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Research Progress on the Involvement of PI3K-AKT Signaling Pathway in the Pathogenesis of Osteoporosis

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Abstract: Osteoporosis is a systemic skeletal disorder characterized by decreased bone mineral density, deterioration of bone microarchitecture, and an elevated susceptibility to fractures. The PI3K-AKT signaling pathway plays a pivotal role in regulating cell survival, proliferation, and differentiation, and is indispensable for normal bone metabolism. Its involvement in the pathogenesis and progression of osteoporosis has not been comprehensively addressed. To elucidate the role of the PI3K-AKT signaling pathway in osteoporosis, particularly its regulation of osteoblast and osteoclast activity and function in autophagy, this review comprehensively summarizes the impact of the PI3K-AKT signaling pathway on bone remodeling processes and recent research advancements, providing valuable references for related disease studies.

Keywords: Osteoporosis; Bone Remodeling; Autophagy; PI3K-AKT Signaling Pathway.

1. Introduction

Osteoporosis represents a significant global public health concern, particularly due to its high incidence and risk among the elderly population. According to the World Health Organization, approximately 200 million women worldwide are affected by osteoporosis, with a prevalence rate as high as 32.0% among individuals over 65 years old in China.[1] This condition not only significantly elevates the risk of fractures in patients, but also profoundly impacts their quality of life and overall survival rate. Revealing the underlying pathological mechanism holds paramount importance in elevating the health status of the elderly demographic.

The PI3K-AKT signaling pathway plays a pivotal role in regulating cell survival, proliferation, and differentiation, and recent research has underscored its central significance in various pathological conditions. In the field of osteoporosis research, it primarily impacts the process of bone remodeling through the regulation of osteoblast and osteoclast activities. The activation of the PI3K-AKT signaling pathway enhances osteoblast proliferation and differentiation, whereas its inhibition stimulates osteoclast activity, thereby exacerbating bone loss.

Moreover, autophagy, a cellular clearance mechanism, is intricately associated with the PI3K-AKT signaling pathway, and its implication in osteoporosis is progressively attracting attention. By modulating the activity of autophagy, the PI3K-AKT signaling pathway exerts an impact on the survival status of osteoclasts, thereby influencing the pathogenesis of osteoporosis.

Given the impact of the PI3K-AKT signaling pathway on osteoporosis progression, this article aims to provide a comprehensive review of its role in regulating osteoblasts and osteoclasts activities, as well as its involvement in bone remodeling, thus offering an overview of research progress in degenerative bone diseases.

2. Pathophysiological Mechanisms of Osteoporosis

The pathophysiological mechanism of osteoporosis involves the intricate interplay among diverse cellular and molecular components, predominantly characterized by dysregulation in the bone remodeling process.[2] Bone remodeling denotes the ongoing process of renewing bone tissue, encompassing two primary phases: bone resorption and bone formation.[3] In healthy adults, this process is finely regulated; however, in patients with osteoporosis, there is an imbalance between bone loss and formation, resulting in a decrease in bone volume and deterioration of bone structure.

The dysregulation of osteoblasts and osteoclasts represents a pivotal pathological mechanism in the pathogenesis of osteoporosis.[4] Osteoblasts are responsible for the process of bone formation, whereas osteoclasts play a crucial role in bone resorption. In osteoporosis, there is an increase in the activity of osteoclasts and a concurrent impairment in the function of osteoblasts.[5] Studies have demonstrated that in osteoporotic mice with FASL deletion in osteoblasts, an augmentation in the quantity and functionality of osteoclasts was observed, indicating that osteoblasts may trigger apoptosis of osteoclasts through the FAS ligand (FASL)/FAS signaling pathway.[6]

Cytokines and growth factors also exert a significant influence on the pathogenesis of osteoporosis. Inflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6), have the potential to enhance osteoclast formation and activity while inhibiting osteoblast function.[7] The fundamental pathology of osteoporosis involves an aberration in the bone remodeling process, resulting in heightened bone resorption and diminished bone formation, ultimately culminating in decreased bone volume and brittle bones.[8]

3. The Composition and Function of the PI3K-AKT Signaling Pathway

The PI3K-AKT signaling pathway constitutes a crucial

signal transduction cascade within cellular systems, playing a widespread role in the regulation of diverse biological processes such as cellular proliferation, differentiation, viability, and metabolic activities.[9]

Various molecules, such as insulin[10], glucose [11], and numerous growth factors and cytokines, have the capacity to activate the PI3K-AKT signaling pathway. In general, these molecules activate receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs) [12], leading to the subsequent activation of PI3K for the generation of phosphatidylinositol 6. The downstream effectors of this pathway mainly consist of phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and the target protein mTOR. PI3K is a lipid kinase capable of phosphorylating PIP2 (phosphatidylinositol-4,5-bisphosphate) to produce PIP3 (phosphatidylinositol-3,4,5-trisphosphate) .[13] The generation of PIP3 represents a pivotal step in the activation of signal pathways, serving as a secondary messenger to initiate downstream AKT protein kinase.[14] After being activated by PIP3, AKT kinase can phosphorylate a variety of substrate proteins, thereby modulating the survival and proliferation of cells.[15] For instance, AKT can undergo phosphorylation to inhibit the pro-apoptotic protein Bad, thereby facilitating cell survival.[16] Moreover, AKT can enhance the expression of cell cycle proteins through the phosphorylation of GSK-3β, thereby facilitating the progression of the cell cycle process.[17]

mTOR serves as a crucial downstream effector molecule of AKT, governing cellular growth and metabolism. mTOR is capable of integrating signals from nutrition, energy, and growth factors to orchestrate processes such as protein synthesis and autophagy. Research has demonstrated that the activity of mTOR is modulated by AKT phosphorylation, a process essential for maintaining cellular energy homeostasis and biosynthesis.[18]

Through the investigation of the PI3K-AKT signaling pathway, researchers have elucidated its pivotal role in cellular physiology and pathological mechanisms, offering potential targets for the treatment of diverse diseases. For instance, PI3K inhibitors and mTOR inhibitors have been extensively investigated for cancer therapy and demonstrate encouraging clinical potential.[19]

4. The Role of the PI3K-AKT Signaling Pathway in Osteoporosis

4.1. Impact on Osteoblast Functionality

Osteoblasts represent a predominant cell population within bone tissue, playing a pivotal role in the processes of bone formation and remodeling. The PI3K-AKT signaling pathway modulates the proliferation, differentiation, and survival of osteoblasts by activating specific downstream effectors such as mTOR and GSK-3β.[20]

Research has demonstrated that the PI3K-AKT signaling pathway also exerts influence on the regulation of osteoblast differentiation. This pathway is capable of facilitating the maturation of osteoblasts by augmenting the activity of Runx2 protein.[21] Furthermore, the PI3K-AKT signaling pathway also exerts a crucial influence on the survival of osteoblasts. The activation of signaling pathways has been shown to inhibit programmed cell death in osteoblasts, primarily through the downregulation of the expression of pro-apoptotic proteins such as Bim and Bad.[22] This mechanism ensures an adequate involvement of osteoblasts in the process of new bone formation during bone remodeling, thereby counteracting the progression of osteoporosis.

The PI3K-AKT signaling pathway exerts regulatory effects on osteoblast activity through diverse mechanisms, offering a novel therapeutic avenue for addressing osteoporosis.

4.2. Repercussions on Osteoclast Function

The PI3K-AKT signaling pathway plays a pivotal role in the regulation of osteoclast activity. Osteoclasts represent the sole cell type within bone tissue endowed with the capacity for bone resorption, and the modulation of their activity exerts a direct impact on the pathogenesis of osteoporosis. Studies have demonstrated that the PI3K-AKT signaling pathway intricately modulates osteoclast differentiation and function through diverse mechanisms.

According to the relevant research findings of Han Junwen[23], the experimental group that activated the PI3K-AKT signaling pathway exhibited a significant increase in the number of osteoclasts, along with an elevated expression level of RANKL (a key factor for osteoclast differentiation) [24] , and a decreased expression level of OPG (bone protective protein).[25] This change suggests that activation of the PI3K-AKT signaling pathway facilitates the differentiation and functional enhancement of osteoclasts.

Moreover, the PI3K-AKT signaling pathway further modulates osteoclast activity by influencing other intracellular molecules, such as NF-κB [26]and c-Fos.[27] NF-κB serves as a pivotal transcription factor in the differentiation process of osteoclasts. Studies have demonstrated that activation of the PI3K-AKT signaling pathway can potentiate NF-κB activity, thereby fostering osteoclast formation and augmenting bone resorption capacity.[28] Meanwhile, c-Fos, a pivotal transcription factor, also plays a critical role in osteoclast differentiation. Activation of the PI3K-AKT signaling pathway can upregulate the expression of c-Fos, thereby further enhancing osteoclast differentiation.[29]

These research findings elucidate the regulatory mechanism of the PI3K-AKT signaling pathway in osteoclast activity, offering a novel perspective on the pathogenesis of osteoporosis and potentially laying a theoretical foundation for the development of new treatment strategies.

5. The PI3K-AKT signaling pathway is involved in the regulation of bone autophagy

Autophagy is a critical cellular degradation and recycling mechanism that plays an essential role in preserving the stability of the intracellular environment and responding to extrinsic stressors.[30] According to the research by Shapiro et al., autophagy plays a crucial role in determining bone mass, structure, and functional remodeling .[31] In the pathological process of osteoporosis, autophagy modulates the equilibrium between osteoblasts and osteoclasts, thereby influencing bone remodeling and contributing to the development of osteoporosis.[32] The PI3K-AKT signaling pathway, an important regulator of autophagy, is increasingly recognized as playing a significant role in the pathogenesis of osteoporosis. [33]

Research has demonstrated that the activation of the PI3K-AKT signaling pathway can suppress autophagy. In the osteoporosis model, activation of mTOR in the PI3K-AKT signaling pathway inhibits autophagic activity, resulting in a

reduction of osteoblasts and an increase in osteoclasts, thereby exacerbating the pathological progression of osteoporosis.[34] In the study conducted by Sarah L. Dallas et al., it was discovered that the autophagy pathway directly regulates TNFSF11/RANKL and CTNNB1/β-catenin, which are pivotal signaling pathways involved in bone mineralization dynamics. Consequently, it can be inferred that autophagy may play a direct or indirect role in the occurrence of osteoporosis.[35]

Autophagy is regulated by FOXO transcription factors to modulate the survival and function of osteoblasts, with FOXO 1, 3, and 4 being widely expressed and relatively abundant in bone and osteoblasts.[36] FOXO activates and effectively induces autophagy through direct binding to its target genes. In the absence of the FOXO gene, osteoblasts trigger oxidative stress, resulting in heightened cell apoptosis and acceleration of cellular aging.[37] Conversely, upregulation of FOXO3 has the potential to mitigate age-related bone loss.[38] Hence, there is evidence to suggest that autophagy is regulated by FOXO transcription factors in order to uphold bone homeostasis.[39] For instance, research has demonstrated that excessive activation of the PI3K-AKT signaling pathway can lead to heightened osteoblast function, while inadequate activation may result in amplified suppression of osteoclast activity, both of which can contribute to the development of osteoporosis.[40] Furthermore, autophagy, a cellular clearance mechanism, is also implicated in the pathogenesis of osteoporosis through regulation by the PI3K-AKT signaling pathway. Research has demonstrated that the PI3K-AKT signaling pathway is involved in the regulation of osteoclast autophagy by modulating the expression of autophagy-related proteins, thereby influencing bone remodeling.[41]

Hence, modulating the PI3K-AKT signaling pathway to regulate autophagy activity may represent a novel therapeutic approach for managing osteoporosis. Future research should further investigate precise regulation of this signaling pathway to optimize bone remodeling processes, offering new insights for the treatment of osteoporosis.

6. The involvement of the PI3K-AKT signaling pathway in various pathological conditions

The PI3K-AKT signaling pathway plays a pivotal role in the pathogenesis of numerous diseases, particularly in the realms of oncology, diabetology, and cardiovascular medicine. In the field of cancer, the aberrant activation of the PI3K-AKT signaling pathway is intricately associated with the proliferation, survival, and augmented anti-apoptotic capacity of tumor cells.[42] Research has demonstrated that the PI3K-AKT pathway exhibits abnormally elevated activation levels across various cancer types, such as breast, prostate, liver, and lung cancers. This directly impacts the efficacy of cancer treatments and patient prognoses.[43], [44], 45, [46]

The PI3K-AKT signaling pathway also exerts a pivotal influence in diabetes research. This pathway is involved in the regulation of insulin secretion by pancreatic beta cells and the responsiveness of muscle and adipose tissues to insulin, thereby impacting glucose metabolism in the body.[47] Research has demonstrated that aberrant PI3K-AKT pathway function is implicated in the pathogenesis of type 2 diabetes, and activation of this pathway can potentiate insulin signal transduction and ameliorate insulin resistance.[48, [49]

In the context of cardiovascular diseases, the PI3K-AKT signaling pathway has demonstrated its significance in safeguarding cardiomyocytes. This pathway facilitates the survival of cardiomyocytes and suppresses apoptosis to mitigate ischemic injury, thereby aiding in the restoration of cardiac function.[50]

7. Conclusion

In conclusion, the PI3K-AKT signaling pathway plays a pivotal role in the pathogenesis of osteoporosis. This pathway significantly modulates bone remodeling by regulating osteoblast and osteoclast activities. It primarily contributes to maintaining bone tissue stability and density through activation and promotion of osteoblast proliferation and differentiation, while inhibiting osteoclast formation and function. Dysregulated activation of the PI3K-AKT signaling pathway is closely associated with osteoporosis development. Given its expression in various cell types, elucidating its cell-specific role in bone tissue represents a crucial research direction. Furthermore, identifying potential drug targets for this signaling pathway may offer novel therapeutic strategies for osteoporosis.

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