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mTOR: Master Regulator, Disease Hub, Therapeutic Target

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Introduction

The mammalian target of rapamycin (mTOR) pathway is a central cellular signaling network that integrates diverse environmental cues to regulate fundamental biological processes. Its dysregulation is implicated in numerous human diseases, making it a critical area for therapeutic development.

The mTOR pathway plays a multifaceted role in various cancers. Its dysregulation suggests mTOR inhibitors as potential therapeutic agents, with research covering molecular mechanisms, clinical applications, challenges, biomarker identification, and combination strategies to overcome resistance [1].

Its critical involvement extends to metabolic disorders like obesity and type 2 diabetes. mTOR signaling integrates nutrient and hormonal cues to regulate glucose homeostasis, lipid metabolism, and insulin sensitivity, with therapeutic strategies targeting mTOR explored for metabolic improvements [2].

In Alzheimer's disease (AD), dysregulation of mTOR signaling contributes to hallmarks such as amyloid-beta accumulation, tau hyperphosphorylation, and impaired autophagy, positioning it as an attractive therapeutic target. Current research summarizes efforts to modulate mTOR for AD treatment, discussing challenges and prospects [3].

The mTOR pathway significantly influences the aging process and age-related diseases. Modulating mTOR activity can impact cellular senescence, autophagy, and protein synthesis, potentially extending lifespan and mitigating age-associated pathologies through various interventions [4].

Furthermore, mTOR signaling intricately regulates the metabolism and function of various immune cells, including T cells, B cells, macrophages, and dendritic cells. It acts as a central hub, integrating nutrient and cytokine signals to orchestrate immune cell differentiation, proliferation, and effector functions, influencing immune responses and inflammatory processes [5].

mTOR signaling also orchestrates fundamental cellular processes like cell growth, autophagy, and senescence. It integrates diverse environmental cues to precisely regulate these processes, critical for cellular homeostasis and organismal health, and its dysregulation has implications in various diseases [6].

The multifaceted role of mTOR signaling is observed in cardiovascular diseases, including heart failure, atherosclerosis, and hypertension. mTOR integrates nutrient and stress signals to regulate cardiomyocyte growth, survival, and vascular function, presenting it as a potential therapeutic strategy for these disorders [7].

In various kidney diseases, from acute kidney injury to chronic kidney disease, mTOR signaling exhibits complex and dualistic roles. It influences key renal cellular processes such as proliferation, apoptosis, fibrosis, and inflammation, representing a challenging but promising therapeutic approach for kidney pathologies [8].

Moreover, mTOR acts as a critical negative regulator of autophagy, a vital cellular catabolic process. It senses nutrient availability and stress signals to control the initiation and progression of autophagy, exploring the therapeutic potential of modulating the mTOR-autophagy axis in conditions like cancer and neurodegeneration [9].

Finally, "mTORopathies" are genetic disorders characterized by dysregulation of the mTOR pathway, primarily affecting the nervous system. This review describes clinical manifestations, genetic underpinnings, and shared molecular mechanisms, emphasizing the therapeutic potential of mTOR inhibitors in managing these debilitating neurological disorders [10].

Description

The mammalian target of rapamycin (mTOR) pathway stands as a central regulatory node in cellular physiology, integrating a myriad of environmental and intracellular cues to govern fundamental processes such as cell growth, proliferation, protein synthesis, and metabolism [6]. This intricate signaling network is vital for maintaining cellular homeostasis, ensuring cells respond appropriately to nutrient availability, energy status, and growth factors [6, 9]. Its pervasive influence means that perturbations in mTOR activity can cascade into widespread cellular dysfunction, contributing to a diverse range of pathological conditions. Understanding this core regulatory function is paramount for appreciating its involvement across various organ systems and disease states [1, 2].

One of the most extensively studied areas is the multifaceted role of mTOR in cancer. Dysregulation of the mTOR pathway is a common feature in many malignancies, driving uncontrolled cell proliferation and survival [1]. Consequently, mTOR inhibitors have emerged as promising therapeutic agents, though challenges persist, necessitating biomarker identification and combination strategies to overcome resistance and enhance efficacy [1]. Beyond oncology, mTOR is critically involved in metabolic disorders like obesity and type 2 diabetes. Here, it finely tunes glucose homeostasis, lipid metabolism, and insulin sensitivity by sensing nutrient and hormonal signals, making it a key target for therapeutic strategies aimed at improving metabolic health [2].

The neurological implications of mTOR dysregulation are also profound, notably in Alzheimer's disease (AD) and a group of genetic conditions termed "mTORopathies." In AD, aberrant mTOR signaling contributes significantly to key pathological hallmarks, including amyloid-beta accumulation, tau hyperphosphorylation, and impaired autophagy, suggesting its potential as a therapeutic target

for neurodegeneration [3, 9]. "mTORopathies" represent a distinct class of neurological disorders, such as tuberous sclerosis complex (TSC), directly resulting from mTOR pathway dysregulation, where inhibitors show promise in managing debilitating symptoms [10]. Furthermore, mTOR's influence extends to the aging process itself and the onset of age-related diseases. Modulating mTOR activity can impact cellular senescence, autophagy, and protein synthesis, offering avenues to potentially extend lifespan and mitigate age-associated pathologies [4].

mTOR signaling plays a crucial role in regulating the metabolism and function of various immune cells, including T cells, B cells, macrophages, and dendritic cells [5]. It serves as a central hub, orchestrating immune cell differentiation, proliferation, and effector functions based on nutrient availability and cytokine signals, thereby shaping overall immune responses and inflammatory processes [5]. In the cardiovascular system, mTOR contributes to the pathogenesis and progression of conditions like heart failure, atherosclerosis, and hypertension. It integrates nutrient and stress signals to regulate cardiomyocyte growth, survival, and vascular function, presenting a compelling therapeutic target for cardiovascular disorders [7]. Moreover, the pathway exhibits complex, often dualistic, roles in kidney diseases, ranging from acute injury to chronic conditions and polycystic kidney disease, influencing processes like proliferation, apoptosis, fibrosis, and inflammation, underscoring its therapeutic challenge and promise in renal health [8].

A key aspect of mTOR's function is its role as a critical negative regulator of autophagy, a vital cellular catabolic process essential for recycling damaged components and maintaining cellular health [9]. mTOR precisely senses nutrient availability and stress signals to control the initiation and progression of autophagy [9]. This intricate mTOR-autophagy axis is a significant therapeutic target in diverse pathological conditions, including cancer and neurodegeneration, where its modulation could restore cellular balance [1, 3, 9]. The broad involvement of mTOR across these disparate conditions highlights its central role in linking fundamental cellular processes to systemic disease states, making it a nexus for future therapeutic development [6].

Conclusion

The mTOR pathway is a critical cellular signaling hub, orchestrating fundamental processes like cell growth, metabolism, and immune responses. Its pervasive influence makes it central to a wide array of human diseases. In cancer, mTOR dysregulation is a common feature, making mTOR inhibitors a focus for therapy, though challenges remain in biomarker identification and combination strategies. The pathway is also deeply involved in metabolic disorders such as obesity and type 2 diabetes, where it regulates glucose homeostasis and insulin sensitivity, offering targets for metabolic improvement.

Beyond these, mTOR signaling plays a complex role in neurodegenerative conditions like Alzheimer's disease, contributing to key pathologies and presenting a therapeutic avenue. It significantly impacts the aging process and age-related diseases by influencing cellular senescence and autophagy, suggesting interventions for healthy aging. Furthermore, mTOR is crucial for immune cell metabolism and function, coordinating immune responses and inflammatory processes. Its regulation extends to cardiovascular diseases, affecting cardiomyocyte growth and vascular function, and exhibits dualistic roles in various kidney diseases, influencing processes like fibrosis and inflammation. The pathway also negatively regulates autophagy, a vital cellular catabolic process, presenting therapeutic potential for conditions like cancer and neurodegeneration. Finally, genetic disorders known as "mTORopathies," primarily affecting the nervous system, underscore the pathway's critical role, with mTOR inhibitors showing promise in managing these conditions.

Acknowledgement

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Conflict of Interest

None.

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