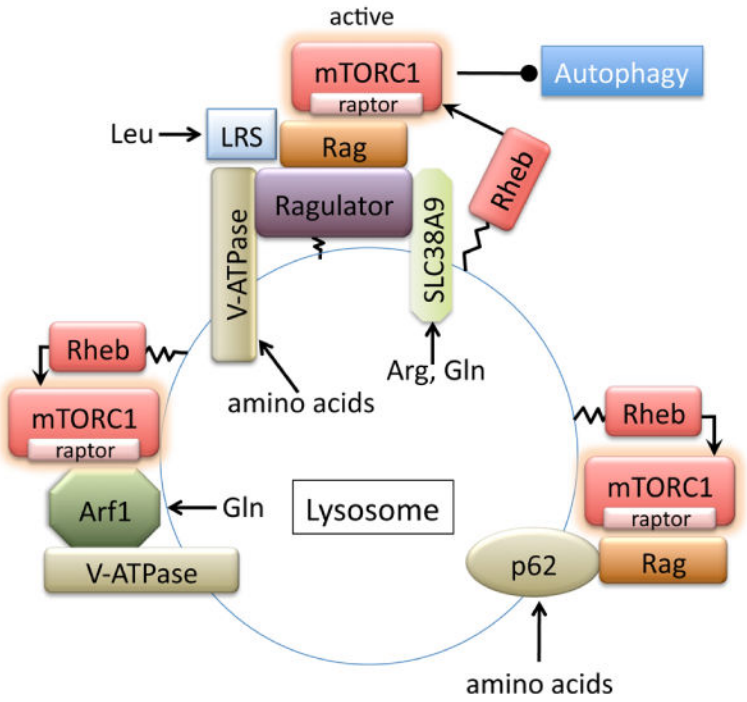

Figure 2. Amino acid-dependent regulation of mTORC1

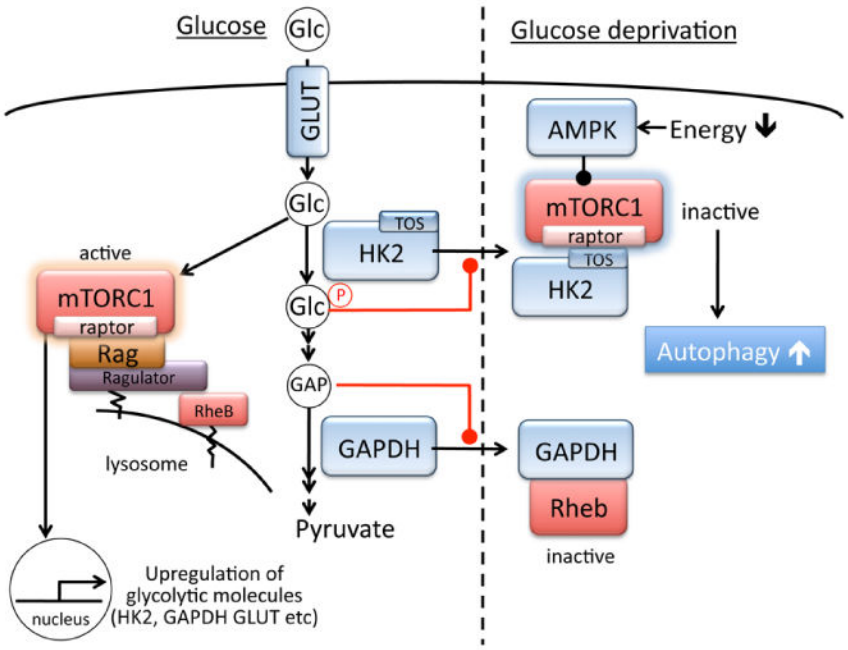

Figure 3. Glucose-dependent regulation of mTORC1

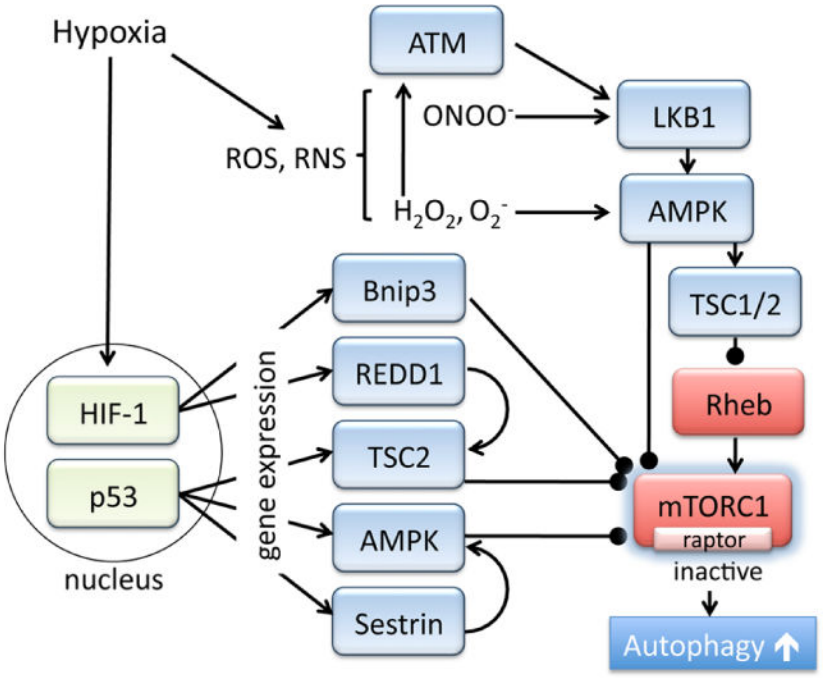

Figure 4. Oxygen-dependent and redox dependent regulation of mTORC1