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Deciphering FOXO3: Functions, Regulation, and Implications in Disease and Therapy

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Abstract: Forkhead box O3 (FOXO3) is a critical transcription factor within the FOXO family that regulates various physiological and pathological processes, including metabolism, stress response, apoptosis, and cell cycle control. FOXO3 activity is primarily regulated by post-translational modifications, including phosphorylation, acetylation, and ubiquitination, while interacting with key pathways such as PI3K/Akt and AMPK. These pathways regulate FOXO3's localization and activity within cells, influencing processes like autophagy, oxidative stress resistance, and longevity. FOXO3 also plays a pivotal role in aging, cancer, metabolic regulation, and neurodegenerative diseases. Research highlights FOXO3's dual role as a tumor suppressor and a contributor to cellular survival under stress, making it an essential target for therapeutic strategies. This review discusses the regulation, biological functions, and therapeutic potential of FOXO3 in various disease contexts.

Keywords: FOXO3; PI3K/Akt Pathway; AMPK Pathway; Longevity; Cancer Therapy.

1. Introduction

Forkhead box O (FOXO) proteins, including FOXO3, are essential transcription factors involved in diverse cellular processes such as apoptosis, cell cycle regulation, oxidative stress response, metabolism, autophagy, and DNA repair. FOXO3 is broadly expressed in human tissues, such as the ovary, skeletal muscle, heart, and spleen, and is essential for cellular homeostasis. Its activity is tightly regulated by post-translational modifications, particularly phosphorylation, which governs its nuclear-cytoplasmic localization and influences key biological functions.

FOXO3 is critically involved in aging and longevity, with specific genetic variants linked to extended lifespan and enhanced stress resistance. It also plays a dual role in cancer, acting as a tumor suppressor under normal conditions but contributing to tumor progression and chemoresistance when dysregulated. Additionally, FOXO3's role extends to neurodegenerative diseases, where it regulates neuronal survival by modulating oxidative stress responses. Its involvement in metabolic regulation further underscores its importance in maintaining energy balance and preventing metabolic disorders.

Given its widespread impact on health and disease, FOXO3 is a promising therapeutic target for conditions such as cancer, metabolic disorders, and age-related diseases. This review provides a comprehensive overview of FOXO3, highlighting its regulatory mechanisms, key functions, and involvement in major physiological and pathological processes. We will explore the signaling pathways that control FOXO3 activity, examine its role in aging, cancer, metabolism, and the nervous system, and discuss its potential as a target for therapeutic intervention.

2. Overview of FOXO3 Regulation and Function

FOXO proteins are a group of transcription factors in mammals, consisting of four members: FOXO1, FOXO3, FOXO4, and FOXO6.[1] The dysregulation of FOXO proteins is known to significantly contribute to metabolic disorders, affect human longevity, and play a role in tumor suppression[2]. FOXO3, a crucial member of the FOXO family, is widely expressed across various human tissues, with particularly high levels in the ovary, skeletal muscle, heart, and spleen. Its biological functions are primarily controlled through phosphorylation, which takes place in both the nucleus and cytoplasm. Phosphorylation in the nucleus promotes FOXO3's movement to the cytoplasm, inhibiting its activity, while phosphorylation in the cytoplasm facilitates its translocation to the nucleus, where it regulates processes like inflammation, glycolysis, autophagy, apoptosis, oxidative stress, cell cycle arrest, and DNA repair.[3] FoxO transcription factors have an evolutionarily conserved role in extending lifespan and act as tissue-specific tumor suppressors in mammals[4].

FOXO3 is a well-studied transcription factor that plays a multifaceted role in various physiological and pathological processes. It regulates several gene networks that influence cellular metabolism, including energy metabolism, cell death, and stress resistance. [5] As a result, FOXO3-regulated signaling pathways not only hold promise as therapeutic targets but also serve as valuable biomarkers for diagnosis, prognosis, and assessing drug response.

3. Signaling Pathways and Regulatory Mechanisms of FOXO3

3.1. FOXO3 and PI3K/Akt Pathway

FOXO3 is essential for regulating cellular processes such as the cell cycle, apoptosis, and oxidative stress response. Numerous studies have highlighted the complex relationship between FOXO3 and the PI3K/Akt signaling pathway across different disease contexts. For instance, a study by Sun et al. demonstrated that silencing Prx1 suppresses pancreatic cancer cell growth and induces apoptosis by targeting FOXO3 and modulating the PI3K/Akt signaling pathway[6]. Similarly, Gao et al. showed that 17β-estradiol protects the extracellular

matrix from degradation by suppressing MMP3 expression through the PI3K/Akt/FOXO3 signaling pathway[7]. In another study, Xie et al. found that GATA6-AS1, an upstream long non-coding RNA (lncRNA), regulates the expression of miR-582. Silencing GATA6-AS1 induces FOXO3, which subsequently activates the PI3K/Akt/Snail signaling pathway, enhancing the growth and metastasis of gastric cancer (GC) cells[8]. Further, Tao et al. suggested that the anti-hyperlipidemic effect of PCE involves activation of the PI3K/Akt signaling pathway and its downstream targets, FOXO3 and ERα[9]. Qi et al. showed that miR-29a-3p inhibits osteosarcoma progression by promoting autophagy and suppressing the IGF1-driven PI3K/Akt/FOXO3 pathway[10]. Lastly, Peng et al. showed that hAMSC-CM and hAMSC-exosomes protect retinal pigment epithelial (RPE) cells from oxidative damage by modulating the PI3K/Akt/FOXO3 signaling pathway[11].

Collectively, these studies highlight the crucial role of FOXO3 and its regulation through the PI3K/Akt pathway in a range of physiological and pathological processes, offering valuable insights for potential therapeutic approaches to various diseases.

3.2. FOXO3 and AMPK Pathway

Several studies have highlighted the intricate relationship between AMPK and FOXO3 in various cellular processes. Cellular energy balance is crucial for maintaining homeostasis, with AMPK serving a central role in responding to low energy by activating energy-producing pathways. AMPK directly regulates FOXO3, a transcription factor involved in oxidative stress resistance, tumor suppression, and longevity. It phosphorylates FOXO3 at six novel regulatory sites, which enhances its transcriptional activity without affecting its localization within the cell. Through genome-wide analysis, it is shown that these phosphorylation sites regulate the expression of specific target genes, underscoring AMPK's role in modulating FOXO3-driven gene expression to maintain energy balance and cellular stress resistance.[12]

Chi et al. found that FOXO3 regulates autophagy in cardiomyocytes under hypoxic conditions, with AMPK facilitating the activation of FOXO3 during this process. Their findings highlight the crucial role of FOXO3 and AMPK signaling in hypoxia-induced autophagy in cardiomyocytes.[13] An et al. demonstrated a synergistic interaction between FOXO3 and AMPK. AMPK facilitates the nuclear translocation of FOXO3 and boosts its transcriptional activity. Additionally, FOXO3 upregulates the expression and activation of AMPKα by directly binding to its promoter and initiating its transcription.[14]

In conclusion, the AMPK/FOXO3 signaling pathway plays a crucial role in maintaining energy balance and cellular stress resistance. AMPK regulates FOXO3 by phosphorylating it at specific sites, enhancing its transcriptional activity without affecting its location within the cell. This interaction is key in processes like hypoxia-induced autophagy in cardiomyocytes and the regulation of AMPKα by FOXO3. These findings emphasize the importance of the AMPK/FOXO3 axis in cellular homeostasis and suggest its potential for therapeutic strategies targeting aging, stress response, and energy-related diseases.

3.3. Other Regulatory Mechanisms of FOXO3

Prior studies have emphasized the crucial role of post-translational modifications (PTMs) in regulating FOXO3 activity, especially in response to oxidative stress-induced neuronal apoptosis. FOXO3 undergoes various PTMs, including phosphorylation, acetylation, ubiquitination, and lysine methylation, which regulate its function.[15] Among these, SIRT1-mediated deacetylation of FOXO3 plays a significant role in enhancing FOXO3's ability to induce cell cycle arrest and enhance stress resistance, while simultaneously inhibiting its pro-apoptotic functions[16]. In response to oxidative stress, FOXO3 becomes activated and promotes the expression of several antioxidant genes, helping the cell counteract oxidative damage. Importantly, FOXO3's activity is tightly controlled by the cellular redox environment, which modulates its function in protecting the cell from oxidative stress-induced injury, thereby maintaining cellular homeostasis.[17]

In summary, in addition to the well-established PI3K/Akt and AMPK signaling pathways, FOXO3 activity is also regulated by various post-translational modifications, including acetylation, phosphorylation, ubiquitination, and lysine methylation. These modifications play a crucial role in FOXO3's ability to respond to oxidative stress and protect cells from damage.

4. Regulatory Roles of FOXO3 in Health and Disease

4.1. FOXO3 and Aging

FOXO3 is a crucial transcription factor that plays a pivotal role in aging and longevity. Its regulation of a wide array of genes, along with its interactions with pathways such as TGF-β/activin and RNAse binding sites, is central to its involvement in the aging process. While challenges persist in understanding the connection between specific FOXO3 variants and exceptional longevity in humans, FOXO3 continues to be a promising target for developing anti-aging treatments. Continued research is essential to fully uncover the mechanisms through which FOXO3 regulates aging and lifespan. [18] A strong correlation has been established between human longevity and certain FOXO3 variants found in intron 2[19].Research shows that SIRT1-mediated deacetylation of FOXO3 may promote increased organismal longevity by redirecting FOXO3-driven responses from apoptosis to enhanced stress resistance[16]. The study by Tang et al. suggests that Rg1 combats aging by modulating the SIRT1-FOXO3 and SIRT3-SOD2 pathways[20].

In conclusion, FOXO3 is crucial in aging and longevity, with its regulatory mechanisms and interactions with various pathways offering potential targets for anti-aging interventions.

4.2. The Role of FOXO3 in Cancer

Recent research has identified FOXO3, a member of the forkhead transcription factor family, as a critical protein often dysregulated in cancer cells. FOXO3 plays a vital role in cellular homeostasis by responding to external signals, influencing the decision between cell survival and apoptosis.[21] For instance, Jeung et al. reported that shikonin triggers apoptosis in specific lung cancer cells by activating the FOXO3a/EGR1/SIRT1 signaling pathway. This implies a potential therapeutic strategy for inducing cell death in lung cancer through modulation of the FOXO3 axis[22]. Similarly, Cao et al. found that promoting SIRT3 reduces cisplatin resistance in lung cancer by regulating the FOXO3/CDT1

axis, highlighting FOXO3's role in modulating chemoresistance[23]. Adjudin has been shown to activate the SIRT3-FOXO3a pathway, and the downregulation of either SIRT3 or FOXO3a significantly diminished its anticancer effects. This suggests that the SIRT3-FOXO3a signaling pathway may be pivotal in the effectiveness of certain cancer treatments[24]. In addition, a study by Guo et al. revealed that MSC-derived EVs containing microRNA-130b-3p promote lung cancer progression by regulating the FOXO3/NFE2L2/TXNRD1 axis, providing insight into how extracellular vesicles influence tumor growth through FOXO3-mediated pathways[25]. Gong et al. uncovered a novel mechanism regulating AMPK/FOXO3a signaling in response to casticin, presenting a potential strategy for targeting cancer stem-like cells in SCLC treatment[26].

Overall, these studies emphasize the vital role of FOXO3 in cancer progression and response to treatment, highlighting its regulation by several signaling pathways, including FOXO3a/EGR1/SIRT1, FOXO3/CDT1, and AMPK/FOXO3a. Targeting these pathways, through the modulation of FOXO3 by small molecules or extracellular vesicles, presents promising strategies to improve cancer therapies, particularly in overcoming chemoresistance and targeting cancer stem-like cells. Further investigation into FOXO3 signaling could pave the way for new cancer treatment strategies.

4.3. FOXO3 and Metabolic Regulation

The regulation of metabolic pathways is a highly intricate process involving multiple transcription factors and signaling networks. Among them, FOXO3 plays a crucial role in coordinating metabolic and physiological processes. Recent studies have highlighted its diverse regulatory functions. Chaves et al. demonstrated that the insulin-FOXO3-Clock signaling pathway is integral to circadian rhythm regulation, suggesting that FOXO3 extends beyond its established roles in metabolism, aging, and disease to influence biological clock function.[27] Meanwhile, Zhang et al. identified FOXO3 and mTOR as central regulators of a metabolic network in erythroblasts, jointly controlling the expression of genes associated with erythroid disorders. [28] Additionally, growing evidence indicates that FOXO3 may also regulate adipogenesis, further underscoring its importance in metabolic homeostasis[29].

Together, these findings highlight FOXO3 as a versatile metabolic regulator, linking circadian rhythms, erythropoiesis, and adipogenesis, and reinforcing its potential as a therapeutic target in metabolic and hematological disorders.

4.4. The Role of FOXO3 in the Nervous System

FOXO transcription factors are essential in regulating neuronal cell death triggered by oxidative stress. Their activity is tightly controlled by various signaling pathways and post-translational modifications, highlighting their significance in cellular stress responses and neurodegenerative processes. [15] Studies have shown that FOXO3 plays a crucial role in the nervous system , regulating neuronal survival and apoptosis. When NGF is depleted, FOXO3 becomes active, increasing BIM transcription, a pro-apoptotic BH3-only protein. This process triggers neuronal death, establishing FOXO3 as a key mediator of programmed cell death. Moreover, FOXO3 directly binds to conserved sites in the bim promoter, and mutations in these sites disrupt BIM activation, preventing neuronal apoptosis. [30] These findings highlight FOXO3 as a promising target for neuroprotective strategies in neurodegenerative disorders.

5. Summary and Conclusion

FOXO3 is a versatile transcription factor essential for regulating cellular survival, stress resistance, and longevity. Through its interaction with key signaling pathways such as PI3K/Akt and AMPK, FOXO3 coordinates cellular responses to oxidative stress, apoptosis, and metabolism. The transcription factor is tightly regulated by post-translational modifications, including phosphorylation and acetylation, which modulate its activity and localization. These regulatory mechanisms allow FOXO3 to function as a central player in maintaining cellular homeostasis.

FOXO3's role extends beyond cellular processes to influence aging, cancer, and neurodegenerative diseases. Its regulation is associated with longevity, where certain FOXO3 variants promote enhanced stress resistance and protection against apoptosis. In cancer, FOXO3 acts as a tumor suppressor, but its dysregulation is linked to tumor progression, metastasis, and chemoresistance. In neurodegenerative disorders, FOXO3's ability to regulate neuronal survival under oxidative stress makes it a promising target for neuroprotective therapies.

The therapeutic potential of FOXO3 is vast, with research focusing on modulating its activity through small molecules, signaling pathway targeting, and extracellular vesicle-based therapies. Continued research into the regulatory mechanisms of FOXO3 and its role in disease will be essential for developing novel treatment strategies aimed at improving health outcomes in aging, cancer, and neurodegenerative diseases. Given its central role in cellular homeostasis and disease, FOXO3 remains an attractive and promising target for therapeutic intervention.

Declaration of Competing Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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