Research Progress of mTOR Signaling Pathway in Metabolic Diseases

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Abstract: Mammalian target of rapamycin (mTOR) is a highly conserved central regulator within cells. It integrates signals from various inputs, including nutrients, energy status, and growth factors, to precisely regulate fundamental cellular processes such as cell growth, proliferation, autophagy, and metabolism through multiple signaling pathways. In recent years, numerous studies have confirmed that the abnormal activation of the mTOR signaling pathway is closely associated with the occurrence and progression of various metabolic diseases. This article aims to summarize the research progress on the mTOR signaling pathway in metabolic diseases such as obesity, type 2 diabetes mellitus, hyperuricemia, and osteoporosis, explore its molecular mechanisms, and provide an outlook on therapeutic strategies targeting mTOR.
***Keywords*:** mTOR; metabolic diseases; obesity; type 2 diabetes mellitus; hyperuricemia; osteoporosis.

1. Introduction

Mammalian target of rapamycin (mTOR) is a highly conserved serine/threonine kinase in mammalian cells that forms two functional complexes: mTORC1 and mTORC2. mTORC1 is highly sensitive to the mitotic state of cells, intracellular energy metabolism, and amino acids. Once activated, it upregulates protein and fat synthesis, accelerates energy metabolism, and inhibits cell autophagy to promote cell growth. mTORC2 is activated by growth factors and insulin. It phosphorylates and activates protein kinase B (AKT), protein kinase C (PKC), and serum and glucocorticoid-regulated kinase (SGK), thereby regulating cell proliferation, apoptosis, metabolism, and cytoskeleton rearrangement[1]. Under chronic nutrient overload conditions, excessive activation of mTOR can lead to a series of metabolic disorders, including insulin resistance, abnormal lipid deposition, and inflammatory responses, which are closely associated with metabolic diseases such as obesity, type 2 diabetes mellitus, hyperuricemia, and osteoporosis[2]. This article summarizes the latest research progress on the mTOR signaling pathway in metabolic diseases.

2. mTOR and obesity

Obesity is a chronic metabolic disease caused by excessive accumulation of body fat, which occurs when energy intake exceeds expenditure.Pathologically, it is characterized by hypertrophy and hyperplasia of adipocytes. mTOR plays a dual role in abnormal fat accumulation and the physiological function of adipose tissue. A high-fat diet can significantly activate mTORC1 in adipose tissue. Research by Porstmann et al[3]. finds that activated mTORC1 promotes the generation of transcription factors such as Sterol Regulatory Element Binding Protein 1 (SREBP1), upregulates the expression of genes related to fat synthesis, and thereby accelerates the synthesis and storage of triglycerides, leading to adipocyte hypertrophy. Enlarged adipocytes secrete a large number of inflammatory factors such as TNF-α and IL-6, creating a state of chronic inflammation. Moreover, excessive activation of mTORC1 has been confirmed as a key factor in adipose tissue inflammation[4]. Studies show that inhibiting mTORC1 in adipocytes of mice with high-fat diet-induced obesity reduces body weight and alleviates insulin resistance [5].

Brown adipose tissue generates heat through thermogenesis, which helps combat obesity and reduce body weight. Inhibiting mTORC1 promotes the browning of white adipose tissue, potentially through its role in suppressing autophagy and regulating mitochondrial metabolism.For example, Specific knockout of Raptor (a key component of mTORC1) in adipocyte precursor cells significantly enhances mice's thermogenic capacity, alleviating obesity caused by a high-fat diet. This intervention alleviates obesity induced by a high-fat diet [6]. These findings provide a theoretical basis for targeting mTORC1 inhibition in adipose tissue as a strategy to treat obesity.

A recent study in 2025 revealed for the first time the impact of obesity on the mTOR signaling pathway. This study focused on the specificity of muscle fiber types. The proportion of type IIa fibers in the skeletal muscle of obese patients was significantly higher than that of type I fibers, at 61.8% compared to 38.1%. Additionally, the key downstream effector

of mTORC1, p70s6K protein, was decreased by 73% in the obese group, while ubiquitinated proteins (total protein ubiquitination, TPU) increased by 32%, indicating that protein synthesis is inhibited and degradation is enhanced in the obese state. The decreased p70s6K and increased ubiquitinated proteins may lead to skeletal muscle dysfunction. This dysfunction could further reduce energy expenditure and accelerate the progression of obesity[7].

3. mTOR and T2DM

Insulin resistance and pancreatic β-cell dysfunction are the main pathological mechanisms behind type 2 diabetes mellitus. These two factors play cen-tral roles in the disease's development. The mTOR signaling pathway plays acomplex and critical role in both insulin resistance and pancreatic β-cell dysfunction.

3.1 mTOR and insulin resistance

In peripheral organs and tissues, including the liver, skeletal muscle, and adipose tissue, persistent overactivation of mTORC1 plays a key role in insulin resistance. mTORC1 inhibits insulin signaling through a negative feedback loop, and the continuously active mTORC1/S6K1 pathway phosphorylates serine sites on insulin receptor substrate-1 (IRS-1), leading to its degradation, which in turn impairs the downstream PI3K-AKT signaling pathway[8]. As a consequence of impaired insulin signaling, The overactivation of mTORC1 in the liver promotes gluconeogenesis and lipogenesis, worsening fasting hyperglycemia and hyperlipidemia. Recent studies have also found that the overactivation of mTORC1 in skeletal muscle impairs mitochondrial function, which reduces glucose oxidative utilization and thereby further aggravates insulin resistance [9].

3.2 mTOR and Islet β Cell Function

The mTOR signaling pathway exerts both beneficial and harmful effects on islet β cell function. Moderate mTORC1 activity is crucial for maintaining the proliferation and the insulin synthesis of β cells. Metabolic disorder caused by prolonged hyperglycemia and exposure to free fatty acids leads to excessive activation of mTORC1. This overactivation may have negative effects. On one hand, it can lead to "overproduction" of insulin, exacerbate endoplasmic reticulum stress and induce β cell apoptosis. On the other hand, persistently activated mTORC1 inhibits autophagy, a key process by which β cells clea-r misfolded proteins and damaged organelles to maintain homeostasis. Impaired autophagy causes accumulation of dysfunctional proteins and organelles, accelerating β cell failure[10].

The precise regulation of insulin secretion by pancreatic β cells is crucial for preventing excessive insulin release. Research by Saar Krell et al[11]. found that acute inhibition of mTORC1 during glucose stimulation enhanced insulin release, indicating that mTORC1 inhibits insulin secretion through an intrinsic feedback mechanism. Further studies revealed that mTORC1 limits vesicle movement and inhibits the second phase of insulin secretion by activating RhoA and promoting F-actin polymerization. This uncovers the mechanism by which the glucose-mTORC1-RhoA signaling axis restricts insulin exocytosis via an autonomous feedback loop, offering new insights into how β cells maintain metabolic balance by regulating insulin secretion.

The role of mTORC2 in pancreatic β cell function has attracted increasing attention. Studies show that mice with β cell-specific knockout of Rictor (a key component of mTORC2) exhibit defects in glucose-stimulated insulin secretion, revealing the indispensable role of mTORC2 in this process [12]. Therefore, when considering targeting mTOR for diabetes treatment, it is essential to weigh its different effects on mTORC1 and mTORC2 to avoid impairing β cell function by inhibiting mTORC2.

4. mTOR and Hyperuricemia

Uric acid is the end product of purine catabolism. Hyperuricemia is characterized by elevated serum uric acid levels caused by purine metabolism disorders. It is a direct cause of gout and closely linked to metabolic syndrome. mTORC1, as a core regulator of anabolic metabolism, directly promotes purine synthesis. Activated mTORC1 enhances the stability of the transcription factor MYC. This upregulates the expression of key enzymes, such as phosphoribosyl pyrophosphate synthetase (PRPS), which accelerates the synthesis of purine nucleotides. Ultimately, this process leads to increased uric acid production[13]. More importantly, mTORC1 has been confirmed as the core molecule linking fructose intake and hyperuricemia. The metabolism of fructose in the liver rapidly consumes ATP, generating AMP, which is then metabolized to uric acid. Additionally, intermediates in the fructose metabolism can directly activate mTORC1. Activated mTORC1 further promotes purine synthesis, forming a positive feedback loop that significantly elevates blood uric acid levels[14]. Studies have shown that Mazdutide activates the glucagon receptor (GCGR) in the liver, activates AMPK, inhibits mTOR/NLRP3/ROS, regulates hepatic oxidative stress and inflammatory responses, and reduces mitochondrial damage. At the same time,

it lowers hepatic xanthine oxidase (XOD) levels, inhibits glycolysis, regulates purine metabolism disorders, and improves hyperuricemia in rats[15].

Uric acid crystals activate the mTOR signaling pathway, which promotes the assembly and activation of the NLRP3 inflammasome. This process leads to the activation of Caspase-1 and release of inflammatory factors such as IL-1β and IL-18. In addition, activation of the mTOR signaling pathway is associated with pyroptosis, a process characterized by continuous cell swelling until the cell membrane ruptures, releasing cellular contents and triggering a strong inflammatory response, thus exacerbating gout [16]. Autophagy is an intracellular degradation process that involves the formation of autophagosomes, which encapsulate damaged organelles and proteins and subsequently fuse with lysosomes for degradation. In regulating gout inflammation, autophagy alleviates it by degrading uric acid crystals and inhibiting NLRP3 inflammasome activation. Furthermore, autophagy can regulate the production and release of cytokines, thus affecting the progression of the inflammatory response. The mTOR signaling pathway is the main negative regulator of autophagy, suppressing the expression of autophagy-related genes (ATG) to inhibit this process. Thus, inhibiting mTOR can activate autophagy and alleviate the inflammatory response in gout[17].

5. mTOR and Osteoporosis

Osteoporosis is a systemic bone disease characterized by decreased bone strength and an increased risk of fractures. The core pathophysiological mechanism is an imbalance in bone turnover, involving bone formation by osteoblasts and bone resorption by osteoclasts. Importantly, the mTOR signaling pathway plays a crucial role in regulating the functions of both cell types.

5.1 mTOR and Osteoblasts

Osteoblasts originate from bone marrow mesenchymal stem cells (BMSCs). The mTOR signaling pathway acts as a "molecular switch" that plays a key role in the differentiation of BMSCs into osteoblasts. In osteoblast precursor cells, activated mTORC1 drives the expression of genes and promotes the translation and activity of key transcription factors such as RUNX2 (Runt-related transcription factor 2), facilitating bone matrix secretion and mineralization [18]. However, with aging or under certain pathological conditions, excessive activation of mTOR may have negative effects, leading to osteoblast senescence characterized by decreased proliferation and increased apoptosis. In aged mouse models, moderate inhibition of mTORC1 can delay osteoblast senescence and enhance their function. This results in increased bone mass [19]. Xanthohumol directly targets and affects mTOR protein, regulating the AKT/mTOR/p70S6K autophagy signaling axis and improving age-related osteoporosis, as shown by studies[20]. This indicates that active components of traditional Chinese medicine show potential in regulating the mTOR pathway to promote osteogenic differentiation. Under conditions of caloric surplus, the mTOR pathway is activated, driving BMSCs to differentiate into adipocytes while inhibiting osteogenic differentiation. In studies of obesity-related osteoporosis, a high-fat diet activates the mTOR-S6K1/4E-BP1 pathway, upregulating the expression of adipogenic markers PPAR-γ and C/EBP-α by 2.5-3.8 times, while osteogenic markers osteocalcin and RUNX2 decrease by 40-65% [21].

5.2 mTOR and Osteoclasts

Osteoclasts are the main functional cells of bone resorption, and their excessive activation is an important pathological mechanism in osteoporosis, arthritis, and other skeletal diseases. mTOR regulates osteoclast activity by controlling autophagy, energy metabolism, and cell differentiation. The receptor activator of nuclear factor κB ligand (RANKL) activates the mTORC1 signaling pathway in precursor cells during osteoclastogenesis induction. mTORC1 provides the energy and material basis for osteoclast multinucleation and activation by regulating cellular metabolic reprogramming (such as enhancing glycolysis) and by controlling the expression of the key transcription factor c-Fos. Specific knockout of Raptor, a key component of mTORC1, significantly impaired RANKL-induced osteoclast formation and their bone resorption function[22]. Autophagy is a key mechanism for maintaining cellular homeostasis, and mTOR, as a key negative regulator of autophagy, is involved in the differentiation process of osteoclast precursors (OCPs). IL-17A promotes OCP differentiation into osteoclasts by inhibiting the phosphorylation of ERK and mTOR, which leads to upregulation of the autophagy-related protein Beclin1 and enhanced autophagic activity[23]. RhoA promotes osteoclastogenesis and bone remodeling through the Akt-mTOR-NFATc1 signaling pathway, and conditional deletion of RhoA in the osteoclast lineage in mouse models leads to severe osteosclerosis, revealing the important role of RhoA in bone metabolism and the key mediating mechanism of the mTOR signaling pathway[24].

Comprehensive inhibition of mTOR can suppress bone resorption; however, it may simultaneously inhibit bone formation. The overall effect on bone mass depends on physiological or pathological conditions. Targeting specific

downstream effector molecules of mTORC1 in osteoclasts can minimize adverse effects on bone formation while inhibiting bone resorption [25].

The mTOR signaling pathway is a core regulator of cellular metabolism. Its dysfunction serves as a common pathological basis for several metabolic diseases, including obesity, diabetes, hyperuricemia, and osteoporosis. However, the complex interactions between mTORC1 and mTORC2, along with tissue-specific effects, cause many side effects when systemic inhibition of mTOR (such as rapamycin) is used clinically to treat metabolic diseases. The mTOR signaling pathway extensively interacts with other metabolic pathways, such as AMPK and autophagy, but its overall regulatory network still requires further elucidation. In-depth research on the mTOR signaling pathway will provide a theoretical foundation for understanding the pathogenesis of metabolic diseases. It will also aid in developing new therapeutic drugs that are both effective and have fewer adverse effects.

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