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mTOR Signaling in Cardiac Physiology and Disease:

Sciarretta et al. mTOR signaling in the cardiovascular system

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Abstract

The protein kinase mTOR (Mammalian or Mechanistic Target of Rapamycin) is an atypical serine/threonine kinase that exerts its main cellular functions by interacting with specific adaptor proteins to form two different multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 regulates protein synthesis, cell growth and proliferation, autophagy, cell metabolism and stress responses, whereas mTORC2 appears to regulate cell survival and polarity.

The mTOR pathway plays a key regulatory function in cardiovascular physiology and pathology. However, the majority of the information available about mTOR function in the cardiovascular system is related to the role of mTORC1 in the unstressed and stressed heart. mTORC1 is required for embryonic cardiovascular development and for postnatal maintenance of cardiac structure and function. In addition, mTORC1 is necessary for cardiac adaptation to pressure overload and development of compensatory hypertrophy. However, partial and selective pharmacologic and genetic inhibition of mTORC1 was shown to extend life span in mammals, reduce pathological hypertrophy and heart failure caused by increased load or genetic cardiomyopathies, reduce myocardial damage after acute and chronic myocardial infarction and reduce cardiac derangements caused by metabolic disorders. The optimal therapeutic strategy to target mTORC1 and increase cardioprotection is under deep investigation.

This article reviews the information available regarding the effects exerted by mTOR signaling in cardiovascular physiology and pathological states.

Keywords

mTOR signaling; mTORC1; rapamycin; hypertrophy; ischemia; metabolism; heart

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Disclosures
None.

Introduction

The protein kinase mTOR was purified and characterized for the first time in mammalian cells in the independent works conducted by Eric Brown[1], David Sabatini[2] and Candace Sabers[3] published in 1994 and 1995. mTOR is an atypical serine/threonine kinase that exerts its main cellular functions by interacting with specific adaptor proteins to form two distinct multiprotein complexes, mTORC1 and mTORC2[4-8]. mTOR signaling plays a key role in the regulation of cell homeostasis and stress responses. mTORC1 is a master regulator of protein synthesis, cell growth and proliferation, ribosomal and mitochondrial biogenesis, autophagy and metabolism. In addition, mTORC1 inhibition during stress is an adaptive response that promotes upregulation of stress-responsive mechanisms. On the other hand, mTORC2 appears to regulate cell survival and polarity[4-8] (Figure 1).

Studies of animal models with loss of function of the components of the mTOR complexes have indicated that mTOR is involved in the regulation of embryonic cardiovascular development and in the control of vital cellular processes necessary for normal postnatal growth and maintenance of cardiac function. Cardiac deletion of mTOR is associated with a high rate of embryonic lethality, and cardiac disruption of the components of mTORC1 is associated with cardiac dilation, dysfunction, apoptosis, mitochondrial and metabolic derangements, heart failure and, ultimately, mortality in the postnatal stage[9-12]. In addition, complete genetic disruption of mTORC1 impairs the ability of the heart to respond to pressure overload and to undergo compensatory hypertrophy, resulting in the development of dilated cardiomyopathy[10]. However, the available evidence suggests that partial and selective inhibition of mTORC1 is cardioprotective during aging and cardiac stress. mTORC1 inhibition extends the life span of mice[13-15]. It also reduces cardiac hypertrophy and improves cardiac function in the presence of pressure overload[16-19] and genetic cardiomyopathies[20-22] and reduces ischemic injury after acute[23, 24] and chronic myocardial infarction[19, 25, 26]. Finally, inhibition of mTORC1 reactivates cardiac autophagy, which is impaired in the presence of obesity and metabolic syndrome[23]. These results are very likely dependent on the fact that a partial inhibition of mTORC1 eliminates the detrimental effects of the maladaptive functions of mTORC1 during cardiac stress, while maintaining its physiological functions. In this regard, it is known that rapalogs do not inhibit all the functions of mTORC1[27]. The degree of mTORC1 inhibition and the mTORC1 physiological functions needed to be preserved to convert the mTORC1 inhibition from detrimental into beneficial during cardiac stress are unclear. In contrast, the information available about the pathophysiological functions of mTORC2 in the heart is still scarce.

This article reviews and interprets the evidence currently available regarding the role of the mTOR signaling pathway in cardiovascular physiology and disease (Table 1).

Biology of the mTOR pathway

The mTOR kinase is an atypical serine/threonine kinase of 289 kDa that belongs to the family of the phosphoinositide 3-kinase related kinase. The mTOR kinase is encoded by a single gene in mammals, but it exerts its main cellular functions by forming mTORC1 and mTORC2 through assembly with specific adaptor proteins[4-8]. The mTORC1 and mTORC2 signaling pathways are evolutionarily conserved, and mTORC1 and mTORC2 represent the

functional homologs of yeast TORC1 and TORC2. However, TOR1 and TOR2 are encoded by distinct genes in yeast, as first identified in Michael Hall's laboratory in 1991[28]. mTOR was isolated and cloned as a physical target of rapamycin through a cellular screening aimed at identifying the binding proteins of the FKB12-rapamycin complex[1-3]. Rapamycin and its analogs bind to the cytosolic protein FKBP12, thereby forming a protein complex that only targets a specific domain of the mTOR protein when it is part of mTORC1. As a consequence of rapamycin-FKBP12 binding, mTORC1 activity is strongly inhibited[4, 6]. Conversely, mTORC2 is relatively insensitive to rapamycin, although it has been demonstrated that prolonged treatment with rapamycin can also reduce the activity of mTORC2 by disrupting the complex[29]. So far, the proteins that are known to bind to mTOR in mTORC1 are Raptor[30], mLST8[31], PRAS40[32], DEPTOR[33] and Tt1/Tel2[34]. On the other hand, mTORC2 contains mTOR, the scaffold protein Rictor[35], SIN1[36], PROTOR[37], mLST8[31], DEPTOR[33] and Tt1/Tel2[34]. The main functions of the proteins forming the mTOR complexes are to maintain the integrity of the complexes, regulate their complex subcellular localization and control their complex interactions with substrates and regulators[4-8] (Figure 2).

The evidence available regarding the biological functions of mTORC1 and mTORC2 suggests that they have distinct cellular functions, substrates and regulators[4-8]. However, based on the current evidence, it is difficult to completely distinguish the function of one complex from the other. It has been shown that the two complexes are functionally interconnected and most of the studies that investigated the role of mTORC1 in the regulation of cellular homeostasis did not precisely rule out the involvement of mTORC2 in these mechanisms. In general, much more is known about the biology of mTORC1 than of mTORC2 (Figure 2). mTORC1 plays a crucial role in the regulation of cellular homeostasis, growth and response to stress. The main function of mTORC1 is the promotion of protein synthesis and, subsequently, cellular growth. The most studied substrates of mTORC1 are S6 kinase 1 (S6K1) and 4E (eIF4E)-binding protein 1 (4E-BP1). mTORC1 phosphorylates and activates S6K1, which in turn promotes mRNA biogenesis and activates the protein translation process. In contrast, mTORC1 inhibits 4E-BP1 and allows the formation of the eIF4F complex that triggers cap-dependent translation[4-8]. Additionally, mTORC1 promotes protein synthesis through translation of the 5'TOP mRNAs and the promotion of ribosomal biogenesis[4-8]. This mechanism explains why mTORC1 activity is often found to be increased in cancer cells[4-8]. mTORC1 also promotes cell proliferation by promoting the *de novo* synthesis of cellular membrane lipids through the SREBP1/2-dependent expression of lipogenic genes[7, 38]. However, mTORC1 not only activates anabolic processes but also inhibits catabolic processes. mTORC1 strongly inhibits autophagy, an evolutionarily conserved intracellular bulk degradation process responsible for the cellular degradation of proteins and organelles[6, 7, 39, 40]. mTORC1 appears to regulate autophagy both at a post-translational and transcriptional level. It phosphorylates the autophagic protein ULK1/2, thereby inhibiting the macrocomplex ULK1/Atg13/FIP200 that promotes autophagosome formation[41]. Additionally, mTORC1 activation inhibits the expression of autophagic proteins, particularly Atg7[23], which is crucial for the initiation of the autophagic process[39]. It has been shown that mTOR significantly inhibits the p73 factor and the transcription factor EB (TFEB) that can induce autophagy through the upregulation of autophagic

proteins such as Atg7[42]. [43, 44]. mTORC1 also plays an important role in the regulation of cellular metabolism.

mTORC1 promotes mitochondrial biogenesis and oxidative metabolism through the PGC-1α-mediated activation of the transcription factor Ying-Yang 1 (YY1)[45]. mTORC1 can activate glycolysis and the oxidative pentose phosphate pathway through the activation of hypoxia-inducible factor-1α and SREBP1/2, respectively[46]. Finally, mTORC1 activity is inhibited by acid deprivation, energy stress, hypoxia, ER stress and genotoxic stress[4-8]. Under these conditions, mTORC1 inhibition allows the upregulation of stress-responsive mechanisms that limit cell death, such as reduction of protein synthesis, autophagy, cell cycle arrest and DNA repair.

The Akt and AMPK pathways represent the most well characterized regulators of mTORC1. In the presence of nutrients and growth factors such as insulin, IGF-1, PDGF and EGF, Akt is activated and, in turn, phosphorylates and activates mTOR or inhibits PRAS40, an endogenous mTORC1 inhibitor [4-8, 32, 47]. On the other hand, AMPK, which is inactive in the presence of nutrients and high ATP levels, is strongly activated during energy deprivation and other types of cellular stress. AMPK activates the TSC1/TSC2 complex[48], which displays a strong GTPase activity and inhibits the small GTP-binding protein, Rheb, a direct mTORC1 activator[49, 50]. GSK-3β can also activate the TSC1/TSC2 complex and inhibit mTORC1 during energy stress[48]. Alternatively, REDD1, which is upregulated during hypoxia, activates TSC2 independently of AMPK and GSK-3β[51]. Rheb can also be inhibited by PRAK during energy deprivation, independently of TSC2[52]. Conversely, the Akt, ERK1/2 and IKKβ pathways inhibit the TSC1/TSC2 complex in response to growth factors and cytokines[53-55]. Recently, a new mechanism promoting the activation of mTORC1 has been elucidated. In the presence of amino acids, Rag GTPases are activated and mediate mTORC1 translocation to lysosome membranes, where mTORC1 is activated by Rheb[56, 57]. This process appears to be negatively regulated by MARK4, independently of Rheb activity[58].

mTORC2 can be activated by insulin and growth factors, whereas it is relatively insensitive to nutrient deprivation[5, 6]. The PI3K pathway was shown to activate mTORC2[59], and it appears that the TSC1/2 complex does as well[60]. mTORC1 appears to inhibit mTORC2 through phosphorylation of Rictor[61], suggesting that mTORC1 and mTORC2 are functionally interconnected. This hypothesis is also strongly supported by the fact that the best known substrate of mTORC2 is Akt, which is phosphorylated at serine 473, particularly in response to insulin[62, 63]. The biological importance of mTORC2-dependent phosphorylation of Akt is not yet understood, since it has been shown that mTORC2 is dispensable for Akt phosphorylation in certain cell types and conditions[64]. Both PKC-α[65] and SGK1[66] have also been shown to be substrates of mTORC2, despite mTORC1 also being shown to regulate SGK1[67]. Whether SGK1 exerts different functions in cardiomyocytes when it is activated by mTORC1 or mTORC2 is unclear. The most studied function of mTORC2 is the regulation of survival and growth, likely through the regulation of Akt and SGK1. SGK1 has been shown to promote cardiomyocyte survival while inhibiting hypertrophy[68], whereas SGK1 chronic activation during heart failure is detrimental[69]. mTORC2 also regulates cell polarity and cytoskeletal organization through

the regulation of PKC-α and RhoA[65]. PKC-α has also been shown to negatively regulate cardiac contractility[70].

The role of mTOR signaling in the regulation of cardiac homeostasis and physiological growth

Given its myriad cellular functions, it is not surprising that the mTOR kinase is necessary for normal regulation of cardiomyocyte homeostasis and growth during both development and the postnatal period (Figure 3). Systemic mTOR and Raptor knockout embryos die early during development, right after implantation[63]. However, embryos with constitutive α-*MHC-Cre*-mediated *mTOR* deletion also display a dramatic mortality starting around E13.5, with only 8% of embryos surviving the developmental stage. Cardiac-specific mTOR knockout embryos present a significant reduction in cardiomyocyte proliferation and an increase in apoptosis, with a 34% reduction of the cardiomyocyte number. As a result, cardiac-specific mTOR knockout embryos present cardiac dilation and dysfunction, with signs of terminal cardiac failure[9]. Consistent with these results, systemic deletion of the *rheb1* gene that extensively reduces mTORC1 activity is embryonically lethal, most likely due to cardiac defects such as ventricular wall thinning and cardiomyocyte apoptosis[71]. Global *rictor* gene deletion that selectively disrupts mTORC2 is also lethal in the developmental stage, and embryos with *rictor* deletion display significant cardiovascular abnormalities[35]. Thus, both mTORC1 and mTORC2 are highly important for cardiac development and embryo survival.

The mTOR pathway also appears vital for the maintenance of cardiac structure and function in the postnatal period and adulthood. Mice with α-*MHC-Cre*-mediated cardiac *mTOR* disruption that do not die during gestation and are born alive die within a few weeks after birth from massive cardiac dilation, dysfunction and heart failure[9]. Constitutive mTOR knockout mice present with derangements in fatty acid metabolism in the heart. Inducible cardiac-specific *mTOR* deletion in adulthood also leads to cardiac dysfunction and heart failure, with chamber dilation and wall thinning. mTOR knockout mice display massive apoptosis, fibrosis, autophagy, mitochondrial abnormalities and dysfunction, sarcomere disarray and ultimately death within 8 weeks after tamoxifen-induced gene deletion. There is a reduction in S6K activity in the hearts of these mice, a surprising over-activation of Akt phosphorylation at serine 473, despite the inactivation of mTORC2, and a marked and progressive accumulation of 4E-BP1 protein. Concomitant ablation of the *Eif4ebp1* gene partially rescues the detrimental effects of mTOR ablation in knockout mice[10]. These data suggest that a main detrimental effect of mTOR deletion in cardiomyocytes is the inhibition of cap-dependent protein translation. Mice with inducible cardiac-specific *raptor* deletion also progressively develop cardiac dilation and dysfunction associated with apoptosis, autophagy and mitochondrial abnormalities. Raptor knockout mice die a few weeks after cardiac-specific tamoxifen-induced gene deletion. A switch from fatty acid to glucose oxidation is observed in Raptor knockout mice[11]. Mice with constitutive α-*MHC-Cre*-mediated cardiac *rheb1* deletion display a dramatic inhibition of the cardiac mTORC1 pathway 5 days after birth, but mTORC1 activity is maintained until at least 3 days after birth[12]. This suggests that Rheb regulates mTORC1 in the heart only in the postnatal period. Rheb knockout mice also rapidly develop cardiac dilation and dysfunction and die within 10

days after birth. This dramatic phenotype is accompanied by a defect in cardiomyocyte growth and sarcomere disarray. Rheb knockout mice do not show increased cardiomyocyte apoptosis and do not die during gestation, differing somewhat from the constitutive cardiac-specific mTOR knockout phenotype. Again, genetic deletion of the *Eif4ebp1* gene partially rescues the phenotype of Rheb knockout mice[12]. Conversely, genetic disruption of *atg5* does not rescue the cardiac phenotype of Rheb knockout mice, thus ruling out involvement of autophagy in these mechanisms. Of note, a significant increase in the LC3II/I ratio was observed in the hearts of Rheb knockout mice, which suggests an increase in autophagy. However, the absolute LC3II level was not found to be increased in these mice, in which Rheb deletion is constitutive (chronic). The apparent discrepancy between these mice and those with inducible (acute) *mTOR* or *raptor* gene deletion, in which the cardiac LC3II level is significantly increased, may be explained by the fact that LC3 is rapidly degraded when autophagic flux is chronically activated, making it more difficult to observe any significant LC3II accumulation[72]. Collectively, these data indicate that mTORC1 is required for maintenance of cardiac structure and function and regulation of cellular metabolism in the postnatal period. No evidence is available thus far regarding the specific role of mTORC2 in the heart in unstressed conditions.

However, while complete deletion of the mTOR pathway in the heart is not compatible with life, both pharmacological and partial genetic disruption of mTORC1 exert beneficial effects during the aging process and appear to increase cardiomyocyte resistance to aging stress. mTORC1 inhibition extends life span in lower organisms[4-8], and pharmacological and partial genetic inhibition of mTOR extend life span in mammals[13-15]. Rapamycin treatment significantly extends life span in mice, regardless of whether it is started early or late in life[13]. Mice with hypomorphic mTOR alleles also live longer, with a significant reduction in the age-dependent functional decline of some organs[15]. S6K1 genetic disruption increases life span in female, though not in male, mice[73]. These beneficial effects may be due to a reduction in energy expenditure over time, inhibition of protein synthesis with reduced cellular senescence and misfolded protein accumulation, renewal of the endogenous stem cell pool, improvement of mitochondrial function and reduction of ROS and activation of autophagy[5, 8]. mTOR inhibition might also be beneficial during aging, particularly in the presence of obesity, through an increase in skeletal muscle insulin sensitivity due to interruption of the negative feedback on IRS-1 by mTORC1[74, 75]. However, it has been demonstrated that chronic rapamycin treatment causes a diabetes-like syndrome due to a loss of pancreatic β-cells[75, 76]. Pharmacological mTOR inhibition has been shown to reduce age-related cardiac abnormalities, such as cardiac hypertrophy and systolic dysfunction. Rapamycin treatment reduced age-induced cardiac inflammation and fibrosis and upregulated genes involved in metabolic function and energy metabolism[14], in line with the rapamycin-induced increase in mitochondrial function[4-8]. Accordingly, caloric restriction, which also increases life span in lower organisms and mammals, was shown to improve diastolic function and reduce cellular senescence in the aged heart, and these effects were associated with a reduction in mTORC1/S6K pathway signaling[5, 8, 77].

Chronic mTOR activation appears to accelerate the cardiac aging process. Obesity and metabolic syndrome, which are associated with chronic cardiac activation of mTOR,

accelerate cardiac aging[23, 78, 79]. Mice with systemic *GSK-3α* deletion present with cardiac hypertrophy, dysfunction and sarcomere abnormalities during aging due to deregulated activation of mTORC1 and inhibition of autophagy[80]. This indicates that GSK-3α is an important negative regulator of mTORC1 function during aging. Chronic Akt1 activation, which activates mTORC1, was shown to worsen aging-induced cardiac hypertrophy and myocardial contractile dysfunction through inhibition of autophagy[81]. This further suggests a potential role of autophagy in the beneficial effects of mTORC1 inhibition during aging. A recent study confirmed that rapamycin extends life span but failed to demonstrate that it prevents senescence in the cardiovascular system[82]. Therefore, additional studies are needed to elucidate the actual impact of mTORC1 inhibition on age-related cardiac abnormalities.

The role of mTOR signaling in the regulation of cardiac hypertrophy

The mTOR pathway appears to play a key role in the development of cardiac hypertrophy (Figure 4). This is not particularly surprising if we consider that cardiac hypertrophy is a process that requires a marked increase in the synthesis of sarcomeric proteins and that the mTOR pathway is a master promoter of protein synthesis. mTORC1 activity is increased during the cardiomyocyte hypertrophic response to β-adrenergic stimulation[83], angiotensin-II[84] and IGF-1[85], and inhibition of mTORC1 inhibits hypertrophy development. mTORC1 is activated during physiological hypertrophy induced by physical exercise and during pathological hypertrophy induced by transverse aortic constriction (TAC) and spontaneous hypertension. However, there is evidence that mTORC1 is later inactivated when cardiac function deteriorates and heart failure develops[10, 11, 86]. The PI3K/Akt pathway contributes significantly to the activation of mTORC1 during the development of cardiac hypertrophy, particularly in response to physical exercise[18, 87, 88]. However, β-adrenergic signaling, the ERK pathway and nitric oxide signaling are also involved in the activation of mTORC1 during the development of cardiac hypertrophy[83, 89, 90]. Furthermore, biomechanical activation of TRPC channels and focal adhesion kinase promote mTORC1 activation during pressure overload[91, 92], and glucose-6-phosphate accumulation contributes to mTORC1 activation in the overloaded heart as well[93]. Thus, a complex network of mechanical, biochemical and metabolic signals are sensed by mTORC1 signaling during cardiac pressure overload.

mTOR inhibition significantly reduces cardiac hypertrophy. Mice with inducible cardiac-specific *mTOR* or *raptor* deletion do not develop compensatory hypertrophy in response to pressure overload and rapidly develop ventricular dilation and cardiac dysfunction associated with apoptosis, autophagy and mitochondrial derangements[10, 11]. Protein synthesis in these animals is significantly reduced. These observations indicate that mTOR is necessary for the development of compensatory cardiomyocyte growth and for cardiac adaptation to pressure overload. Total disruption of mTOR signaling not only abrogates hypertrophy but also impairs the capacity of the heart to adapt to stress.

In contrast, partial genetic and pharmacological inhibition of mTORC1 appears to inhibit pathological cardiac hypertrophy while still maintaining the ability of the heart to adapt to increased load (Figure 4). Rapamycin pretreatment blunts cardiac hypertrophy development in response to pressure overload[16]. Rapamycin administration also regresses both

established compensated and decompensated cardiac hypertrophy induced by TAC and improves cardiac function in mice with decompensated hypertrophy[17]. Rapamycin activates Akt, promotes protein ubiquitination and inhibits apoptosis in the pressure-overloaded rat myocardium[94], and it reduces cardiac hypertrophy and fibrosis in spontaneously hypertensive rats[95]. Mice with heterozygous cardiac-specific *rheb1* deletion show reduced activation of mTORC1 during pressure overload, and reduced cardiac hypertrophy and fibrosis[19]. The mTORC1 inhibitor astragaloside IV also reduces hypertrophy and fibrosis during pressure overload[19]. An interesting study recently showed that mTORC1 is activated during pressure overload through Akt-dependent inactivation of PRAS40. Cardiac overexpression of PRAS40 inhibited mTORC1 signaling, prevented cardiac hypertrophy development during TAC, and even reduced established TAC-induced hypertrophy. Importantly, PRAS40 overexpression preserved cardiac function during long-term pressure overload and reduced fibrosis[18]. A constitutively active form of PRAS40 was also able to reduce the development of physiological hypertrophy in response to physical exercise[18]. This is consistent with the evidence that PI3K inhibition and Akt1 disruption blunt the establishment of physiological hypertrophy in response to exercise[87, 96]. However, whether this effect is dependent on mTORC1 activation still needs to be addressed. In fact, it has been shown that cardiomyocyte-restricted overexpression of a dominant-negative form of mTOR that efficiently inhibits mTORC1 signaling does not affect the development of either exercise-induced or isoproterenol-induced hypertrophy[97]. Additional studies of the mTORC1 components using loss-of-function animal models would be useful to further investigate this issue. Furthermore, it will be important to elucidate the downstream signals that mediate the pro-hypertrophic effects of mTORC1 in the future. Of note, existing evidence indicates that S6Ks are not involved in the regulation of either physiological or pathological hypertrophy[98], whereas it is likely that 4E-BPs play a role[10].

While a considerable amount of evidence indicates that mTORC1 activation is absolutely required for the development of pathological cardiac hypertrophy, it seems that mTORC1 activation alone is not sufficient to induce cardiac hypertrophy. In fact, neither constitutively active nor wild-type mTOR overexpression in the mouse heart induces a significant increase in cardiac mass[97, 99]. These data must be reconciled with the evidence that Akt overexpression[100], cardiomyocyte-restricted LKB1 deletion[101] and cardiac TSC1 deletion[102] are all associated with extensive development of cardiac hypertrophy that can be reversed by rapamycin treatment. The most reasonable explanation for the lack of induction of hypertrophy by mTOR overexpression is the existence of multiple signaling pathways that are modulated and contribute in an integrated manner to the synthesis of sarcomeric myofibrils and increase the cardiomyocyte volume during the establishment of pathological hypertrophy. Each of these pathways is strictly required for inducing hypertrophy, but if they are activated individually, particularly in the absence of a mechanical load, they cannot induce hypertrophy. Of note, Song et al. showed that cardiac overexpression of wild-type mTOR preserves cardiac function during pressure overload through inhibition of NF-κB signaling and myocardial inflammation, in apparent disagreement with the beneficial effects of mTORC1 inhibition discussed above. mTOR overexpression did not significantly increase the mTORC1 signaling during TAC in this study; instead, it actually decreased phosphorylation of S6K[99]. Therefore, it is possible that, in the specific transgenic mouse

model described in this paper, overexpressed mTOR preferentially modulates signaling pathways that are cardioprotective without activating maladaptive signals. Activation of mTORC2 by mTOR overexpression may also contribute to the preservation of cardiac function during TAC. Unfortunately, the information available on the specific role of mTORC2 in the regulation of cardiomyocyte growth and cardiac adaptation to pressure overload is scarce and no studies on cardiac-specific mTORC2 loss-of-function animal models have been published.

Therefore, mTORC1 appears to be a potentially highly therapeutic target for treating human diseases associated with pathological cardiac hypertrophy and cardiomyopathy. In mouse models of LEOPARD disease, which is caused by a mutation of the *PTPN11* gene that abolishes the catalytic activity of the SHP2 protein, cardiac ERK/MAPK signaling is inactivated and mTOR activity is increased in a deregulated manner. LEOPARD disease is characterized by the presence of hypertrophic cardiomyopathy, myocardial disarray, fibrosis, conduction defects and cardiac dysfunction. mTORC1 inhibition by rapamycin completely rescues the cardiac phenotype of these animals[20]. In a model of hypertrophic cardiomyopathy caused by a mutation of the *TRIM63* gene encoding for the MuRF1 protein, cardiac mTOR was also found to be activated[103]. Cardiac mTOR activation and autophagy inhibition were observed even in mouse models of cardiomyopathy caused by Lamin A/C gene mutation, through ERK1/2-dependent activation of DUSP4. Pharmacological mTORC1 inhibition reactivated autophagy and significantly improved cardiac function, muscle dystrophy and survival of these animals[21, 22]. These effects were associated with a reduction of abnormal desmin accumulation[21]. Overall, these results indicate that deregulated cardiac mTORC1 activation is the pathophysiological mediator of cardiac hypertrophy and dysfunction in different types of cardiomyopathy. The exception to this general observation is represented by doxorubicin-induced cardiomyopathy, in which mTOR signaling inhibition seems to contribute to a reduction of cardiac mass and development of cardiac dysfunction independently of cardiomyocyte apoptosis[104]. Thus, it appears that, in this condition, the combination of doxorubicin toxicity and mTOR inhibition affects cardiomyocytes detrimentally by promoting cardiac atrophy. Whether an exaggerated activation of autophagy plays a role in the detrimental effects induced by doxorubicin is unclear.

The role of mTOR signaling in ischemic injury

Accumulating lines of evidence indicate that mTOR regulates the cardiomyocyte response to energy deprivation and ischemia (Figure 5). In lower organisms and mammalian cell lines, mTORC1 is inhibited during energy deprivation[4-8]. mTORC1 inhibition preserves the energy status through the reduction of cellular energy expenditure and activation of autophagy and, thus, promotes survival. Through its activation of autophagy, mTORC1 inhibition is required for postnatal survival before lactation begins[105] and preserves skeletal muscle integrity and function[106]. Similarly, rapamycin promotes survival of nutrient-deprived cardiomyocytes through autophagy activation[107]. We recently demonstrated that mTORC1 is inhibited during cardiomyocyte energy deprivation and ischemia through the inhibition of Rheb[23]. Forced reactivation of Rheb/mTORC1 signaling inhibited autophagy activation in energy-deprived cardiomyocytes through Atg7 inhibition and promoted

cardiomyocyte death both *in vitro* and *in vivo*. This effect was associated with depletion of ATP levels and misfolded protein accumulation. On the other hand, inhibition of the Rheb/mTORC1 signaling pathway limited cardiomyocyte death during energy stress. These results indicate that Rheb is a main regulator of mTORC1 during cardiomyocyte energy stress and that Rheb/mTORC1 inhibition is an adaptive cellular response that promotes survival through activation of autophagy. In fact, when autophagy was restored in Rheb-overexpressing cardiomyocytes, cell survival was rescued during energy stress[23]. Autophagy is also regulated during energy deprivation through mTORC1-independent mechanisms, such as AMPK-dependent Ulk1 phosphorylation[41], phosphorylation/activation of TIP60 by GSK-3β, which in turn activates Ulk1[108], and production of ROS by Nox4 in the endoplasmic reticulum[109]. However, Rheb/mTORC1 inhibition is a required signaling event to promote autophagy activation in energy-deprived cardiomyocytes in tight coordination with the other pathways regulating the autophagic machinery. Of note, we previously observed that, during prolonged myocardial ischemia without reperfusion, inhibition of GSK-3β activation was associated with autophagy inhibition and increased ischemic injury through mTORC1 reactivation, which was rescued by rapamycin treatment[24]. Inhibition of AMPK activation in the ischemic heart also led to decreased autophagy and increased ischemic injury[110]. Therefore, based on our findings, we propose that Rheb integrates the signals from AMPK and GSK-3β in ischemic cardiomyocytes, thereby mediating mTORC1 inhibition and autophagy activation.

mTORC1 inhibition also appears to be beneficial during chronic ischemic injury (Figure 5). mTORC1 is activated in the remote myocardium during chronic myocardial infarction as a consequence of increased load and contributes to ventricular remodeling[25, 26]. Pharmacological mTORC1 inhibition with everolimus reduces cardiac dilation and infarct size and improves cardiac function during chronic myocardial infarction. These effects are associated with activation of autophagy and inhibition of proteosome activity[25]. Mice with partial cardiac Rheb deletion display better cardiac function after experimental myocardial infarction and a reduction of infarct size and cardiac dilation as compared to control mice, thus corroborating our evidence of a beneficial effect of Rheb inhibition during acute ischemia[19]. Rapamycin and S6K inhibitors reduce cardiac ischemic remodeling and cardiomyocyte apoptosis through PDK1-dependent activation of the Akt pathway[111]. Völkers et al. have recently provided compelling evidence that the balance between mTORC1 and mTORC2 activity is important for the regulation of ischemic damage and cardiac remodeling after myocardial infarction[26]. They demonstrated that cardiac overexpression of PRAS40 inhibits mTORC1, reduces ischemic injury, apoptosis and cardiac remodeling and improves cardiac function through the preservation of SERCA2a function during chronic myocardial infarction. The protective effects of PRAS40 were mediated by mTORC2 and by activation of the Akt pathway. Conversely, mTORC2 inhibition by *in vivo* AAV9-mediated cardiac Rictor knockdown caused deterioration of cardiac function and remodeling after myocardial infarction[26]. Therefore, while this study confirms the beneficial effects of mTORC1 inhibition during ischemic injury, it also demonstrates that mTORC2 promotes survival under ischemic conditions and highlights the importance of developing new selective mTORC1 inhibitors that do not affect or possibly even increase mTORC2 activity. PRAS40 or Rheb inhibitors could be potential candidates.

Additional studies should also be conducted to elucidate the substrates mediating the protective effects of mTORC2 in the ischemic heart. Akt1 is certainly one of these. Previous studies demonstrated that, in some cases, genetic inhibition of PI3K or Akt1 can confer beneficial effects to the ischemic heart[112, 113]. Therefore, it is likely that mTORC2 also protects the ischemic heart through other Akt1-independent mechanisms. In this regard, in a recent elegant work, mTOR overexpression was found to partially reduce cardiomyocyte death during hypoxia *in vitro* through mTOR-dependent direct activation of NF-κB and inhibition of Bnip3 expression[114]. It will be interesting to evaluate the relative contribution of mTORC2 activation by mTOR overexpression with respect to mTORC1 in regulating these mechanisms. This intriguing hypothesis would also be consistent with the evidence that mTORC2 activates Akt1 and that Akt1 is a positive regulator of NF-κB[114].

The role of mTOR signaling in reperfusion injury is still controversial (Figure 5). mTORC1 is rapidly activated in the heart during reperfusion. Rapamycin reduces infarct size in *ex vivo* and *in vivo* ischemia-reperfusion models through activation of the JAK2/STAT3 signaling pathway when administered before ischemia[115]. Simvastatin reduces ischemia-reperfusion injury through inhibition of mTOR and activation of mitophagy[116]. On the other hand, rapamycin was not cardioprotective during ischemia-reperfusion when administered before the reperfusion phase[24]. We previously observed that inhibition of GSK-3β in transgenic mice with cardiac-specific overexpression of dominant-negative GSK-3β reduces reperfusion injury through mTORC1 hyper-activation[24]. These results suggest that mTORC1 may exert some protective effects during the reperfusion phase. We found that mTORC1 activation by GSK-3β inhibition reduces reperfusion injury by limiting exaggerated activation of autophagy, which is maladaptive[110]. Alternatively, mTORC1 may regulate mPTP opening, it promotes mitochondrial biogenesis, which may favor cardiac recovery after ischemia, and it may promote upregulation of antioxidant genes through the activation of PGC-1α[24, 45, 117]. Previous reports indicated that rapamycin abolishes the cardioprotective effects of ischemic preconditioning, indicating that ROS-induced mTORC1 activation mediates the protection associated with ischemic preconditioning[118]. Consistent with the idea that mTORC1 exerts a protective effect during reperfusion damage, a recent study found that cardiac-specific mTOR overexpression reduces chronic cardiac remodeling after *in vivo* ischemia-reperfusion. Although the effects of mTOR overexpression on acute ischemic injury after ischemia-reperfusion were not evaluated *in vivo*, mTOR overexpression was found to reduce necrosis, as evaluated by Evans blue dye perfusion, and myocardial inflammation in an *ex vivo* model of ischemia-reperfusion[119]. It is also possible that, in this study, the protective effects mediated by mTOR overexpression are dependent upon mTORC2 activation, which is required for cardiomyocyte survival during ischemia and limitation of chronic ischemic remodeling[26]. Collectively, these data indicate that mTORC1 inhibition is protective during ischemia through the activation of autophagy, the reduction of protein synthesis and the subsequent activation of mTORC2. On the other hand, mTORC1 appears to potentiate physiological mechanisms during reperfusion. Ideally, mTORC1 should be inhibited before an ischemic episode and reactivated at the time of reperfusion in patients suffering an acute myocardial infarction. However, in the clinical setting, patients with acute myocardial infarction usually experience prolonged periods of ischemia (hours) before coronary perfusion can be reestablished. Furthermore, in certain

cases, coronary flow is not restored or coronary reperfusion is not indicated. Ischemia is a major determinant of myocardial damage in patients with acute coronary syndrome[120]. Therefore, it is very likely that, in patients with acute myocardial ischemia, the beneficial effects of mTORC1 inhibition largely overcome the potential harmful effects during reperfusion. Additional studies are needed to better investigate this issue.

The role of mTOR in the regulation of cardiac metabolism

mTOR signaling appears to be deeply involved in the regulation of cardiac metabolism. In mice with cardiac mTOR disruption induced in adulthood, fatty acid oxidation was significantly decreased, whereas glucose oxidation was increased[121]. Expression of fatty acid metabolism genes such as fatty acid-binding protein 3, medium-chain acyl-CoA dehydrogenase and hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein)-α and -β was reduced, and carnitine palmitoyl transferase-1 and -2 enzymatic activities were also decreased. These metabolic abnormalities were not associated with a reduction in the abundance of PGC-1α, a master regulator of fatty acid oxidation genes[121]. In contrast, in cardiac-specific Raptor knockout mice, significant downregulation of ERRα, PGC-1α and PPAR-α was observed[11]. Again, fatty acid oxidation was reduced and glucose utilization was increased in the hearts of Raptor knockout mice. This was accompanied by a reduction in carnitine palmitoyl transferase-1β and malonyl-CoA decarboxylase-1 expression levels. Importantly, all these changes were observed in mTOR and Raptor knockout mice while cardiac function was still preserved. In Raptor knockout mice, a reduction of mitochondrial content was also seen after TAC, which is consistent with a reduction of PGC-1α, since PGC-1α promotes mitochondrial biogenesis and function[11]. Of note, recent evidence suggests that mTOR can also promote cardiomyocyte mitochondrial function in response to insulin through the regulation of NF-κB[122].

However, mTOR not only regulates metabolism but is also affected by metabolic alterations. It is now well-established that tissue mTORC1 activity is increased in the presence of nutritional excess, obesity and metabolic syndrome (Figure 6)[4-8, 75]. Deregulated mTORC1 activation further deteriorates the cellular metabolic status, promotes cellular senescence and ultimately leads to organ dysfunction[4-8, 75, 123]. AMPK is usually inhibited under these conditions, suggesting that it is involved in a main intracellular mechanism leading to mTORC1 activation. It is possible that Rag GTPases also contribute to organ mTORC1 activation in obesity and metabolic syndrome. In the presence of metabolic alterations, increased energy status, high cardiac and circulating levels of lipids and amino acids, hyperinsulinemia and increased serum levels of cytokines and adipokines would all likely lead to activation of mTORC1 signaling[4-8, 75, 123].

In dietary and genetic models of obesity and metabolic syndrome, basal mTORC1 activity was found to be increased in the liver, where it promotes insulin resistance, contributes to dyslipidemia and may predispose to cancer development, in adipose tissue, where it promotes fat deposition, in the kidney, where it causes autophagy inhibition and podocyte loss, in skeletal muscle, where it promotes insulin resistance and fat deposition, and, ultimately, in the vasculature and in the heart[4-8, 75, 123]. High fat diet-induced obesity leads

to an increased activation of the Akt/mTOR pathway in the vasculature that causes endothelial senescence and increases the susceptibility to peripheral ischemia. These effects are rescued by rapamycin[124]. We recently found that, in a model of dietary obesity and metabolic syndrome, autophagy is suppressed in the heart through deregulated activation of Rheb and mTORC1 activity. This suggests that Rheb/mTORC1 activation contributes to pathological cardiac growth in obesity and metabolic disorders[125]. We found that the activity of Rheb and mTORC1 remains higher during ischemia, which, in contrast, is associated with Rheb/mTORC1 inhibition in the hearts of lean animals[23]. Accordingly, autophagy was significantly inhibited in the hearts of obese mice, and this was associated with increased susceptibility to ischemic injury. Rapamycin administration or partial *mTOR* deletion significantly reduced infarct size following ischemia through the restoration of autophagy[23]. Therefore, our results provide a mechanistic explanation for the reduction in ischemic tolerance associated with metabolic abnormalities and suggest that mTORC1 inhibition is a valid therapeutic option to reduce ischemic injury in subjects with acute coronary syndromes, particularly those with metabolic syndrome. Subsequent studies have confirmed that either autophagosome formation or autophagic flux is impaired in the hearts of obese and diabetic animals, and these effects were found to be associated with increased mTORC1 activity and the development of cardiac abnormalities. In a swine model of metabolic syndrome, a reduction in autophagosome formation was associated with mTOR activation, increased apoptosis, reduced mitochondrial function and derangements of cardiac structure and function[126]. In a model of high fat diet-induced obesity, cardiac autophagosome formation was reduced, mTOR activity was increased and cardiac function was decreased. These effects were rescued by rapamycin and worsened by genetic adiponectin disruption[127]. Interestingly, obesity and metabolic syndrome not only affect autophagosome formation but also autophagic flux. Deregulated activation of cardiac Akt2 is involved in the activation of the mTOR pathway and in the disruption of autophagic flux in the hearts of obese mice. These abnormalities are rescued by Akt2 genetic disruption[128]. In a model of streptozotocin-induced diabetes, autophagosome formation and flux were impaired in the heart, and these effects were associated with increased mTOR activity[129]. However, whether autophagy inhibition in the diabetic heart is maladaptive or adaptive at baseline is still unclear[129, 130]. Obesity was also found to be associated with inhibition of autophagosome formation in the kidney through mTORC1 activation and in the liver in mice[131, 132]. This suggests that mTORC1 inhibition in subjects with obesity could be beneficial not only to the heart but also to other organs, specifically through autophagy reactivation[79]. Further studies are encouraged to investigate this issue.

Perspectives

Many aspects of the pathophysiology of mTOR signaling still remain unclear. First of all, it will be important to study the specific function of mTORC2 at baseline and during stress. This can be achieved through the characterization of cardiac-specific Rictor knockout mice. Much effort still needs to be made to discover the substrates of mTORC1 and mTORC2 that mediate their specific effects and the mechanisms that regulate them in response to growth factors, nutrients and stress. Not much is known about the cross-talk between mTORC1 and mTORC2, but it is very likely that the complexes tightly regulate one another in specific contexts and share some functions. In addition, the specific functions of the different adaptor

proteins of mTORC1 and mTORC2 in different cardiomyocyte cellular processes need to be addressed. Finally, the subcellular localization of mTORC1 and mTORC2 in cardiomyocytes at baseline and during stress should be investigated.

mTORC1 activation is maladaptive during aging, cardiac hypertrophy development, myocardial ischemia and in the presence of obesity and metabolic syndrome. Therefore, it is important to find the optimal mTORC1 inhibitor that would be most beneficial under these conditions. Ideally, this inhibitor should selectively inhibit the maladaptive functions of mTORC1 without affecting its physiological effects. It is known, for example, that prolonged treatment with rapamycin disrupts mTORC2 and can cause insulin resistance[4-8]. To succeed in this difficult task, it will be important to study both the direct regulators of mTORC1 involved in its maladaptive functions, such as Rheb, PRAS40 or astrin[133], and its direct substrates in these mechanisms. Additional studies of different components of mTOR signaling with heterozygous loss-of-function models are also encouraged. It will also be interesting to investigate whether there is a structural advantage to having the mTORC1 protein present, even if it is inhibited. Of note, previous studies indicated a beneficial effect of mTORC1 inhibition in preserving the stem cell pool, reducing stem cell exhaustion and increasing stem cell function[4-8]. Cardiac stem cells have been shown to be involved in the regulation of cardiomyocyte turnover, but the cardiac stem cell pool decreases during aging and disease[134]. It would be interesting to evaluate whether mTORC1 inhibition can preserve the cardiac stem cell pool during stress and, if so, whether this effect contributes to the protective effects of mTORC1 inhibition in cardiac diseases.

Finally, the information available about the physiological role of mTOR signaling in the vasculature is scarce. There is some evidence indicating that prolonged rapamycin treatment reduces endothelial cell viability and function and promotes monocyte recruitment, vascular inflammation and susceptibility to thrombosis[135, 136]. Conversely, S6K inhibition reduces tissue factor release and vascular inflammation[135]. mTORC2 was found to promote survival and proliferation of pulmonary artery vascular smooth muscle cell during pulmonary hypertension[137]. Studies of mTOR components via vascular-specific loss-of-function models are required to understand the involvement of mTOR signaling in vascular cellular processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

FKB12	FK506-binding protein of 12 kDa
Raptor	regulatory-associated protein of mTOR
mLST8	mammalian lethal with sec-13 protein 8
PRAS40	proline-rich Akt substrate 40 kDa
DEPTOR	DEP domain-containing mTOR-interacting protein
Rictor	rapamycin-insensitive companion of mTOR
SIN1	stress-activated map kinase-interacting protein 1
PROTOR	protein observed with rictor
SREBP1/2	sterol regulatory element-binding protein 1/2
ULK1/2	unc-51-like kinase 1/2
FIP200	focal adhesion kinase family interacting protein of 200 kDa
Atg	autophagy-related gene
YWHA	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation proteins
PPAR-α	peroxisome proliferator-activated receptor α
PPAR-β	peroxisome proliferator-activated receptor β
PGC-1α	PPAR-β coactivator 1α
AMPK	adenosine monophosphate-activated protein kinase
IGF-1	insulin growth factor 1
PDGF	platelet-derived growth factor
EGF	Epidermal growth factor
TSC1/2	tuberous sclerosis protein 1/2
Rheb	Ras homolog enriched in brain
GSK-3	Glycogen synthase kinase 3
REDD1	regulated in development and DNA damage response 1
PRAK	p38-regulated/activated kinase
ERK1/2	extracellular-signal-regulated kinase 1/2
NF-κB	nuclear factor κB
IKKβ	inhibitor of nuclear factor κB kinase β
MARK4	microtubule-associated protein/microtubule affinity-regulating kinase 4
PI3K	phosphoinositide 3 kinase
SGK1	serum- and glucocorticoid-induced protein kinase 1

PKC-α	protein kinase C-α
RhoA	Ras homolog gene family, member A
LKB1	liver kinase B1
LEOPARD	Lentigines, ECG conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth and sensorineural Deafness
MAPK	mitogen-activated protein kinase
MuRF1	Muscle RING-finger protein-1
DUSP4	Dual specificity protein phosphatase 4
PDK1	phosphoinositide-dependent kinase-1
SERCA2a	sarco/endoplasmic reticulum Ca^{2+-}ATPase 2a
AAV9	adeno-associated virus 9
Bnip3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3
JAK2	Janus kinase 2
STAT3	signal transducer and activator of transcription 3
mPTP	mitochondrial permeability transition pore
TRPC	transient receptor potential canonical
SHP2	SH2 domain-containing protein tyrosine phosphatase-2

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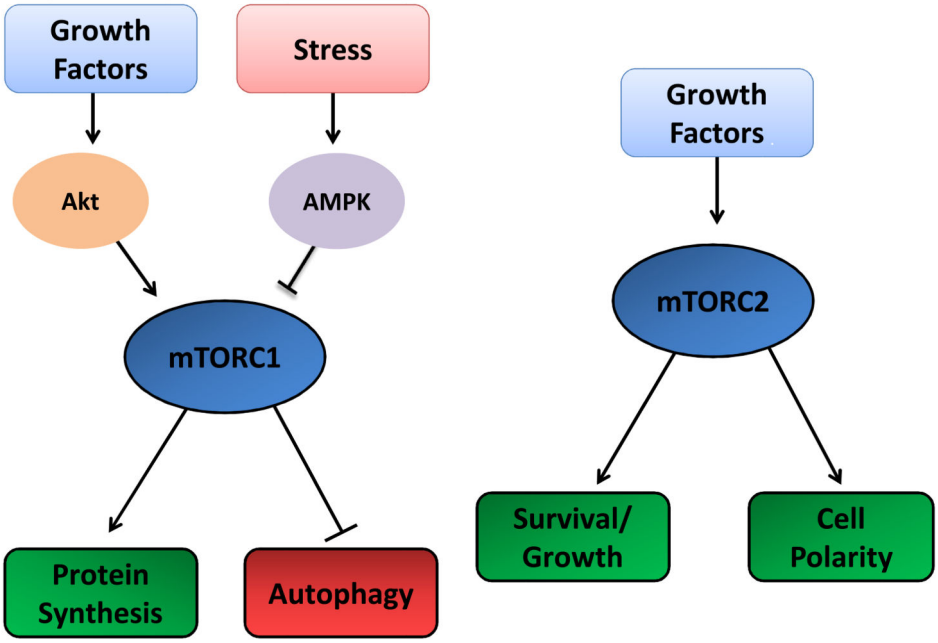

Figure 1. General cellular functions of mTORC1 and mTORC2

This figure summarizes the most well characterized functions of mTORC1 and mTORC2. mTORC1 regulates protein synthesis and autophagy in response to growth factors and stress. mTORC2 is known to regulate cell growth, survival and polarity.

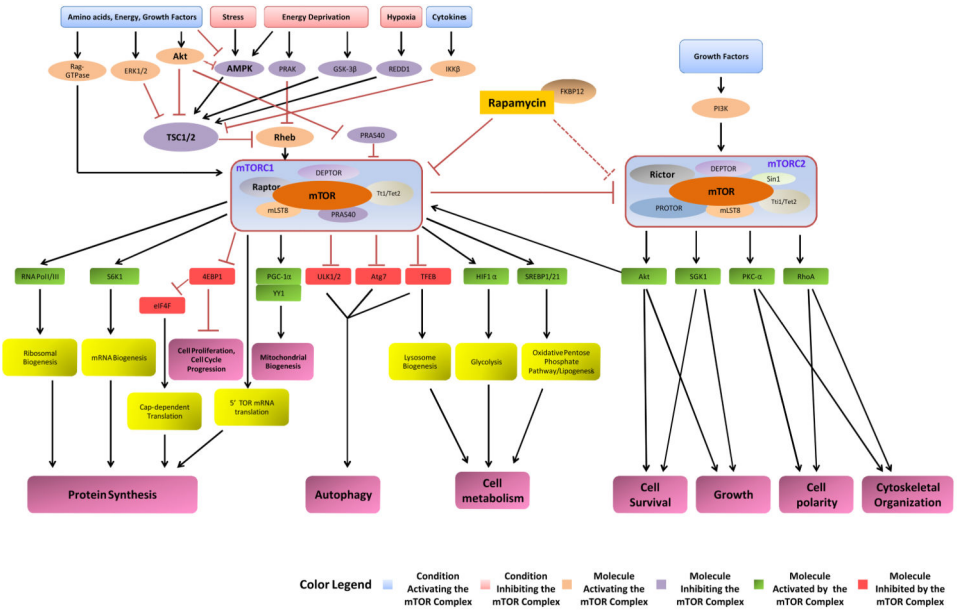

Figure 2. General overview of the mTOR signaling pathway

The Dashed line signifies that rapamycin inhibits mTORC2 in specific cell types or after prolonged treatment.

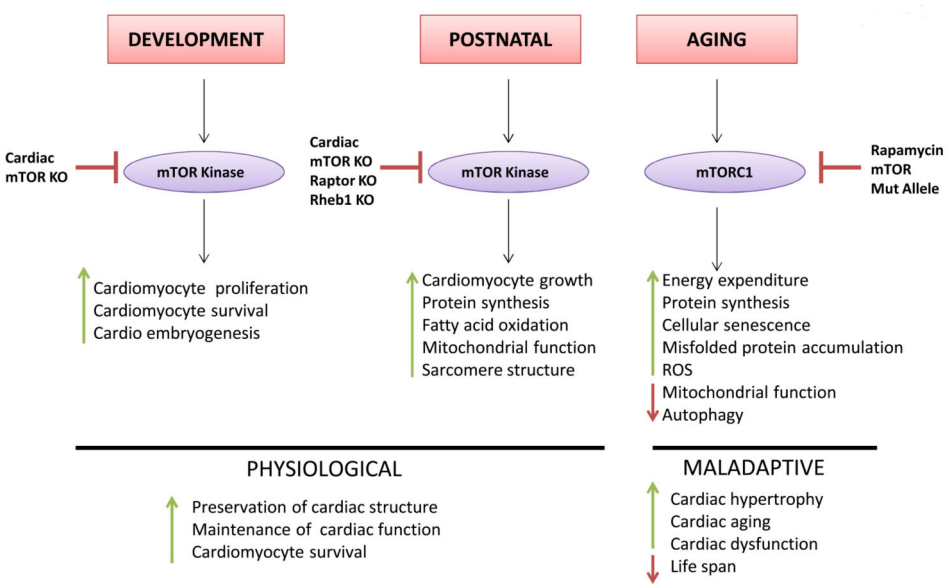

Figure 3. The role of mTOR in the regulation of cardiac homeostasis

mTOR is required for cardiomyocyte growth and for the preservation of cardiac structure and function in unstressed conditions. However, partial inhibition of mTOR appears to be beneficial during the aging process. The pharmacological modulators of mTOR and the animal models with genetic modifications of the components of the mTOR signaling pathway that have been used in the studies focused on the role of mTOR in cardiac physiology are displayed.

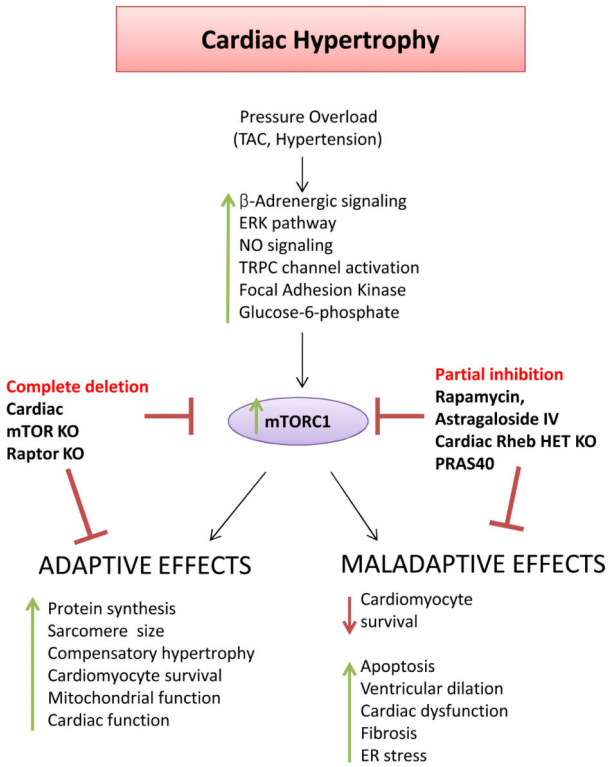

Figure 4. The role of mTOR in cardiac hypertrophy

mTOR activation promotes pathological hypertrophy during pressure overload. However, mTOR kinase is also required for physiological mechanisms that are necessary for cardiac adaptation to cardiac overload. The pharmacological modulators of mTOR and the animal models with genetic modifications of the components of the mTOR signaling pathway that have been used in the studies focused on the role of mTOR in cardiac hypertrophy are displayed.

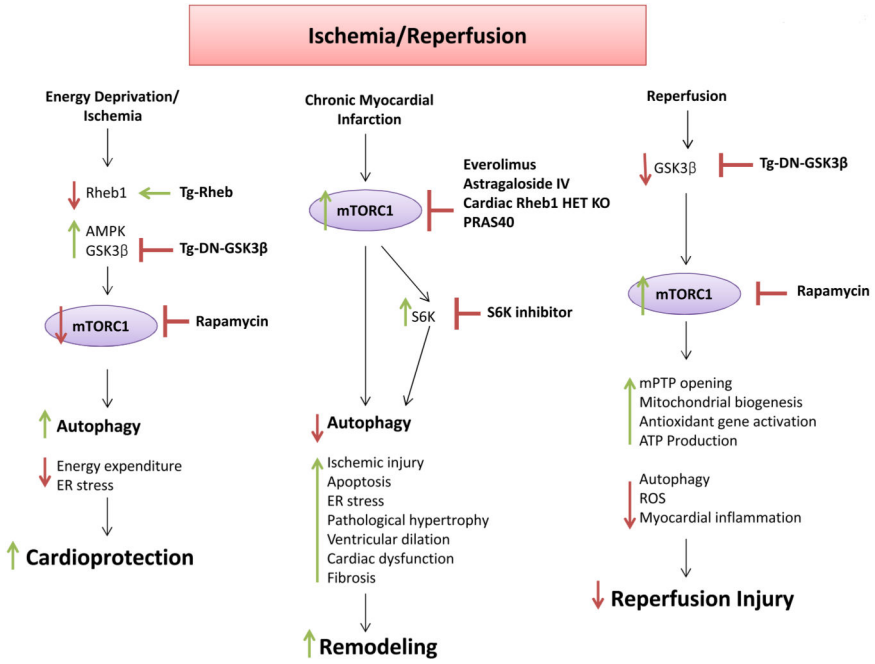

Figure 5. The role of mTORC1 in ischemia-reperfusion

mTORC1 inhibition is protective during ischemia through the upregulation of adaptive mechanisms. On the other hand, mTOR is reactivated during reperfusion and takes part in the regulation of physiological processes. The pharmacological modulators of mTOR and the animal models with genetic modifications of the components of the mTOR signaling pathway that have been used in the studies focused on the role of mTOR in ischemia-reperfusion are displayed.

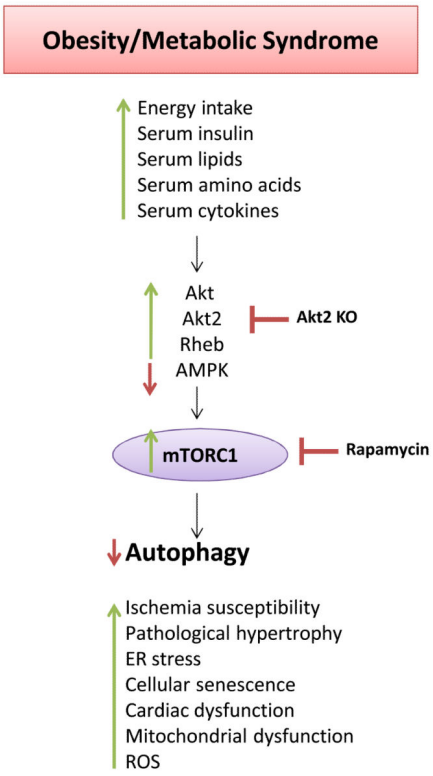

Figure 6. Cardiac mTORC1 activation in metabolic disorders

Cardiac mTORC1 activation contributes to cardiac abnormalities in obesity, metabolic syndrome and diabetes.

Table 1

Main studies that investigated the role of m TOR kinase in the regulation of cardiac physiology and response to stress *in vivo.*

CARDIAC CONDITION	STUDY	TYPE OF MTOR MODULATION AND ANIMAL MODEL	EFFECT ON THE HEART
DEVELOPMENT/ PHYSIOLOGICAL CONDITIONS	Zhu Y et al (9)	Constitutive *α-MHC-CRE*-mediated *mTOR* gene deletion	High embryonic lethality due to cardiac failure. Massive cardiac dilation, dysfunction, heart failure and early mortality in the postnatal stage. Metabolic derangements.
	Zhang D et al (10)	Tamoxifen-induced *α-MHC-CRE*-mediated *mTOR* deletion during adulthood	Massive cardiac dilation, apoptosis, autophagy, mitochondrial abnormalities, sarcomere disarray, cardiac dysfunction, heart failure and early mortality.
	Shende P et al (11)	Tamoxifen-induced *α-MHC-CRE*-mediated *mTOR* deletion during adulthood	Massive cardiac dilation, apoptosis, autophagy, mitochondrial abnormalities, sarcomere disarray, metabolic abnormalities, cardiac dysfunction, heart failure and early mortality.
	Tamai T et al (12)	Constitutive *α-MHC-CRE*-mediated *rheb1* gene deletion	Reduction of mTORCl activity 5 days after birth. Defect in physiological cardiac growth. Cardiac dilation, dysfunction and heart failure. Mortality within 10 days after birth.
AGING	Flynn JM et al (14)	Pharmacological mTOR inhibition using rapamycin	Reduced age-induced cardiac inflammation and fibrosis. Upregulation of energy metabolism.
	Zhou et al (77)	Systemic GSK3-alpha deletion	Cardiac hypertrophy, dysfunction and sarcomere abnormalities during aging through mTOR activation and autophagy inhibition.
CARDIAC HYPERTROPHY	Zhang D et al (10)	Tamoxifen-induced *α-MHC-CRE*-mediated *mTOR* deletion during adulthood and pressure overload	Inhibition of compensatory hypertrophy.

CARDIAC CONDITION	STUDY	TYPE OF MTOR MODULATION AND ANIMAL MODEL	EFFECT ON THE HEART
			Inhibition of protein synthesis. Rapid cardiac dilation, apoptosis, cardiac dysfunction and heart failure.
	Shende P et al (11)	Tamoxifen-induced *α-MHC-CRE*-mediated *mTOR* deletion during adulthood and pressure overload	Inhibition of compensatory hypertrophy. Inhibition of protein synthesis. Rapid cardiac dilation, cardiac dysfunction and heart failure.
	Shioi T et al (16)	mTORC1 inhibition using rapamycin and then pressure overload	Inhibition of pathological cardiac hypertrophy and preservation of cardiac function.
	McMullen JR et al (17)	mTORC1 inhibition using rapamycin in mice with established TAC-induced cardiac hypertrophy	Regression of compensated and decompensated hypertrophy. Improved cardiac function in the latter.
	Volkers M et al (18)	AAV9-mediated PRAS40 overexpression in hearts subjected to pressure overload	Prevention of TAC-induced pathological hypertrophy and myocardial fibrosis. Maintenance of cardiac function.
	Wu X wt al (19)	Constitutive *α-MHC-CRE*-mediated heterozygous *rheb1* gene deletion and then pressure overload	Reduction of TAC-induced hypertrophy and fibrosis.
	Marin TM et al (20)	Mouse model of LEOPARD disease treated with rapamycin	Regression of hypertrophic cardiomyopathy and cardiac disarray.
	Choi et al. (21); Ramos FJ et al (22)	Mouse model of cardiomyopathy caused by Lamin A/C mutation treated with pharmacological mTORC1 inhibition	Autophagy reactivation and improved cardiac function, muscle dystrophy and increased survival.
	Song X et al (96)	*α-MHC-CRE*-mediated mTOR overexpression	No increase in cardiac mass. Preservation of cardiac function and reduced myocardial inflammation through inhibition of NF-κB signaling.
CARDIAC ISCHEMIA and REPERFUSION	Sciarretta S et al (23)	Pharmacological inhibition of mTORC1 during prolonged ischemia. Prolonged ischemia in mice with *a-MHC-CRE*-mediated Rheb overexpression	Inhibition of ischemia-induced mTORC1 downregulation and autophagy activation. Increased infarct size after ischemia that is reversed by

CARDIAC CONDITION	STUDY	TYPE OF MTOR MODULATION AND ANIMAL MODEL	EFFECT ON THE HEART
			rapamycin treatment.
	Zhai P et al (24)	Mice with *α-MHE-CRE*-mediated dominant negative-GSK-3P overexpression and systemic heterozygous *GSK-3β* deletion subjected to prolonged ischemia and I/R	GSK-3β is activated during prolonged ischemia but inhibited during reperfusion. Genetic inhibition of GSK-3β increases ischemic injury after prolonged ischemia but reduces reperfusion injury through a deregulated activation of mTORC1.
	Buss SJ et al (25)	mTORC1 inhibition with everolimus during chronic myocardial infarction	Reduction of infarct size, pathological growth and cardiac dilation. Improvement of cardiac function. Activation of autophagy.
	Volkers M et al (26)	AAV9-mediated PRAS40 cardiac overexpression and Rictor knockdown in mice subjected to chronic myocardial infarction	Overexpression of PRAS40 inhibits mTORC1, reduces ischemic injury, apoptosis and cardiac remodeling and improves cardiac function in an mT0RC2-dependent manner. Rictor knockdown causes deterioration of cardiac function and remodeling after myocardial infarction.
	Di R et al (109)	Rapamycin and S6K inhibitors during chronic myocardial infarction	Reduction of cardiac ischemic remodeling and cardiomyocte apoptosis.
	Aoyagi T et al (117)	*α-MHC-CRE*-mediated mTOR overexpression and I/R	Inhibition of cardiac remodeling after I/R *in vivo*, and reduction of necrosis and myocardial inflammation after I/R *ex vivo*.
METABOLIC DISORDERS	Wang CY et al (122)	Rapamycin treatment during high fat diet-induced obesity	Akt and mTOR are activated in the vasculature of obese animals. Rapamycin inhibits endothelial senescence and the increased susceptibility to peripheral ischemia in obese animals.
	Sciarretta et al (23)	Rapamycin treatment and partial inducible mTOR genetic disruption in mice with high fat	Ischemia-induced autophagy activation is

CARDIAC CONDITION	STUDY	TYPE OF MTOR MODULATION AND ANIMAL MODEL	EFFECT ON THE HEART
		diet-induced obesity and metabolic syndrome subjected to prolonged ischemia	inhibited in the hearts of obese animals through deregulated activation of Rheb and mTORC1. Infarct size after ischemia is larger in obese animals. Pharmacological and partial genetic inhibition of mTOR rescue autophagy and reduce ischemic injury in obese mice.
	Li ZL et al (123)	Swine model of metabolic syndrome	Increased cardiac mTOR level and reduction of cardiac autophagy that is proportional to the degree of the derangements of cardiac structure and function.
	Guo R et al (124)	Rapamycin in mice with high fat diet-induced obesity	Increased mTOR activity and reduced autophagosome formation in the hearts of obese mice, associated with reduction of cardiac function. Cardiac function is rescued by rapamycin and deteriorated by genetic adiponectin disruption.
	Xu X et al (125)	Mice with systemic Akt2 knockout subjected to high fat diet	mTOR activation and disruption of autophagic flux in the hearts of obese mice. Akt2 deletion rescues autophagic flux and cardiac dysfunction in obese animals.
	Xu X et al (126)	Streptozotocin-induced diabetes	Cardiac autophagosome formation and flux are impaired in diabetic mice. These effects are associated with increased mTOR activity.