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# Investigating the Mechanistic Target of Rapamycin and Analogous Pathways in Cardiovascular Diseases to Augment Cardiac Functionality

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## ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of global mortality, especially in low- to middle-income countries, with heart failure accounting for 34% of deaths, totaling 62.5 million premature deaths in the past decade. Despite initial improvements in survival rates, mortality due to heart failure remains concerning, indicating a decline in the heart's compensatory capacity as age advances. To understand the molecular complexities of CVDs, this narrative review extensively explored databases such as Scopus, Web of Science, and PubMed using specific inclusion criteria to select articles from experimental studies, clinical trials, animal studies, and observational studies published after the year 2000. Conversely, exclusion criteria were applied to omit articles irrelevant to the topic or published before 2000. The extensive literature search revealed, surprisingly, the largely unexplored potential of targeting the mTOR pathway for the treatment of CVDs. Previous studies suggest that mTOR modulation could reshape cardiac disease pathways, though clinical evidence remains limited. Recent findings underscore mTOR dysregulation in cardiac diseases and show promise in mitigating dysfunction through mTOR inhibition, despite challenges in clinical translation. Understanding mTOR's crosstalk with other pathways illuminates the complexity of cardiac disease. This review emphasizes mTOR's significance in coronary artery disease (CAD) and ischemic heart disease (IHD), suggesting avenues for further research and clinical applications to improve cardiovascular disease management and reduce heart failure-related mortality.

**Keywords**: Coronary artery disease; ischaemic heart disease; mTOR pathway.

## INTRODUCTION

The mechanistic Target of Rapamycin (mTOR) is a highly conserved serine/threonine protein kinase that functions as a central regulator of cellular growth, proliferation, metabolism, and survival. It is a key component of two distinct multiprotein complexes: mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2)[13]. mTORC1 is primarily known for its role in regulating protein synthesis, cell growth, and metabolism in response to nutrient availability, growth factors, and energy status. Activation of mTORC1 promotes anabolic processes such as protein synthesis and lipid biosynthesis while inhibiting catabolic processes such as autophagy[13]. Key upstream regulators of mTORC1 include the PI3K/Akt pathway, which is activated by growth factors such as insulin and insulin-like growth factor 1 (IGF-1), and the AMP-activated protein kinase (AMPK) pathway, which senses cellular energy levels. Upon activation, mTORC1 phosphorylates downstream targets such as ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), leading to enhanced protein synthesis and cell growth[31].

mTORC2, on the other hand, regulates cell survival, cytoskeletal organization, and metabolism. Akt phosphorylation at Serine 473 by mTORC2 is crucial for

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its full activation and plays a central role in promoting cell survival and proliferation. Additionally, mTORC2 has been closely associated with the regulation of cytoskeletal dynamics through its phosphorylation of substrates such as protein kinase C alpha (PKCα) and serum/glucocorticoid-regulated kinase 1 (SGK1)[31].

Dysregulation of mTOR signalling has been implicated in a wide range of diseases, including cancer, metabolic disorders, neurodegenerative, and cardiovascular diseases[33]. In cancer, aberrant activation of mTOR signalling is commonly observed due to mutations or alterations in upstream regulators such as PI3K, Akt, and PTEN, leading to uncontrolled cell growth and proliferation. Abnormal mTOR signalling has also been implicated in metabolic disorders such as obesity, type 2 diabetes, and insulin resistance highlighting the complex interplay between mTOR signalling and metabolic homeostasis[33] making it an attractive target for therapeutic intervention in several pathologies including cardiovascular.

**1) Coronary Artery Disease (CAD)**

**The pathophysiology of coronary artery disease**

In the genesis of coronary artery disease (CAD), the initiation of atherosclerotic plaque formation emerges as a pivotal precursor (Figure 1). Atherosclerosis, a multifactorial phenomenon linked to predisposing conditions including diabetes, hypertension, chronic infection, lipid abnormalities, intra-abdominal/visceral obesity, and hypertension, assumes a paramount role in this intricate process.[1] Notably, heightened levels of visceral adipose tissue significantly augment the susceptibility to coronary artery disease. Substantial evidence implicates inflammation as a pivotal player in atherosclerotic plaque development.[2] This inflammatory cascade is orchestrated through the activation of nuclear factor kappa B (NfκB) and transforming growth factor beta (TGFβ) pathways, culminating in the release of cytokines, inflammatory cells, and adhesion factors that contribute to endothelial dysfunction. Additionally, hemodynamic forces induced by blood flow elicit endothelial dysfunction, characterized by the upregulation of factors such as endothelin, vascular endothelial growth factors (VEGF), cytokines, adhesion factors, and other pro-inflammatory mediators.[3]

Furthermore, the increased uptake of oxidized low-density lipoprotein (oxLDL) serves as a potent chemo-attractant for lymphocytes and macrophages into the intima of the blood vessel. Macrophages laden with oxLDL, along with T cells, platelets, and smooth muscle cells, coalesce to form fatty streaks, arresting motility and fostering atherogenic microenvironments. Foam cells within the intimal wall release growth factors, promoting stromal cell proliferation and extracellular remodelling, thereby propelling the progression of fatty streaks into granuloma formation. Neovascularization of the plaque surfaces culminates in the development of an atheroma plaque.[4] The p53 signalling pathway, integral to apoptosis, precipitates the rupture of atherosclerotic plaques, prompting subsequent platelet aggregation at the rupture site and the clinical manifestation of coronary artery disease symptoms.[2]

Research endeavours underscore the pivotal role of nutrients, particularly lipids and carbohydrates, in regulating gene expressions of glycolytic and lipogenic enzymes. These molecular signals exert their influence through key genes such as sterol responsive element-binding protein, 1 and 2 (SREBP) and the mammalian target of rapamycin (mTOR).

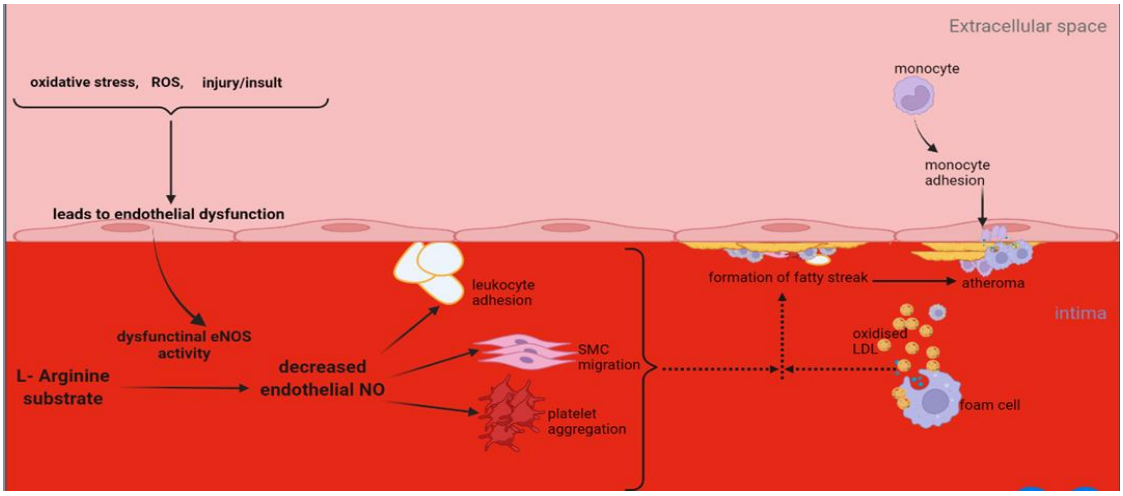


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**Figure 1. Pathophysiology of coronary artery disease**

Figure 1 illustrates the development of an atherosclerotic plaque. The initial trigger for atherogenesis is either oxidative stress or injury/insult to the arterial wall. The resulting injury leads to endothelial dysfunction, characterized by impaired eNOS activity. Consequently, smooth muscle cells migrate, leukocytes adhere, and platelets aggregate, culminating in the formation of a fatty streak within the vessel wall's intima. Simultaneously, LDL oxidation occurs, accompanied by the accumulation of monocytes, macrophages, and oxidized LDL, which give rise to foam cells. These foam cells adhere to the fatty streak, leading to the formation of an atherosclerotic plaque. Clinical manifestations of coronary artery disease occur when the atherosclerotic plaque ruptures.

**Role of mTOR in CAD**

mTOR assumes a pivotal role in diverse pathophysiological processes within the cardiovascular system.[5] Specifically, mTORC1, a component of the mTOR complex orchestrates the synthesis of membrane lipids in cells by activating SREBP1/2 and transcription factor genes governing fatty acid and cholesterol metabolism.[5] The activation of SREBP1/2 by mTORC1 can occur directly through the phosphorylation of S6K-1 or indirectly via the phosphorylation of Lipin 1, a negative regulator of SREBP1/2.[6] Dysregulation of SREBPs induces dysfunction in lipogenesis and fatty acid metabolism, contributing to cardiovascular diseases, diabetes mellitus, and obesity.[7] In specific cardiovascular conditions such as coronary artery disease, SREBP genes exhibit significant expression in epicardial adipose tissue (EAT), situated between the epicardium and the pericardium.[8] Overexpression of SREBPs is linked to the exacerbation of coronary atheroma, and studies associate the upregulation of SREBP genes with early-stage atherosclerosis, even at normal plasma lipid levels.[9]

Endothelial dysfunction serves as a pivotal element in the progression from a plaque to an atheroma, primarily driven by reduced availability of endothelial nitric oxide (eNO). eNO, synthesized by endothelial nitric oxide synthetase (eNOS), encoded by chromosome 7 in humans, predominantly exists in the vasculature, regulating vessel permeability and promoting angiogenesis.[10,11] Additionally, eNOS plays a vital role in inhibiting leukocyte adhesion to the endothelial wall, preventing the migration of smooth muscle cells (SMC), and averting platelet aggregation in the cardiovascular system.[12] eNOS phosphorylation is regulated through various pathways involving calmodulin and multiple phosphorylation events, with serine 1177 phosphorylation

being the primary regulator.[13] (Figure 2). Among the kinases involved in eNOS phosphorylation, phosphor kinase B and C (PKB and PKC) play a significant role.[14] The phosphorylation of serine 1177 occurs downstream of the phosphoinositide 3 kinase pathway.[15,16] Insulin, HDL, estradiol, and VEGF can enhance serine 1177 phosphorylation through the AKT/PKB pathway, while the phosphorylation of threonine at 459 reduces eNOS activity. VEGF, in particular, phosphorylates Ser1177 and dephosphorylates threonine 459.[17] Conversely, PKC dephosphorylates Ser1177 and phosphorylates threonine 459, decreasing eNOS activity.[18] A defective AKT/eNOS mechanism resulting in increased phosphorylation of eNOS at Ser1177 leads to endothelial dysfunction and accelerated atherogenesis.

The impairment of endothelial function due to injury or insult manifests as alterations in eNO and serves as an early indicator of vascular diseases.[19] Conditions such as oxidative stress and the presence of reactive oxygen species (ROS) render eNOS pro-atherogenic through 'uncoupling of eNOS', causing dysfunctional eNOS activity.[13] Under normal physiologic conditions, the generation of endothelial nitric oxide by eNOS depends on the co-factor tetrahydrobiopterin (BH4).[20] In pathological conditions like atherosclerosis, there is a decrease in endothelial BH4 production, an increase in the formation of the eNOS inhibitor asymmetric dimethyl arginine (ADMA), and an increase in arginase activity, which collectively reduce the substrate of eNOS, L-arginine into urea and ornithine. This leads to superoxide anion (O2-) production and decreased NO release, initiating a cascade of oxidative damage that disrupts endothelial function and overall cardiac health.[21,22] Recent studies on mice reported that an increase in S6 kinase activity, a downstream target of mTORC1, enhances superoxide generation and decreases NO function due to eNOS uncoupling.[23] (Figure 2). Therefore, it can be inferred that S6 kinase activation by mTORC1 phosphorylates eNOS, leading to oxidative stress and endothelial dysfunction- precursors to atherosclerosis and coronary artery disease. Given the crucial role of mTORC1 in cellular metabolism and nitric oxide signalling, a comprehensive understanding of the implications of mTORC1-mediated phosphorylation of eNOS is imperative.

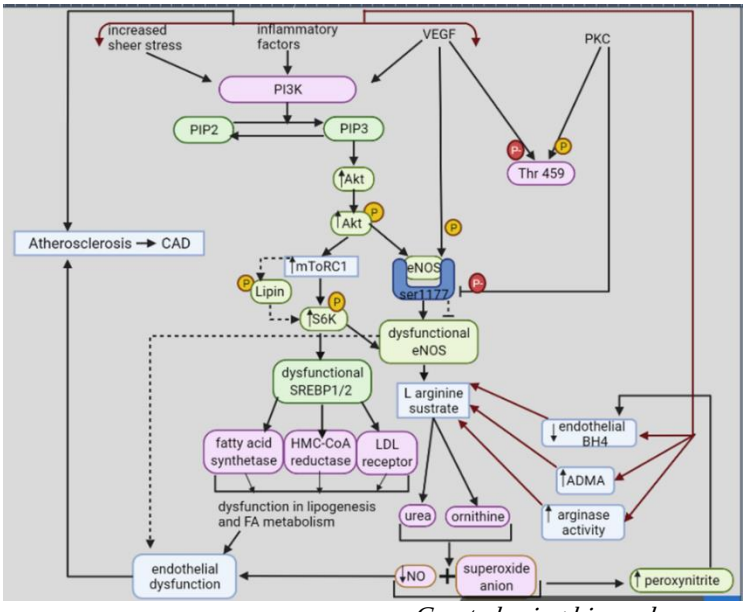


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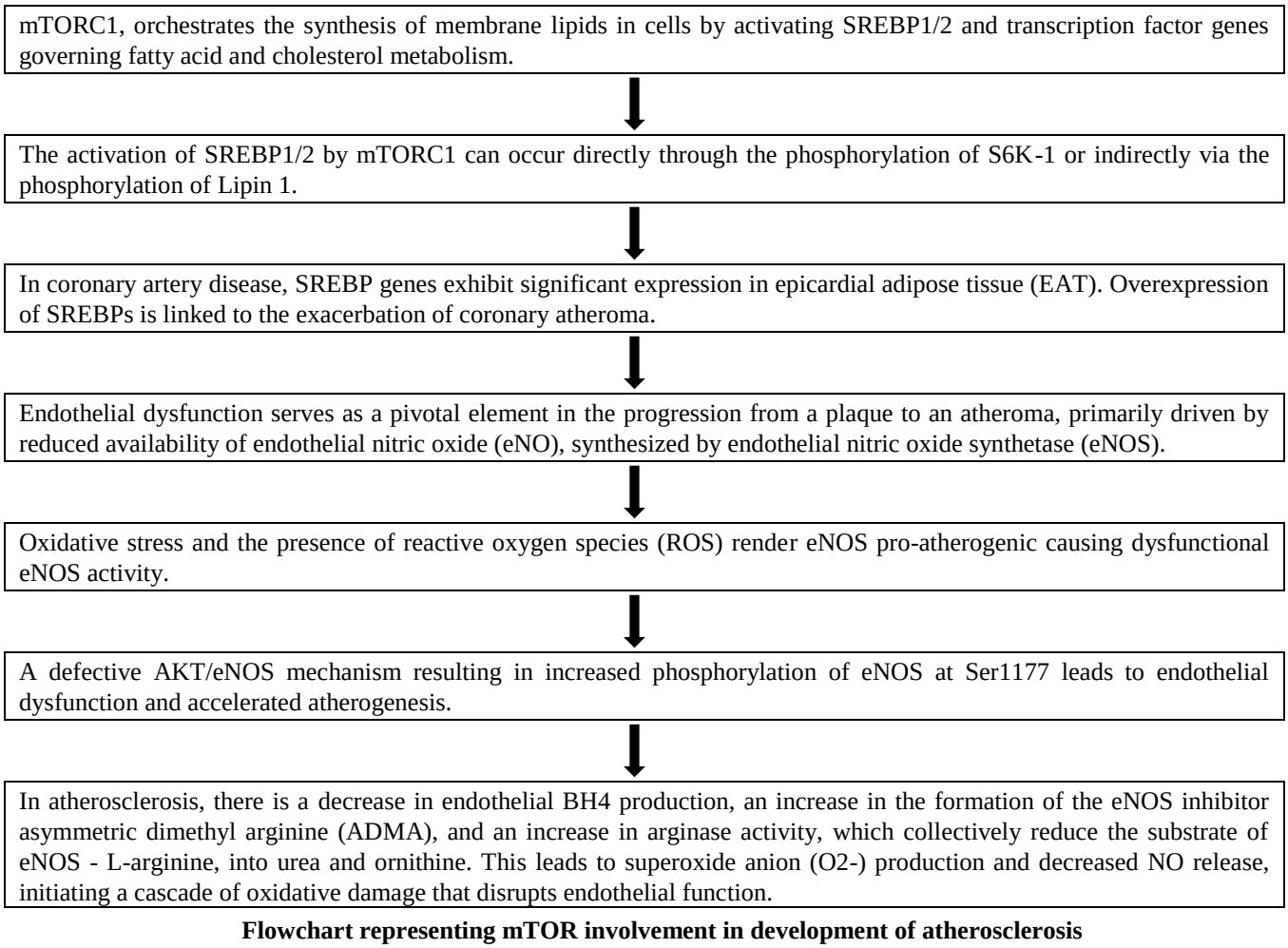
**Figure 2. The Role of mTOR in the pathogenesis of CAD**

Figure 2 depicts the involvement of mTOR in the development of coronary artery disease (CAD). The activation of mTORC1, facilitated by upstream Akt signaling, initiates the phosphorylation of its downstream substrate, S6 Kinase. This phosphorylation event precedes the disruption of lipogenesis and fatty acid metabolism through the dysregulation of SREBP1/2. Additionally, the activation of upstream Akt also impairs eNOS function and its activity on its substrate, L-arginine, ultimately leading to the generation of free radicals such as superoxide and peroxynitrite. These free radicals contribute to endothelial dysfunction, which serves as a precursor to CAD. Factors such as increased shear stress, inflammatory mediators, and VEGF indirectly promote endothelial dysfunction by reducing the availability of endothelial BH4, a critical co-factor for eNOS, and increasing levels of ADMA.




**Flowchart representing mTOR involvement in development of atherosclerosis**

**Inhibition/ knockout of mTOR in CAD**

mTOR, a pivotal regulator of cellular energy and nutrient homeostasis, can be effectively hindered by mTOR inhibitors such as rapamycin and everolimus. This intervention leads to the suppression of lymphocyte cell proliferation directed towards the atherosclerotic region and hampers cell cycle progression.[24] Rapamycin specifically targets mTORC1, resulting in the inhibition of p70S6K, which, in turn,

downregulates cyclooxygenase -2 (COX-2) and inducible nitric oxide synthase (iNOS). These proteins are crucial contributors to inflammation and have been implicated in the heightened production of VEGF.[24]

Various animal experimental models have employed rapamycin or rapalogs like everolimus to impede mTOR and scrutinize its impact on atherosclerosis progression. These models have demonstrated that rapalogs effectively inhibit mTORC1, eliciting a potent anti-atherosclerotic effect by:[25]

i) Curtailing smooth muscle cell proliferation,

ii) Suppressing macrophage activity,

iii) Hampering the recruitment and migration of monocytes to the vessel wall, and

iv) Diminishing de novo protein synthesis through the dephosphorylation of downstream mTORC1 targets, specifically p70S6K and 4E-BP1.

Conversely, mTORC1 inhibition prompts the activation of the mTORC2 pathway, instigating cell survival and autophagy. This molecular cascade prevents the transition of early-stage atherosclerotic plaques into fully formed plaques.[26] Investigations on the inflammatory response in arterial atherosclerotic plaques in Apo-E knockout mice have unveiled that mTORC1 inhibition in early plaques results in eNOS phosphorylation within the atherosclerotic regions. This phenomenon leads to reduced migration of smooth muscle cells and diminished adhesion of monocytes to the area, effectively curtailing the size of fatty streaks.[27] Notably, treatment with mTOR inhibitors in LDLR-/- mice has demonstrated substantial delays in the progression of small-sized plaques into fully developed atherosclerotic plaques.[28]

**Key findings:**

Role of mTORC1 in Lipid Metabolism: The involvement of mTORC1 in regulating lipid synthesis via SREBP1/2 activation elucidates its contribution to cardiovascular diseases such as atherosclerosis. Dysregulation of SREBPs leads to dysfunction in lipogenesis and fatty acid metabolism, exacerbating conditions like coronary artery disease. Understanding these pathways highlights potential therapeutic targets aimed at modulating mTORC1 activity to mitigate lipid-related cardiovascular risks.

Impact of Endothelial Dysfunction on Atherogenesis: The elucidation of endothelial dysfunction mechanisms, particularly involving eNOS phosphorylation, underscores its pivotal role in atherosclerosis development. Dysfunctional eNOS activity, influenced by factors like oxidative stress and ROS, leads to impaired endothelial function and reduced nitric oxide availability, initiating a cascade of events culminating in atherosclerotic plaque formation. Targeting pathways involved in eNOS regulation, such as the AKT/PKB pathway, may offer therapeutic avenues for restoring endothelial function and preventing atherogenesis.

Link between mTORC1 Activation and Endothelial Dysfunction: The identified association between mTORC1 activation, S6 kinase activity, and eNOS phosphorylation provides further insights into the role of mTOR signalling in endothelial dysfunction and atherosclerosis. Enhanced S6 kinase activity, downstream of mTORC1, contributes to eNOS uncoupling and subsequent oxidative stress, further exacerbating endothelial dysfunction and promoting atherogenesis. This highlights the potential of targeting mTORC1 signalling pathways to alleviate endothelial dysfunction and prevent cardiovascular diseases.

Overall, these findings underscore the intricate interplay between mTOR signalling, lipid metabolism, endothelial function, and atherosclerosis, offering potential therapeutic targets for intervention in cardiovascular diseases. A comprehensive understanding of these pathways is crucial for developing targeted therapies aimed at improving cardiac health and preventing the progression of cardiovascular diseases.

**2. Ischaemic Heart Disease (IHD)**

**The pathophysiology of Ischaemic Heart Disease (IHD)**

Myocardial infarction (MI), stemming from the

occlusion of coronary arteries, represents a sudden cardiac event with potential fatal outcomes irrespective of age, gender, or ethnicity. Despite heightened awareness and endeavors in resuscitation the mortality rate persists at approximately 10% during the acute phase and around 25% during the chronic phase of MI.[29] The restoration of blood flow to the myocardium following ischemia induces a paradoxical damage known as "ischemia/reperfusion injury," often culminating in heart failure despite successful reperfusion. Consequently, an episode of acute myocardial infarction comprises two primary phases: the ischemic phase, stemming from coronary artery occlusion and the formation of an infarct zone in the myocardium, and the reperfusion phase, wherein blood flow is reinstated.[29] Both ischemia and reperfusion events inflict detrimental effects on cardiac tissue.[29] (Figure 3). Given the substantial impact of ventricular remodeling on the prognosis of MI, it becomes imperative to discern pathways that either facilitate or impede this process to formulate safer therapeutic interventions. Molecules such as phosphoinositide-kinase 3 and Akt exhibit cardioprotective effects through the mTOR pathway, which assumes a pivotal role as the primary regulator of cellular functions and the central coordinator of diverse signaling pathways.[30]

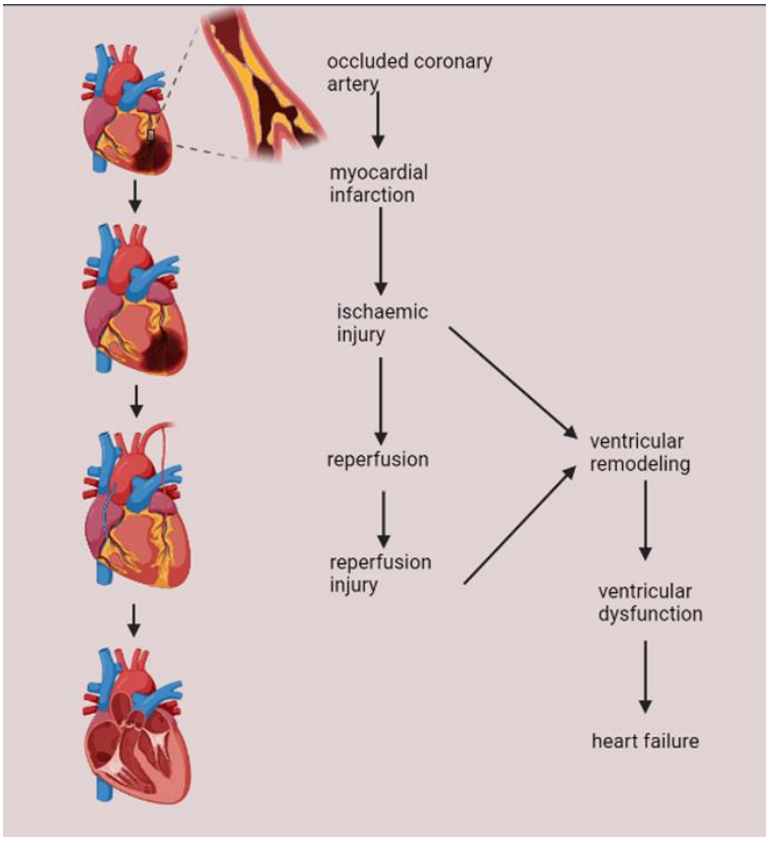



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**Figure 3. Pathophysiology of Ischaemic Heart Disease (IHD)**

Fig. 3 depicts representation of coronary artery occlusion due to long term predisposing factors lead to sudden cardiac events like myocardial infarction. The episode of a MI has two phases, an ischaemic phase where there is reduced or no blood supply beyond the point of occlusion and a reperfusion phase in which blood supply is restored. Each of these phases cause cardiac injury and activates signalling pathways both detrimental and beneficial to cardiac recovery.

**Role of mTOR in IHD**

Investigations utilizing myocardial infarction (MI) models in mice have delineated the nuanced influence of the mTOR signalling pathway, specifically governed by mTOR phosphorylation and the dynamics of mTORC1 and mTORC2.[31] In the context of MI, both mTORC1 and mTORC2 undergo phosphorylation, and the induction of mTORC2 expression through autophagy manifests a protective effect during the ischemic phase of ischemia-reperfusion, whereas mTORC1 proves beneficial during the reperfusion phase.[32] (Figure 4). Notably, research underscores the cardioprotective role of mTORC2 activation in cardiomyocytes, with its genetic deletion or knockdown of Rictor, a downstream substrate of mTORC2, exacerbating cell survival.[33] The inhibition of Rictor leads to diminished phosphorylation of Akt at Serine 473, inadequate phosphorylation of downstream Akt targets like Forkhead box protein O (FoxO), and heightened cell death.[34] Previous investigations have proposed that mTORC2 governs substrate specificity for downstream Akt targets, including FoxO, glycogen synthase kinase-3 (GSK-3), and tuberous sclerosis 2 (TSC-2).[35]

During the reperfusion phase, the activation of p70S6 kinase, a downstream target of mTORC1, stimulates protein synthesis and eventual myocardial hypertrophy in response to MI. Conversely, phosphorylation of 4E-BP1, another downstream substrate of mTOR, inhibits protein synthesis, with mTOR inactivating 4E-BP1 during hypertrophy.[36] Downstream, inhibition of the ubiquitin-proteasome system attenuates the pro-inflammatory response mediated by NfkB.[37] PRAS40, a proline-rich Akt substrate, acts as both a substrate and a component of mTORC1, inhibiting mTORC1 activity post-infarction.[38] Phosphorylation of PRAS40 by either Akt or mTORC1 prompts its dissociation from mTORC1, relieving its inhibitory effect on mTORC1.[38] Elevated expression of PRAS40 confers protection post-myocardial infarction by mitigating against ischemic injury and steering myocytes towards mTORC2 signaling.[39]

Ras homolog enriched in brain (Rheb), functioning as an upstream regulator of mTOR and an energy sensor, undergoes regulation by various kinases, including Akt, AMPK, and glycogen synthase kinase-3β, through tuberous sclerosis complex proteins 1/2 (TSC).[40] In conditions of low cellular energy, such as ischemia, AMPK activates TSC1/2, culminating in the inhibition of Rheb and subsequent suppression of mTORC1. This suppression mitigates the phosphorylation of p70S6K and 4E-BP1, leading to diminished protein synthesis and energy conservation during the ischemic phase. Glucose deprivation during ischemia redirects cardiomyocytes towards the activation of the mTORC2 pathway and autophagy. Animal models with Rheb overexpression exhibited a reduction in autophagy genes under conditions of energy deprivation, emphasizing the pivotal role of Rheb in autophagy regulation as a protective mechanism for cardiomyocytes in the ischemic state.[41]

However, prolonged ischemia induces dephosphorylation and activation of GSK-3β, while reperfusion inhibits its activity. GSK-3β, expressed via the mTOR pathway, exhibits cardioprotective effects during both ischemia and reperfusion. The upstream regulation of GSK-3β by Akt,[42] which phosphorylates TSC2, resulting in mTORC1 inactivation,[43] plays a pivotal role. The suppression of GSK-3β during reperfusion facilitates cardioprotection by regulating the opening of the mitochondrial permeability transition pore (mPTP) through direct phosphorylation.[44]

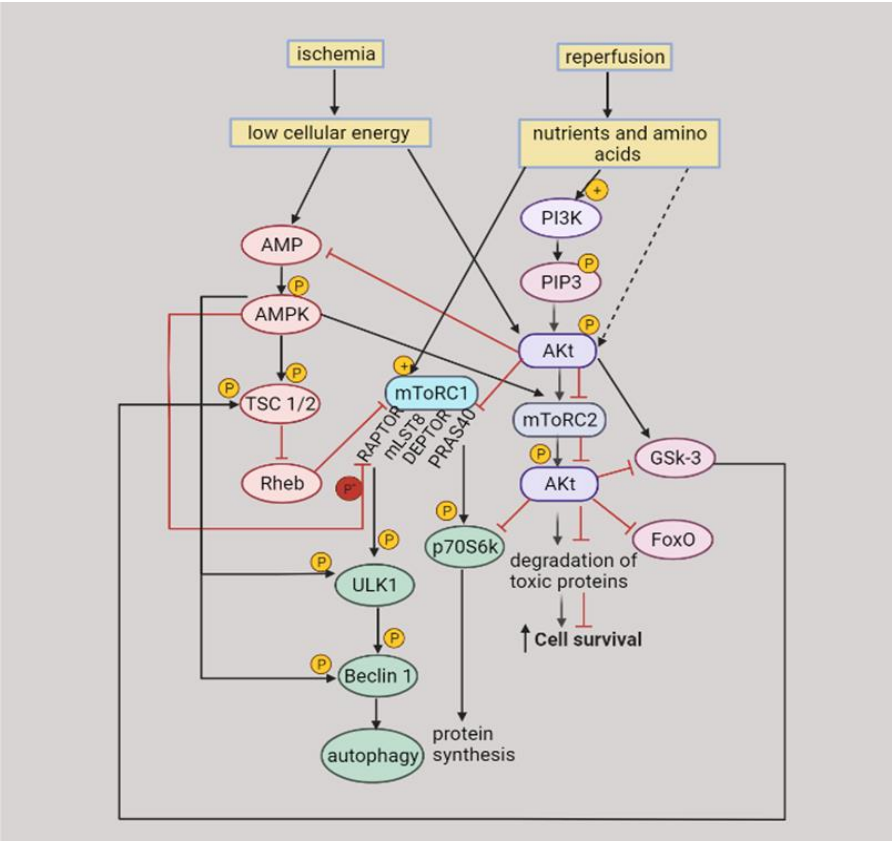


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**Figure 4. Role of mTOR in pathogenesis of IHD**

Fig.6 The two components of mTOR – mTORC1 and mTORC2 have a role to play during the reperfusion and ischemic phases respectively. mTORC1 is activated during the reperfusion phase when blood supply is restored and in the presence of nutrients and amino acids leading to protein synthesis and eventual myocardial hypertrophy, while mTORC2 is activated during the ischemic phase via the AMPK-Akt pathway which inhibits mTORC1 and activates autophagy genes like beclin, FOXO and Atg 7, ulk which bring about cell survival through degradation of toxic proteins which is a protective mechanism for cardiomyocytes in ischemic state

In conditions of low cellular energy, such as ischemia phase of MI, AMPK activates TSC1/2, culminating in the inhibition of Rheb and subsequent suppression of mTORC1. This suppression mitigates the phosphorylation of p70S6K and 4E-BP1, leading to diminished protein synthesis and energy conservation during the ischemic phase.

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Glucose deprivation during ischemia redirects cardiomyocytes towards the activation of the mTORC2 pathway and autophagy.

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During the reperfusion phase of MI, the activation of p70S6 kinase, a downstream target of mTORC1, stimulates protein synthesis and eventual myocardial hypertrophy.

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PRAS40, a proline-rich Akt substrate, acts as both a substrate and a component of mTORC1, inhibiting mTORC1 activity post-infarction. Elevated expression of PRAS40 confers protection post-myocardial infarction by mitigating against ischemic injury and steering myocytes towards mTORC2 signaling.

↓

mTORC2 governs substrate specificity for downstream Akt targets, including FoxO, glycogen synthase kinase-3 (GSK-3), and tuberous sclerosis 2 (TSC-2). However, prolonged ischemia induces dephosphorylation and activation of GSK-3β, while reperfusion inhibits its activity.

↓

GSK-3β, expressed via the mTOR pathway, exhibits cardioprotective effects during both ischemia and reperfusion.

**Flowchart representing mTOR involvement in development of ischemic heart disease**

**Inhibition/ knockout of mTOR in IHD**

In vivo experiments utilizing Langendorff-perfused rat and rabbit hearts involved the administration of the mTOR inhibitor rapamycin, either preceding the onset of reperfusion subsequent to ischemia or before the commencement of ischemia itself. Notably, when rapamycin was given before the initiation of reperfusion, the absence of ischemic preconditioning, which typically imparts cardioprotection in ischemia-reperfusion injury, was observed. However, administration of rapamycin prior to the onset of ischemia proved effective in limiting the size of the ensuing infarction.[45] In GSK-3β knock-out C57BL/6J mice, the adverse effects associated with GSK-3β inhibition during prolonged ischemia were ameliorated upon treatment with rapamycin.[42]

**Key findings**

Understanding Ischemia/Reperfusion Injury: The description of MI's two primary phases, ischemia, and reperfusion, underscores the complex nature of the cardiac damage inflicted during these events. Ischemia/reperfusion injury, characterized by paradoxical damage upon restoration of blood flow, significantly contributes to the development of heart failure post-MI. This recognition emphasizes the importance of developing therapeutic strategies targeting both ischemic and reperfusion phases to mitigate cardiac damage and improve outcomes.

Role of mTOR Pathway in Cardio-protection: The identification of molecules such as phosphoinositide-kinase 3 and Akt, which exhibit cardioprotective effects through the mTOR pathway, offers promising therapeutic targets for MI treatment. The mTOR pathway's central role in regulating cellular functions and coordinating various signalling pathways suggests its potential as a key

mediator in modulating cardiac response to ischemic injury. Targeting this pathway could potentially mitigate ischemia/reperfusion injury and improve cardiac outcomes post-MI.

In essence, these findings enhance our understanding of the pathophysiology of MI, particularly the detrimental effects of ischemia/reperfusion injury, and provide insights into potential therapeutic interventions. Developing targeted therapies that modulate the mTOR pathway to protect against cardiac damage may represent a promising approach for improving outcomes in MI patients.

**Current research and emerging perspectives**

In cardiovascular biology, mTORC1 activation is pivotal for facilitating adaptive cardiac hypertrophy, while mTORC2 safeguards cardiomyocyte viability during pressure overload[46]. mTORC1 inhibition holds promise in ameliorating cardiac remodelling and failure, thereby extending longevity in murine models and potentially affording cardio-protection in humans. Despite limited clinical evidence, pharmacologically targeting mTOR, emerges as a prospective therapeutic avenue for cardiovascular diseases.

Rapamycin and rapalogs such as everolimus have emerged as effective agents in mitigating cardiac dysfunction and remodelling, in animal models of cardiac hypertrophy and heart failure, induced by transverse aortic constriction. These findings underscore the therapeutic promise of targeting mTOR via rapamycin and rapalogs like everolimus as nanoparticles [51] in addressing hypertrophic disease and its associated heart failure[48]. Compelling evidence also suggests that metformin indirectly modulates mTORC1 activity via both AMPK-dependent and -independent mechanisms, exhibiting efficacy in attenuating atherosclerosis in multiple animal models [49]. Although phytopharmaceuticals have demonstrated potential in laboratory studies, challenges remain in effectively translating their efficacy into clinical applications, especially regarding their delivery [50].

The specificity of mTOR inhibitors and the potential for off-target effects pose significant considerations. The complex involvement of mTOR in cardiovascular pathologies underscores the need for highly selective modulators capable of selectively targeting mTOR complexes. Novel compounds with drug-likeness properties should undergo rigorous evaluation in both preclinical models and clinical trials [52], specifically designed to assess their impact on cardiac development, physiology, and stress response following mTOR modulation. Rigorous preclinical and clinical studies are imperative to ascertain the long-term safety and efficacy of targeting mTOR across diverse scenarios of cardiac diseases. A profound understanding of the intricate crosstalk between mTOR and other signalling pathways will not only provide new insights into the complexity of cardiac disease pathophysiology but also offer a comprehensive perspective on the multifaceted role of mTOR in cardiovascular diseases.

**Acknowledgements & Conflict of interest**

The author is the sole contributor to this review article and declares that there is no financial, academic, or personal interests that have influenced the work reported in this paper.

## REFERENCES


1. Hansson G.K. Inflammation, atherosclerosis, and coronary artery disease. *N. Engl. J. Med.* 2005; 352(16):1685-1695.
2. Pawitan J. Molecular pathogenesis of atherosclerosis and implication for therapy. *Int. Med. J. Malays.* 2010; 9(2):7-14.
3. Walpola P.L., Gotlieb A.I., Cybulsky M.I. and Langille B.L. Expression of ICAM-1 and VCAM-1 and monocyte adherence in arteries exposed to altered shear stress. *Arterioscler. Thromb. Vasc. Biol.* 1995; 15(1):2-10.
4. Samson S., Mundkur L. and Kakkar V.V. Immune response to lipoproteins in atherosclerosis. *Cholesterol* 2012; 2012:571846.
5. Düvel K., Yecies J.L., Menon S., Raman P., Lipovsky A.I., Souza A.L. et al. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol. Cell* 2010; 39(2):171-183.
6. Peterson T.R., Sengupta S.S., Harris T.E., Carmack A.E., Kang S.A., Balderas E. et al. mTOR complex 1 regulates lipin 1 localization to control the SREBP pathway. *Cell* 2011; 146(3):408-420.
7. Brown M.S. and Goldstein J.L. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. *Cell* 1997; 89(3):331-340.
8. Pérez-Belmonte L.M., Moreno-Santos I., Cabrera-Bueno F., Sánchez-Espín G., Castellano D., Such M. et al. Expression of sterol regulatory element-binding proteins in epicardial adipose tissue in patients with coronary artery disease and diabetes mellitus: preliminary study. *Int. J. Med. Sci.* 2017; 14(3):268-274.
9. Robinet P., Védie B., Chironi G., Gariépy J., Simon A., Moatti N. et al. Characterization of polymorphic structure of SREBP-2 gene: role in atherosclerosis. *Atherosclerosis* 2003; 168(2):381-387.
10. Halcox J.P., Schenke W.H., Zalos G., Mincemoyer R., Prasad A., Waclawiw M.A. et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; 106(6):653-658.
11. Förstermann U. and Sessa W.C. Nitric oxide synthases: regulation and function. *Eur. Heart J.* 2012; 33(7):829-837.
12. Davies M.G. and Hagen P.O. The vascular endothelium. A new horizon. *Ann. Surg.* 1993; 218(5):593-609.
13. Yang Z. and Ming X.F. mTOR signalling: the molecular interface connecting metabolic stress, aging and cardiovascular diseases. *Obes. Rev.* 2012; 13 Suppl 2:58-68.
14. Sessa W.C. eNOS at a glance. *J. Cell Sci.* 2004; 117(Pt 12):2427-2429.
15. Fulton D., Gratton J.P., McCabe T.J., Fontana J., Fujio Y., Walsh K. et al. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature* 1999; 399(6736):597-601.
16. Huang P.L. eNOS, metabolic syndrome and cardiovascular disease. *Trends Endocrinol. Metab.* 2009; 20(6):295-302.
17. Dimmeler S., Dernbach E., Zeiher A.M. Phosphorylation of the endothelial nitric oxide synthase at ser-1177 is required for VEGF-induced endothelial cell migration. *FEBS Lett.* 2000; 477(3):258-262.
18. Michell B.J., Chen Z.P., Tiganis T., Stapleton D., Katsis F., Power D.A. et al. Coordinated control of endothelial nitric-oxide synthase phosphorylation by protein kinase C and the cAMP-dependent protein kinase. *J. Biol. Chem.* 2001; 276(21):17625-17628.
19. Davignon J. and Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004; 109(23 Suppl 1):III27-III32.
20. Tiefenbacher C.P., Bleeke T., Vahl C., Amann K., Vogt A., Kübler W. Endothelial dysfunction of coronary resistance arteries is improved by tetrahydrobiopterin in atherosclerosis. *Circulation* 2000; 102(18):2172-2179.
21. Alp N.J., McAteer M.A., Khoo J., Choudhury R.P.,

Channon K.M. Increased endothelial tetrahydrobiopterin synthesis by targeted transgenic GTP-cyclohydrolase I overexpression reduces endothelial dysfunction and atherosclerosis in ApoE-knockout mice. *Arterioscler. Thromb. Vasc. Biol.* 2004; 24(3):445-450.

22. Peng H., Zhuang Y., Harbeck M.C., He D., Xie L., Chen W. Serine 1179 Phosphorylation of Endothelial Nitric Oxide Synthase Increases Superoxide Generation and Alters Cofactor Regulation. *PLoS One* 2015; 10(11):e0142854.
23. Rajapakse A.G., Yepuri G., Carvas J.M., Stein S., Matter C.M., Scerri I. et al. Hyperactive S6K1 mediates oxidative stress and endothelial dysfunction in aging: inhibition by resveratrol. *PLoS One* 2011; 6(4):e19237.
24. Tarantino G., Capone D. Inhibition of the mTOR pathway: a possible protective role in coronary artery disease. *Ann. Med.* 2013; 45(4):348-356.
25. Marx S.O., Jayaraman T., Go L.O., Marks A.R. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. *Circ. Res.* 1995; 76(3):412-417.
26. Jung C.H., Ro S.H., Cao J., Otto N.M., Kim D.H. mTOR regulation of autophagy. *FEBS Lett.* 2010; 584(7):1287-1295.
27. Naoum J.J., Woodside K.J., Zhang S., Rychahou P.G., Hunter G.C. Effects of rapamycin on the arterial inflammatory response in atherosclerotic plaques in Apo-E knockout mice. *Transplant. Proc.* 2005; 37(4):1880-1884.
28. Mueller M.A., Beutner F., Teupser D., Ceglarek U., Thiery J. Prevention of atherosclerosis by the mTOR inhibitor everolimus in LDLR-/- mice despite severe hypercholesterolemia. *Atherosclerosis* 2008; 198(1):39-48.
29. Nallamothu B.K., Bradley E.H., Krumholz H.M. Time to treatment in primary percutaneous coronary intervention. *N. Engl. J. Med.* 2007; 357(16):1631-1638.
30. Dazert E., Hall M.N. mTOR signaling in disease. *Curr. Opin. Cell Biol.* 2011; 23(6):744-755.
31. Zoncu R., Efeyan A., Sabatini D.M. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* 2011; 12(1):21-35..
32. Aoyagi T., Kusakari Y., Xiao C.Y., Inouye B.T., Takahashi M., Scherrer-Crosbie M. Cardiac mTOR protects the heart against ischemia-reperfusion injury. *Am. J. Physiol. Heart Circ. Physiol.* 2012; 303(1):H75-H85.
33. Hung C.M., Garcia-Haro L., Sparks C.A., Guertin D.A. mTOR-dependent cell survival mechanisms. *Cold Spring Harb. Perspect. Biol.* 2012; 4(12):a008771.
34. Ronnebaum S.M., Patterson C. The FoxO family in cardiac function and dysfunction. *Annu. Rev. Physiol.* 2010; 72:81-94.
35. Guertin D.A., Stevens D.M., Thoreen C.C., Burds A.A., Kalaany N.Y., Moffat J. Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. *Dev. Cell* 2006; 11(6):859-871.
36. Pham F.H., Sugden P.H., Clerk A. Regulation of protein kinase B and 4E-BP1 by oxidative stress in cardiac myocytes. *Circ. Res.* 2000; 86(12):1252-1258.
37. Pye J., Ardeshirpour F., McCain A., Bellinger D.A., Merricks E., Adams J. Proteasome inhibition ablates activation of NF-kappa B in myocardial reperfusion and reduces reperfusion injury. *Am. J. Physiol. Heart Circ. Physiol.* 2003; 284(3):H919-H926.
38. Wiza C., Nascimento E.B., Ouwens D.M. Role of PRAS40 in Akt and mTOR signaling in health and disease. *Am. J. Physiol. Endocrinol. Metab.* 2012; 302(12):E1453-E1460. PMID: 22354785.
39. Völkers M., Toko H., Doroudgar S., Din S., Quijada P., Joyo A.Y. Pathological hypertrophy amelioration by PRAS40-mediated inhibition of mTORC1. *Proc. Natl. Acad. Sci. U. S. A.* 2013; 110(31):12661-12666.
40. Inoki K., Li Y., Xu T., Guan K.L. Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. *Genes Dev.* 2003; 17(15):1829-1834.
41. Sciarretta S., Zhai P., Volpe M., Sadoshima J.

Pharmacological modulation of autophagy during cardiac stress. *J. Cardiovasc. Pharmacol.* 2012; 60(3):235-241.

42. Zhai P., Sciarretta S., Galeotti J., Volpe M., Sadoshima J. Differential roles of GSK-3β during myocardial ischemia and ischemia/reperfusion. *Circ. Res.* 2011; 109(5):502-511.
43. Matsui Y., Takagi H., Qu X., Abdellatif M., Sakoda H., Asano T. Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin 1 in mediating autophagy. *Circ. Res.* 2007; 100(6):914-922.
44. Juhaszova M., Zorov D.B., Kim S.H., Pepe S., Fu Q., Fishbein K.W. Glycogen synthase kinase-3beta mediates convergence of protection signaling to inhibit the mitochondrial permeability transition pore. *J. Clin. Invest.* 2004; 113(11):1535-1549.
45. Fuglesteg B.N., Tiron C., Jonassen A.K., Mjøs O.D., Ytrehus K. Pretreatment with insulin before ischaemia reduces infarct size in Langendorff-perfused rat hearts. *Acta Physiol. (Oxf.)* 2009; 195(2):273-282.
46. Sciarretta S., Forte M., Frati G., Sadoshima J. New insights into the role of mTOR signaling in the cardiovascular system. *Circ. Res.* 2018; 122(3):489-505.
47. Sanches-Silva A., Testai L., Nabavi S.F., Battino M., Pandima Devi K., Tejada S., et al. Therapeutic potential of polyphenols in cardiovascular diseases: Regulation of mTOR signaling pathway. *Pharmacol. Res.* 2020; 152:104626. https://doi.org/10.1016/j.phrs.2019.104626
48. Bishu K., Ogut O., Kushwaha S., Mohammed S.F., Ohtani T., Xu X., et al. Anti-remodeling effects of rapamycin in experimental heart failure: dose response and interaction with angiotensin receptor blockade. *PLoS One.* 2013; 8:e81325.
49. Griffin S.J., Leaver J.K., Irving G.J. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia.* 2017; 60:1620-1629.
50. K P., V M. A review of safety, quality, regulation, and delivery approaches for phytopharmaceuticals. *Jordan J. Pharm. Sci.* 2024 Jun. Available from: https://jjournals.ju.edu.jo/index.php/jjps/article/view/1768
51. Kzar H.H., Al-Gazally M.E., Wtwt M.A. Everolimus loaded NPs with FOL targeting: preparation, characterization and study of its cytotoxicity action on MCF-7 breast cancer cell lines. *Jordan J. Pharm. Sci.* 2022 Mar 1. Available from: https://jjournals.ju.edu.jo/index.php/jjps/article/view/286
52. Widyananda M.H., Kurniasari C.A., Alam F.M., Rizky W.C., Dings T.G.A., Ansori A.N.M., Antonius Y. Exploration of potentially bioactive compounds from fingerroot (Boesenbergia rotunda L.) as inhibitor of atherosclerosis-related proteins (CETP, ACAT1, OSC, sPLA2): An in silico study. *Jordan J. Pharm. Sci.* 2023 Sep 23. Available from: https://jjournals.ju.edu.jo/index.php/jjps/article/view/1609

# التحقيق في الهدف الميكانيكي للرابامايسين والمسارات المماثلة في أمراض القلب والأوعية الدموية لزيادة وظائف القلب

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## ملخص

تعد أمراض القلب والأوعية الدموية السبب الرئيسي للوفيات العالمية، خاصة في البلدان المنخفضة الدخل إلى المتوسطة الدخل، حيث يمثل قصور القلب 34٪ من الوفيات، حيث بلغ مجموعها 62.5 مليون حالة وفاة مبكرة في العقد الماضي. على الرغم من التحسينات الأولية في معدلات البقاء على قيد الحياة، لا تزال الوفاة بسبب قصور القلب مثيرة للقلق، مما يشير إلى انخفاض في القدرة التعويضية للقلب مع تقدم العمر. من أجل فهم التعقيدات الجزيئية للأمراض القلبية الوعائية، استكشفت هذه المراجعة السردية على نطاق واسع قواعد البيانات مثل Scopus وWeb of Science وPubMed مع معايير إدراج محددة لاختيار مقالات من الدراسات التجريبية والتجارب السريرية والدراسات على والدراسات القائمة على الملاحظة المنشورة بعد عام 2000. وعلى العكس من ذلك، استخدمت معايير الاستبعاد لاستبعاد المقالات التي لا صلة لها بالعنوان أو التي نشرت قبل عام 2000. كشف البحث المكثف في الأدبيات، بشكل مدهش، عن الإمكانات غير المستكشفة لاستهداف مسار mTOR لعلاج الأمراض القلبية الوعائية. تشير الدراسات السابقة إلى أن تعديل mTOR يمكن أن يعيد تشكيل مسارات أمراض القلب، على الرغم من أن الأدلة السريرية محدودة. تؤكد الأدلة الحديثة على عدم تنظيم mTOR في أمراض القلب، مما يبشر بالخير في التخفيف من الخلل الوظيفي من خلال تثبيط mTOR، على الرغم من التحديات في الترجمة السريرية. إن فهم الحديث المتبادل ل mTOR مع المسارات الأخرى يسلط الضوء على تعقيد أمراض القلب. تؤكد المراجعة على أهمية mTOR في مرض الشريان التاجي CAD وأمراض القلب الإقفارية IHD، مما يقترح طرقا لمزيد من البحث والتطبيقات السريرية لتحسين إدارة أمراض القلب والأوعية الدموية وتقليل الوفيات المرتبطة بقصور القلب.

**الكلمات الدالة:** مرض الشريان التاجي. مرض القلب الإقفاري، مسار mTOR.

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