Advances in the mTOR Pathway in Cardiomyocyte Senescence-Induced Heart Failure: A Postprint

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Abstract

Heart failure represents the end-stage phase of various cardiac diseases with poor prognosis, and its pathogenic risk increases significantly with age and cardiomyocyte senescence. The mammalian target of rapamycin (mTOR) pathway plays a critical role in the pathophysiology of cardiomyocyte senescence. This article reviews the latest research progress on the mTOR pathway in heart failure induced by cardiomyocyte senescence and explores intervention strategies for delaying cardiomyocyte aging. Persistent activation of mTOR complex 1 (mTORC1) during cardiomyocyte senescence drives pathological cardiac remodeling and accelerates the onset and progression of heart failure through mechanisms including regulation of protein synthesis, lipid metabolism, and inhibition of autophagy; whereas inhibiting excessive mTORC1 activation can delay cardiac aging processes in aged animals and extend lifespan. This article provides novel insights for alleviating senescence-induced heart failure, which may help reduce the disease burden on society.

Full Text

Preamble

Research Progress of mTOR Pathway in Heart Failure Caused by Myocardial Aging

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Abstract

Heart failure represents the end-stage of numerous cardiac diseases with poor prognosis, and its risk increases significantly with age and myocardial cell aging. The mammalian target of rapamycin (mTOR) pathway plays a key role in the pathophysiology of cardiomyocyte aging. This article reviews the latest research progress on the mTOR pathway in heart failure caused by myocardial cell aging and explores potential intervention strategies to delay cardiomyocyte aging. During cardiomyocyte aging, sustained activation of mTOR complex 1 (mTORC1) drives pathological cardiac changes and accelerates the progression of heart failure by regulating protein synthesis, lipid metabolism, and inhibiting autophagy. Conversely, inhibiting mTORC1 overactivation can slow cardiac aging and extend lifespan in elderly animals. This article provides new insights into alleviating age-related heart failure and may help reduce the societal disease burden.

Keywords

Heart failure; Cardiac aging; Mammalian target of rapamycin; Protein synthesis; Lipid metabolism; Autophagy

In recent years, as population aging has accelerated in China, the incidence of heart failure (HF) has increased steadily. Currently, China's population aged 60 and above has reached 264 million, accounting for 18.7% of the total population, and the number of HF patients has grown from 4.5 million in 2016 to 8.9 million in 2022, with the number of elderly HF patients doubling every decade [1]. Age-related HF has become a major challenge for medical diagnosis and treatment systems; however, current approaches can only delay disease progression rather than achieve an effective cure.

Cardiomyocyte aging manifests as protein misfolding and accumulation, cellular hypertrophy, and increased apoptosis [2], leading to various cardiac diseases with end-stage HF. Studies have shown that the mammalian target of rapamycin (mTOR) pathway plays a key role in the physiology and pathology of cardiomyocyte aging. Particularly, mTOR complex 1 (mTORC1) participates in cardiac development and regulates protein synthesis, lipid metabolism, and autophagy, thereby influencing cardiomyocyte aging. This review summarizes research progress on the mTOR pathway in cardiomyocyte aging-induced HF and explores interventions to delay cardiomyocyte aging.

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1. Cardiomyocyte Aging Induces Heart Failure

Aging leads to pathological remodeling of cardiomyocytes and interstitium, manifested by increased cardiomyocyte apoptosis and necrosis, enlarged cardiomyocyte volume, and other pathological changes that not only directly impair cardiac function but also further exacerbate cardiac dysfunction by inducing compensatory hypertrophy of residual cardiomyocytes and compensatory fibrosis of cardiac tissue [3]. Evidence indicates that cardiomyocyte number declines with age [4]; TAKEUCHI et al. [5] demonstrated that the left ventricular mass-to-volume ratio in healthy individuals increases significantly with age, with decreased left ventricular compliance, further confirming the impact of aging on cardiac structure.

Cardiomyocyte aging is a key driver of various cardiovascular diseases, including myocardial fibrosis, arrhythmia, and ischemic heart disease, ultimately leading to HF [6]. In myocardial fibrosis, senescent cells secrete large amounts of pro-fibrotic factors such as transforming growth factor-β, inducing excessive proliferation of fibroblasts and increased collagen deposition [7]. Myocardial fibrosis reduces myocardial flexibility, impairs cardiac reserve capacity, causes diastolic dysfunction, and hinders normal ventricular filling [8]. Additionally, the fibrotic process alters cardiac electrical signal conduction pathways, thereby increasing arrhythmia risk [9]. Ischemic heart disease further exacerbates cardiomyocyte aging and necrosis through mechanisms such as oxidative stress and inflammatory responses [10]. With advancing age, the proportion of senescent cardiomyocytes increases, and these pathological changes gradually accumulate, eventually preventing the heart from effectively adapting to stressors such as exercise or acute illness [11], significantly reducing the capacity to regulate cardiac output and ultimately leading to HF.

2. Role of mTOR Pathway in Cardiomyocyte Aging

2.1 Structure and Basic Function of the mTOR Pathway

In mammals, mTOR forms two distinct complexes: mTORC1 and mTORC2. Both share a common core comprising mTOR, DEP domain-containing mTOR-interacting protein (DEPTOR), and mammalian lethal with SEC13 protein 8 (mLST8). Additionally, mTORC1 contains proline-rich Akt substrate 40 kDa (PRAS40) and regulatory-associated protein of mTOR (Raptor), while mTORC2 contains mammalian stress-activated protein kinase interacting protein 1 (mSIN1) and rapamycin-insensitive companion of mTOR (Rictor) [12]. Both complexes can be activated by growth factor signals, and mTORC2 activity is also influenced by mTORC1.

mTORC1 is activated by nutrients such as amino acids and growth factor signals, while its activity is suppressed when cellular energy is depleted. Upstream regulation of mTORC1 primarily occurs through AMP-activated protein kinase (AMPK) and tuberous sclerosis complex (TSC), a key negative regulator of mTORC1 [13]. Downstream targets of mTORC1 include sterol regulatory element-binding protein (SREBP), S6 kinase (S6K1), and eukaryotic translation initiation factor 4E-binding protein (4E-BP1), which regulate various cellular behaviors and functions including protein synthesis, lipid metabolism, and autophagy [14]. Furthermore, mTORC1 regulates mTORC2 through three negative feedback pathways and one positive feedback pathway: mTORC1 phosphorylates and activates growth factor receptor-bound protein 10 (GRB10), negatively regulating the insulin/insulin-like growth factor (IGF-1) signaling upstream of mTORC2 and hindering mTORC2 activation [15]; the mTORC1 downstream target S6K1 can also inhibit mTORC2 through phosphorylation of insulin receptor substrate 1 (IRS1) [16]; mTORC1 activation can disrupt mTORC2 integrity through E3 ubiquitin ligase TRAF2, enhancing mTORC1 assembly [17]; and mTORC1 can promote CD122 expression, sensitizing NK cells to interleukin-15 (IL-15), whose signaling promotes mTORC2 activation [18].

Due to the lack of specific inhibitors for mTORC2, research on this complex remains incomplete [19-20]. mTORC2 can be activated by growth factor signals but is relatively insensitive to nutrients. The most prominent effect of mTORC2 activation is stimulation of the Akt pathway, promoting expression of aging-related proteins [21]; mTORC2 can activate serum- and glucocorticoid-regulated kinase 1 (SGK1), which has been shown to promote cardiomyocyte survival while inhibiting cardiac hypertrophy, though chronic activation of SGK1 during HF can lead to adverse ventricular remodeling [22-23]; mTORC2 can also regulate cell polarity and cytoskeletal organization through modulation of protein kinase C-α (PKC-α) and Ras homolog family member A (RhoA). Additionally, mTORC2 regulates mTORC1 through two negative feedback pathways and one positive feedback pathway [20]: mTORC2 can negatively regulate IRS1 and solute carrier family 7 member 5 (SLC7A5) to suppress mTORC1 activation signals, while it can upregulate mTORC1 through activation of the IGF-Akt axis.

mTOR plays an indispensable role during growth and development, but moderate inhibition of mTOR activity in old age is cardioprotective, reducing cardiac aging phenotypes and extending lifespan [14]. Mice with cardiac-specific mTOR inhibition mediated by α-myosin heavy chain-Cre recombinase die within weeks after birth due to severe cardiac dilation, dysfunction, and HF [24]; studies have found that the expression abundance of mTOR complexes in the heart negatively correlates with maximum lifespan in mammals [25]; mTOR drives cardiovascular aging, promoting metabolic disorders, cellular hypertrophy, and fibrosis, ultimately leading to age-related HF [26]; inhibiting mTOR expression can reduce cardiac aging phenotypes such as hypertrophy and diastolic dysfunction in rodents and rhesus monkeys [27].

2.2 mTORC1 Promotes Protein Synthesis

Overall, mTORC1 promotes protein synthesis, thereby regulating compensatory cardiac hypertrophy and maintaining cardiac function during pressure overload. However, persistent activation of mTORC1 in the aging heart leads to pathological cardiac hypertrophy [27]. mTORC1 promotes protein synthesis through two distinct mechanisms, playing a key role in the progression of cardiac hypertrophy. On one hand, mTORC1 promotes mRNA translation through downstream substrates and effectors. Phosphorylation of S6K1 at the Thr389 site leads to S6K1 activation, which then phosphorylates programmed cell death protein 4 (PDCD4) and causes its degradation, relieving PDCD4' s inhibition of protein translation and promoting protein synthesis [28]. On the other hand, S6K1 promotes ribosome biogenesis by upregulating transcription of tRNA-encoding genes, ribosome biogenesis factors, and ribosomal proteins, thereby driving protein synthesis [29]. Beyond S6K1, mTORC1 activation also phosphorylates 4E-BP1, releasing it from eukaryotic translation initiation factor 4E (eIF4E) and exposing eIF4E' s phosphorylation sites, relieving inhibition of cap-dependent translation and promoting protein synthesis [30].

Furthermore, mTOR can function as a downstream target of certain genes in cardiac hypertrophy. Studies using mouse transverse aortic constriction models and in vitro cell experiments have demonstrated that kallikrein 11 promotes protein synthesis and cardiac hypertrophy through the mTOR signaling pathway [31]; research on tripartite motif-containing protein 44 (TRIM44, which possesses E3 ubiquitin ligase activity) in mouse in vivo and in vitro models showed that TRIM44 deficiency in cardiomyocytes inhibits the Akt/mTORC1 cascade associated with cardiac hypertrophy, thereby promoting cardiac aging through enhanced protein synthesis, increased lipogenesis, and suppressed autophagy [32].

2.3 mTORC1 Regulates Lipid Metabolism

Cardiac aging is accompanied by significant alterations in lipid metabolism, with aged hearts showing decreased fatty acid oxidation and increased glycolysis. Reduced fatty acid oxidation can lead to lipid accumulation, causing lipotoxicity and cardiomyopathy during aging and increasing HF risk [33]. mTORC1 is closely associated with lipogenesis and fatty acid oxidation. mTORC1 has been shown to activate sterol regulatory element-binding protein (SREBP) in rat hepatocytes, thereby activating acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase involved in lipogenesis, leading to increased fat synthesis [34]. Regarding fatty acid oxidation, mTORC1 can promote the shift from fatty acid oxidation to glycolysis by enhancing hypoxia-inducible factor 1α expression [35]. NACARELLI et al. [36] found that rapamycin-treated cells showed increased fatty acid β-oxidation and catabolism, while SOLIMAN et al. [37] discovered that increased mTOR activity could reduce adipose triglyceride lipase expression, increase de novo lipogenesis, and inhibit lipolysis. In summary, mTORC1 promotes lipogenesis while inhibiting fatty acid oxidation,

thereby causing lipotoxicity during aging; thus, moderate inhibition of mTORC1 is beneficial.

2.4 mTORC1 Inhibits Autophagy

Studies have shown that autophagy is reduced in the aging heart, leading to accumulation of dysfunctional organelles and toxic proteins, sarcomere disarray, and mitochondrial swelling and disruption, which cause cardiomyopathy phenotypes and overall cardiac dysfunction. Activating autophagy can extend lifespan and reduce age-related cardiac hypertrophy and fibrosis [38]. mTORC1 negatively regulates autophagy at both transcriptional and post-translational levels, reducing autophagosome and autolysosome formation [39]. At the transcriptional level, activated mTORC1 reduces expression of autophagy proteins such as ATG7 by regulating transcription factor EB (TFEB), thereby inhibiting autophagy [40]. mTORC1 can also negatively regulate lysosome biogenesis by modulating transcription factors TFE3 and ZKSCAN3 [41]. At the post-translational level, mTORC1 phosphorylates unc-51-like kinase 1 (ULK1) and ATG13, thereby inhibiting the activity of the ULK1-ATG13-FIP200 complex, which is critical for autophagosome formation [42].

2.5 mTORC2 and Cardiac Aging

As previously mentioned, the primary effect of mTORC2 activation is stimulation of the Akt pathway, promoting expression of aging-related proteins. In terms of autophagy, CHANG et al. [43] found in Drosophila that knocking down upstream inhibitory signaling molecules of mTORC2 revealed a role for mTORC2 in promoting autophagy and thereby slowing cardiac aging; while in Caenorhabditis elegans, inhibiting mTORC2 and its downstream effectors increased autophagy activity [44]; and in mice, SGK1 inhibition could also promote autophagosome formation [45]. Regarding lipid metabolism, LIU et al. [46] found that high-fat diet in Drosophila promoted recruitment of dynamin-related protein 1, thereby enhancing mitochondrial proliferation and fat metabolism, while knocking down the Rictor subunit of mTORC2 inhibited this process; mTORC2 may mediate the redistribution of subcutaneous white adipose tissue to visceral fat in elderly individuals, thereby increasing cardiovascular disease risk [47-49]. For overall lifespan, knockout of the Rictor subunit of mTORC2 shortened lifespan in male mice but had no effect on females [50]. Subsequently, ARRIOLA et al. [51] performed ovariectomy on female mice with liver-specific Rictor knockout and found that the ovariectomized group showed significantly increased median lifespan, while castration of male mice with Rictor knockout did not alleviate their shortened median lifespan. Therefore, exploring mTORC2' s role in aging requires consideration of specific tissues, organs, and sex factors to avoid confounded results. Additionally, most existing mTOR inhibitors cannot selectively target mTORC2 [19-20], and current studies have yet to reach consistent conclusions; thus, the molecular mechanisms of selective mTORC2 inhibition and its effects on aging require further investigation.

3. Interventions to Improve Cardiomyocyte Aging

The role of mTORC1 in organismal lifespan and cardiac aging has been established, and inhibiting mTORC1 expression holds promise for ameliorating aging. However, for mTORC2, inhibition produces side effects such as insulin resistance and diabetes [52-53]. Studies have shown that treatment with the mTORC1 inhibitor rapamycin can improve prolonged diastolic time and reduce myocardial stiffness in aged mice [54]; mice receiving rapamycin treatment from late life show longer average lifespan, while those treated from early life show reduced age-related learning and memory deficits [55]; mice with downregulated insulin and IGF-1 signaling exhibit reduced mTORC1-S6K1 activity and extended lifespan [56]. These studies demonstrate that inhibiting mTORC1 activity can delay cardiac functional decline and extend lifespan in multiple organisms.

Clinically, rapamycin is currently used primarily to prevent transplant rejection [57], and its effects on human cardiac aging require further investigation. In the aging heart, decreased defense capacity and immune impairment are important causes of cardiomyopathy [58]; rapamycin can immunomodulate T cells by inhibiting Th1, Th2, and Th17 cell differentiation while promoting regulatory T cell differentiation, potentially slowing aging [59]. A Phase II clinical trial is underway to determine whether rapamycin can improve cardiac function in elderly HFpEF patients (NCT04996719); another clinical trial evaluating whether rapamycin can improve immune, cognitive, and cardiac function in older adults is also being advanced (NCT02874924).

Beyond mTOR inhibitors, caloric restriction (CR) can also inhibit mTORC1 expression. CR primarily exerts anti-aging and lifespan-extending effects by inhibiting the mTORC1 pathway. When cellular energy is depleted, AMP-activated protein kinase (AMPK) is activated and suppresses mTORC1 activity through phosphorylation of tuberous sclerosis complex 2 (TSC2) or Raptor [60]. Studies have found that adding a single essential amino acid, methionine, to the diet of Drosophila under dietary restriction was sufficient to extend lifespan, while caloric intake above optimal levels shortened lifespan, demonstrating the effectiveness of CR in extending lifespan [61]. In primates, CR has been further proven to extend lifespan and delay age-related diseases, including age-related malignancies, cardiovascular aging, neurodegenerative diseases, and other degenerative conditions [62]. In humans, multiple studies have shown that CR can improve cardiac metabolism, reverse age-dependent cardiac hypertrophy, improve diastolic dysfunction and impaired myocardial function, and extend lifespan [63-64].

Conclusion

The mTOR pathway plays a crucial role in cardiac physiology and pathology, exerting key regulatory functions in cardiac development, structure, and maintenance. During aging, persistent activation of mTORC1 causes pathological cardiac changes through regulation of protein synthesis, lipid metabolism, and autophagy, leading to a series of cardiac diseases that ultimately result in HF. Inhibiting mTORC1 activation during aging has been proven to delay cardiac aging and extend lifespan in multiple organisms. However, future efforts must further advance clinical trials of mTORC1 inhibitors to improve cardiac function in aging, while the molecular mechanisms of selective mTORC2 inhibition and its effects on aging also require further investigation. This review primarily summarizes and discusses the mechanisms of mTOR pathway action in cardiomyocyte aging-induced HF and potential interventions, providing new insights for future strategies to delay HF caused by cardiomyocyte aging.

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