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Regulation of mitochondrial function by FOXOs in ischemic stroke and Alzheimer's disease

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ONE SENTENCE SUMMARY

We summarized the involvement of FOXO proteins in modulating mitochondrial structure and function across diverse conditions, including cerebral ischemia and Alzheimer's disease.

ABSTRACT

Transcriptional control is a pivotal mechanism governing various cellular processes. FOXO proteins, a subgroup of the forkhead family of transcription factors, play a key role in determining cell fate. The localization and function of FOXO proteins are regulated by post-translational modifications to control target gene expression, with a pronounced impact on various aspects of mitochondrial function, including mitochondrial dynamics, biogenesis, and quality control. Mitochondria stand out as the primary target of FOXO transcription factors, which recruit downstream signaling factors to govern mitochondrial processes. Essential signaling pathways are modulated by FOXOs, exemplified by their regulation of mitochondrial biogenesis through SIRT1-Pgc1α and NRF1-TFAM, as well as their influence on mitochondrial dynamics involving Mfn1, Mfn2, Drp1, and Fis1. Furthermore, FOXOs demonstrate the ability to upregulate and downregulate genes that serve as modulators in oxidative and apoptosis cascades. The functional role of FOXO proteins is highly context-dependent, varying with cell type, organ, and specific FOXO isoform. Notably, FOXOs emerge as prominent players in various pathological conditions, including ischemic conditions, neurodegenerative diseases, cancer, and metabolic disorders. Unraveling the complex role of FOXOs in mammalian cell pathology positions them as promising therapeutic targets receptive to pharmacological treatment. This review aims to provide insights into the intricate roles of FOXOs in mitochondria, illuminating their potential as therapeutic targets amenable to pharmacological intervention in diverse pathological contexts, particularly in ischemic stroke and Alzheimer's disease.

Key words: FOXO; transcription factor; mitochondrial structure; mitochondrial function; mitochondrial biogenesis; autophagy; mitochondrial homeostasis; ischemia; stroke; Alzheimer's disease

List of abbreviations:

FOXO	Forkhead box class O
AD	Alzheimer's disease
NRF1/2	Nuclear respiratory factor 1/2
TFAM	Mitochondrial transcription factor A
MFN1	Mitofusin-1
MFN2	Mitofusin-2
AMPK	AMP-activated protein kinase
Drp1	Mitochondrial dynamin-related protein 1
Fis1	Mitochondrial fission 1
mtDNA	Mitochondrial DNA
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
STAT3	Signal transducer and activator of transcription 3
ROS	Reactive oxygen species
OXPHOS	Oxidative phosphorylation complex
PI3K	Phosphoinositide-3-kinase
JNK	c-Jun N-terminal kinase
NADH	Nicotinamide adenine dinucleotide
ERK	Extracellular signal-regulated kinase
SIRT1	Silent information regulator 1
SOD	Superoxide dismutase 2
ER/PR	Estrogen and progesterone receptor
ILGS	Insulin-like growth factor signaling
Aβ	β-amyloid
IP3R	Inositol 1,4,5-trisphosphate receptors
PLK1	Polo-like kinase 1

INTRODUCTION

Transcription factors serve as pivotal regulators that coordinate and harmonize a variety of cellular functions. The forkhead box class O proteins (FOXOs) are a subgroup of the forkhead family of transcription factors that consist of four structurally and functionally related proteins: FOXO1 (also referred to as FKHR), FOXO3 (also known as FOXO3a), FOXO4 (also known as AFX1), and FOXO6[1,2]. These proteins represent mammalian homologs of daf-16 in *C. elegans*, and were originally identified as tumor suppressors; oxidative stress sensors; and cell survival modulators to regulate cell survival, proliferation, metabolism, response to oxidative stress, apoptosis, and aging[3]. Under oxidative stress or the absence of the cellular survival drive of growth factors, FOXOs translocate to the nucleus and upregulate a series of target genes, thereby promoting cell growth arrest and apoptosis[4,5].

Mitochondria, the intracellular organelles responsible for cellular respiration, play a fundamental role in mammalian cells. Mitochondrial functions are mainly controlled by their biogenesis, dynamics, and autophagy. Structurally, mitochondria are composed of four distinct parts: the outer membrane, intermembrane space, inner membrane, and matrix. While the outer membrane is highly permeable, the inner membrane exhibits limited permeability[6–8]. Within the inner membrane of mitochondria, five oxidative phosphorylation complexes facilitate the production of ATP from ADP, utilizing NADH and oxygen. Accumulating evidence highlights a significant role of FOXOs in regulating mitochondrial structure and function, thereby governing cell survival and death. This review aims to summarize current knowledge regarding the connections between FOXO signaling and regulation of mitochondrial structure and function in both physiological and neuropathological conditions, including ischemic brain injury and Alzheimer's disease (AD).

FOXOS PROTEINS AND THEIR INTRACELLULAR TRAFFICKING AND TURNOVER

Among the four members of FOXO proteins, FOXO1, FOXO3, and FOXO4 are ubiquitously expressed, while FOXO6 is specifically expressed in the liver, skeletal muscle, and the hippocampus[9,10]. The intracellular trafficking of FOXO proteins, dictated by post-translational modifications (PTM), especially phosphorylation and dephosphorylation, as well as extracellular and intracellular signals, determines their ability to bind to DNA in the nucleus[11,12] (Figure 1). The forkhead domain of FOXO acts as a DNA-binding domain, influencing the transcription of target genes and the expression of associated proteins upon binding. Similar to many other transcription factors, FOXOs undergo PTMs, such as Akt-mediated phosphorylation that help the proteins localize in the cytoplasm where they bind to 14-3-3 proteins[13,14]. On the other hand, phosphorylation of FOXO proteins facilitates their degradation through the ubiquitin-proteasome system[15]. It is also noted that ubiquitylation of FOXOs confers different effects on FOXO functions: polyubiquitylation of FOXO1 and FOXO3

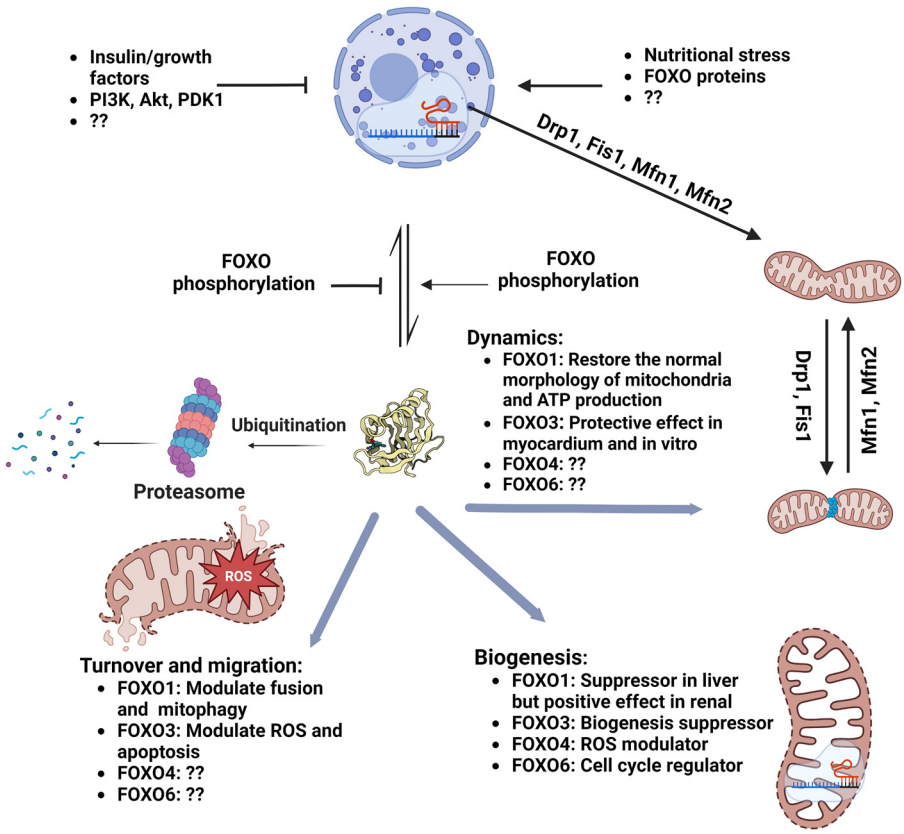

Figure 1. FOXOs modulate mitochondrial dynamics, biogenesis, quality control, and ROS production
Nutritional stress or starvation dephosphorylates FOXOs, while insulin, growth factors, PI3K, Akt, and ADK1 phosphorylate FOXOs. Dephosphorylated FOXOs translocate into the nucleus to act on their target genes, including those regulating mitochondrial dynamics, biogenesis, quality control, and ROS production. However, polyubiquitination of FOXOs mediates the proteins to the proteasome for degradation, resulting in removal of the proteins.

enhances their degradation by the proteasome (Figure 1), whereas monoubiquitylation of FOXO4 leads to its nuclear localization and thereby increases transcriptional activity[10].

FOXOS REGULATE MITOCHONDRIAL BIOGENESIS

FOXO proteins play crucial roles in modulating mitochondrial biogenesis. In response to environmental changes and various physiological conditions, such as growth factors, nutritional variations, and oxidative stress, the expression level and activities of FOXO proteins are altered among different cells and organ types[16]. Of the four FOXO proteins, FOXO1 has emerged as a key player in mitochondrial function and biogenesis (Figure 1). For instance, glucagon regulates mitochondrial biogenesis through FOXO1 in hepatocytes, and deleting the FOXO1 gene results in the loss of mitochondrial function. Glucagon activates intracellular signaling, leading to FOXO1 activation and subsequently increasing nuclear respiratory factor 1(NRF1), mitochondrial transcription factor A (TFAM), and mitofusin-2 (MFN2)[17]. Pgc1α, an essential factor for mitochondrial biogenesis activated by SIRT1, is influenced by FOXO1 upstream, and NRF1-TFAM which acts downstream of the SIRT1-Pgc1α cascade. In response to ischemia-reperfusion injury, however, FOXO1 is upregulated, which is associated with decreased mitochondrial biogenesis in the kidney. Importantly, pre- and post-treatment of mice with a selective FOXO1 inhibitor promotes mitochondrial biogenesis, reduces ROS production and apoptosis, and suppresses mitophagy in the kidney[18]. In liver cells, one study has shown that nobiletin, a natural flavonoid with antioxidant property, could activate the SIRT/FOXO3 and PGC-1α pathways and elevate the expression of proteins that control mitochondrial dynamics and biogenesis. In contrast, inhibition of SIRT/FOXO3 abolished the beneficial effects of nobiletin[19], suggesting the effect of nobiletin is mediated via SIRT/FOXO3. In cardiomyocytes, FOXO3 also has a protective effect in cardiotoxic conditions via inhibition of Fis1 expression[20]. However, there is limited evidence about the role of FOXO6 in mitochondrial biogenesis.

FOXOS REGULATE MITOCHONDRIAL DYNAMICS

Mitochondrial dynamics, encompassing parameters such as number, morphology, transport, and quality of mitochondria within cells, play a pivotal role in regulating various cellular processes, impacting cellular metabolism, proliferation, differentiation, cell division, and overall cell function. Several FOXO downstream pathways, including AMP-activated protein kinase (AMPK), mitochondrial fusion proteins (Mfn1, Mfn2), mitochondrial dynamin-related protein 1 (Drp1), mitochondrial fission 1 protein (Fis1), the dynamin superfamily of GTPases, and FOXO proteins, intricately govern mitochondrial dynamics[21]. In hepatocytes, for instance, FOXO1 upregulates Mfn1 and Mfn2 while down-regulating the main fission proteins Drp1 and Fis1 (Figure 1). This orchestrated regulation results in enlarged mitochondria[21]. However, in some pathological conditions, FOXO1 appears to have an adverse effect on mitochondrial dynamics by disrupting the process, leading to deformed mitochondria, reduced ATP levels, and abnormal cellular function, whereas deleting the FOXO1 gene can restore normal mitochondrial morphology and ATP production[18,22]. These data underscore the central role of FOXO1 in regulating mitochondrial dynamics.

The role of FOXO3 in mitochondrial dynamics, particularly in cardiomyocytes and stem cells, is intricate. In cardiomyocytes, FOXO3 inhibits mitochondrial fission by suppression of Fis1 protein expression, conferring cardio protection. Interestingly, FOXO3 also demonstrated the enhancement of mitochondrial fission and myocyte death by promoting mitochondrial fragmentation mediated via Drp1[23]. It remains unknown why these different experiments lead to conflicting results but one possibility for this may be that different experimental conditions and model systems were used in the studies.

To date, no reports have been published regarding the roles of FOXO4 and FOXO6 in mitochondrial dynamics. Abnormalities in mitochondrial dynamics are associated with a variety of diseases, including neurodegenerative disorders and some cancers that exhibit defects in mitochondrial dynamics. There is limited research about the role of FOXO6 in mitochondrial homeostasis. In aged rat kidney tissue culture, calorie restriction upregulates FOXO6 and increases FOXO6 activity, which contribute to age-related oxidative stress modification[24].

FOXOS REGULATE MITOCHONDRIAL QUALITY CONTROL

Mitochondrial quality control is integral to maintaining a healthy mitochondrial population within cells. It encompasses proteostasis, mitochondrial dynamics, mitochondrial biogenesis, and mitochondrial autophagy (or mitophagy), collectively working to regulate the number and health of mitochondria (Figure 1). The balance between autophagy and biogenesis of mitochondria is crucial in defining mitochondrial turnover[25,26]. Additionally, mtDNA plays a pivotal role in quality control, as its heterogeneity and mutations can impact protein diversity, membrane potential, the oxidative electron transport complex, mitochondrial biogenesis, and overall functionality[27,28].

In the context of aging-related conditions, exercise interventions in old rats with sarcopenia demonstrated a down-regulation of the phosphorylation of Akt, mTOR, and FOXO3, accompanied by increased p-AMPK. This orchestrated response of signaling molecules regulates autophagy and mitochondrial quality control, having a beneficial effect on ameliorating sarcopenia by modulating Akt/mTOR and Akt/FOXO3 signaling, ultimately contributing to enhanced mitochondrial quality control[29]. Moreover, the deletion of FOXO genes, including FOXO1, 3, and 4, increased muscle strength in young and aged mice. This effect was attributed to suppression of atrophic factors, including Gadd45a and Ube4a. Additionally, FOXO gene deletion improved mitochondrial function by preserving the oxidative phosphorylation complex (OXPHOS) in both young and aged groups[30].

In diabetes mellitus, rats with type 1 or type 2 diabetes (T1DM or T2DM, respectively) exhibited excessive FOXO1 activation in the myocardium and decreased activation of signal transducer and activator of transcription 3 (STAT3). Vice versa, selective inhibition of FOXO1 activation, either through a specific FOXO1 inhibitor (AS1842856) or through FOXO1 siRNA transfection, improved STAT3 activation, mitophagy, mitochondrial fusion, and reduced the mitochondrial fission in isolated cardiomyocytes exposed to high glucose. This intervention also alleviated cardiac dysfunction and pathological damage, improving STAT3 activation, mitophagy, and mitochondrial dynamics in diabetic db/db mice. Furthermore, AS1842856 enhanced mitochondrial function, as indicated by increased mitochondrial membrane potential and adenosine triphosphate production, and decreased production of mitochondrial reactive oxygen species (ROS) in isolated cardiomyocytes exposed to high glucose[31]. These findings underscore the intricate connections between FOXO proteins, mitochondrial quality control, and the pathophysiology of various conditions, offering potential avenues for therapeutic intervention.

FOXOS REGULATE MITOCHONDRIAL GENE EXPRESSION AND DNA PROLIFERATION

Various nucleus-encoded transcription factors, such as mtTFA, NF-κB, p43, T3, CREB, p53, and Stat3, translocate to the mitochondria to regulate mitochondrial gene transcription and translation[32,33]. The OXPHOS complexes, encoded by both mitochondrial and nuclear genomes, are influenced by FOXO3 to regulate complex synthesis in mitochondria[34]. The role of FOXO proteins in regulating mitochondrial DNA replication via DNA polymerase subunit gamma, TFAM, or other molecular machinery remains poorly understood. A recent study identified a signaling pathway, AMPK–FOXO–IP3R, as responsible for neurological defects resulting from mtDNA mutation[35]. This highlights the intricate and multifaceted involvement of FOXO proteins in mitochondrial structure and function, underscoring the need for further research to elucidate their diverse roles and potential therapeutic implications.

FOXOS REGULATE ROS PRODUCTION AND APOPTOSIS

ROS are natural by-products of aerobic metabolism when NADPH utilizes molecular oxygen as a substrate to generate ROS[36]. While mitochondria are the primary sites of ROS generation, external factors such as hypoxia can exacerbate free radical conditions[37]. In cases where antioxidant systems fail to detoxify excessive ROS, oxidative stress ensues, leading to structural alterations and damages of DNA, lipids, and proteins; inflammation; and apoptosis. A substantial body of evidence highlights the crucial role of FOXO proteins in maintaining ROS and antioxidant balance at the cellular, organ, and systemic levels[38]. FOXO proteins modulate oxidative stress by influencing the levels of proteins that directly and indirectly control the antioxidant system. Notably, FOXO proteins enhance the antioxidative effect by upregulating metalloproteins[39–41], SOD, catalase[42], DNA repair proteins, and selectively degrading oxidatively targeted proteins[43,44]. While FOXO3 has been demonstrated to induce genes that protect against ROS, suggesting a critical role in maintaining low cellular ROS levels, recent findings indicate that FOXO3 may also elevate mitochondrial ROS levels in primary neurons and neuroblastoma cells[45]. In a neural cell culture model of spinocerebellar ataxia type 3, FOXO4 and ataxin migrate to the nucleus, enhancing FOXO4 binding to the SOD2 gene promoter, leading to reduction of ROS and cytotoxicity[42].

During myogenesis, PGC-1α acts as a buffer against oxidative stress that typically occurs in the differentiation phase by promoting the expression of antioxidant enzymes. Downregulation of PGC-1α impairs antioxidant expression, leading to a burst of ROS and oxidative damage to proteins. Simultaneously, there is a reduction in mitochondrial mass and function, accompanied by increased mitophagy through the ROS/FOXO1 pathway[46]. These intricate regulatory mechanisms highlight the interconnected roles of FOXO proteins, SIRT3, and PGC-1α in maintaining cellular redox homeostasis and mitochondrial function.

FOXOS IN PATHOLOGICAL CONDITIONS

FOXOs in ischemic brain injury

In many studies, the overall FOXO expression and activities were shown to increase in the condition of ischemic stroke (Figure 2). The role of FOXO proteins in ischemic stroke was first elucidated by Won et al., who investigated the activation of FOXO1 and its involvement in cell death. Activation of FOXO1 was found to be associated with reduced Akt activity following ischemic stroke[47]. Recent studies have indicated that Epoxyeicosatrienoic acids (also known as 15-EET) can upregulate SIRT1 expression and phosphorylate FOXO1 through AMPK phosphorylation. This signaling cascade optimizes mitochondrial dynamics, alters fission and fusion, maintains neuronal morphological and structural integrity, and mitigates neurological defects induced by cerebral ischemia/reperfusion[48].

Among the FOXOs proteins, the FOXO3 isoform is well-studied in the condition of cerebral ischemia. In transient cerebral ischemia, FOXO3 demonstrated a decrease in the hippocampal CA1 region during the acute phase (12 hours) but exhibited a marked increase in total expression three days post-ischemia, with peak immunoreactivity observed on day 5 after ischemia[49]. In a mouse middle cerebral artery occlusion stroke model and primary neuronal culture of the transient ischemic stroke model, miR-182 inhibition protected blood-brain barrier integrity by reducing endothelial cell apoptosis through the mTOR/FOXO1 pathway. Rapamycin/AS1842856, an mTOR/FOXO1 pathway inhibitor, also showed similar beneficial effects[50].

Ischemic pre-conditioning can upregulate Akt activity, leading to FOXO inhibition and promotion of neuronal survival against subsequent severe ischemic insults[51]. Despite structural and functional similarities, different FOXOs have diverse physiological roles in mammals[52,53]. For instance, downregulation of FOXO4 suppresses oxidative stress-induced cell death in proangiogenic cells, promoting neovascularization in ischemic limbs[54]. Conversely, in the human adenocarcinoma colon cancer cell line, the expression of FOXO proteins strongly counters mitochondrial ROS production[55].

FOXOs also modulate inflammation, a major mechanism that induces brain injury following ischemic stroke[56,57]. In the heart, a study suggested FOXO4 was involved in mediating inflammation following cardiac ischemia, via enhancement of the interaction of leukocytes with the endothelial cells of blood vessels thereby promoting early tissue inflammation[58]. A comprehensive understanding of the biological functions of FOXOs in ischemic stroke-induced cell death holds the potential for the development of effective therapeutics for treating this disorder.

While numerous reports discuss the effects of ischemia on mitochondrial dynamics, only a very limited number of publications link FOXO proteins to mitochondrial dynamics following brain ischemia[48]. Therefore, additional studies are needed to better understand the role of FOXOs in mitochondrial dynamics in response to the ischemia and/or reperfusion condition.

FOXOs in Alzheimer's diseases

In addition to regulating neural cell differentiation[59,60] and development of the nervous system, FOXO proteins may also be involved in the pathogenesis of AD[61,62]. Besides post-translational modifications, the trafficking of FOXOs across the cell plays a crucial role in cellular control in the central nervous system. The insulin-like growth factor signaling (ILGS) and c-Jun N-terminal kinase (JNK) pathways define the trafficking of FOXO proteins. ILGS, a conserved pathway, is integral to cell function in the CNS, and dysfunction in this pathway is associated with T2DM, with FOXO being a key component of this signaling pathway[63]. Given the common age-related factor between T2DM and AD, FOXO proteins could represent a common influence in both conditions, especially considering the observed association between T2DM and an increased risk of AD progression. In aged mice, FoxO3 protein is reduced in the cortex. A study using the FOXO3-deficient mice has revealed

that loss of FOXO3 led to cortical astrogliosis and altered lipid metabolism. This is associated with impaired metabolic homeostasis and β-amyloid (Aβ) uptake in primary astrocyte cultures[64]. Notably, mitochondrial dysfunction and structural changes are recognized as early events in the cell death and pathology of AD[65–67], reinforcing the potential involvement of FOXO proteins in the development and progression of AD through mitochondrial changes.

Another significant mechanism in AD pathophysiology is neuroinflammation, which is linked to mitochondrial damage, mitochondrial DNA damage, and overactivation of glial cells in the brain[68,69] (Figure 2). Functionally, FOXO protein activity is negatively regulated by phosphorylation via the phosphoinositide-3-kinase (PI3K)-Akt pathway, a well-established cell survival pathway[4,5]. In AD conditions, amyloid-beta (Aβ) inhibits the Akt signaling pathway[70–73], activating FOXOs and contributing to neurodegeneration[74–76]. Specifically, FOXO3 has been implicated in Aβ-induced mitochondrial dysfunction in cultured neurons[77]. FOXO3 is important in restraining astrocyte proliferation during proinflammatory cytokine stimulation, while loss of function of FOXO3 may be responsible for the proliferation of astrocytes in the severe form of reactive astrogliosis[78]. These findings underscore the intricate involvement of FOXO proteins in the complex pathophysiology of AD, offering potential avenues for further exploration and therapeutic intervention.

THERAPEUTIC POTENTIAL OF TARGETING FOXOS

The wealth of publications and data from experimental and clinical research converge on the consensus that FOXO proteins hold significant therapeutic potential in diverse fields, including metabolic diseases, neurodegenerative disorders, and ischemic diseases. Much of this potential is attributed to their pivotal role in mitochondrial control. The FOXO signaling pathway is increasingly considered a promising avenue for the treatment of neurodegenerative diseases, such as AD and dementia, both of which encompass mitochondrial damage, oxidative stress, excitotoxicity, β-amyloid (Aβ), and tau toxicity in their pathophysiology[79–82]. Given the limited efficacy of current therapies for these conditions, the focus is shifting towards addressing core cellular mechanisms, with the mammalian FOXO pathway emerging as a novel target with therapeutic potential. Pharmacological agonists and antagonists, including compounds like Actinomycin and Rapamycin that target FOXOs or their upstream and downstream pathways, are being explored for their potential in designing therapeutic interventions.

In the realm of cancer, FOXO proteins play a crucial role in modulating cancer cells through mitochondria-dependent apoptosis and autophagy[83]. This opens the possibility of designing various inhibitors or agonists for application in cancer treatments. Among intracellular organelles, mitochondria stand out as key players in determining cell fate during cancer, and FOXO proteins exert their influence through orchestrating mitochondria-dependent processes, like apoptosis and autophagy[84]. The tissue-specific nature of FOXO roles underscores the potential for designing various inhibitors or agonists tailored for application in different cancers. FOXO1, in particular, has been identified as a tumor suppressor in a wide range of cancers[85]. For instance, in prostate cancer, the Polo-like kinase 1 (PLK1)-dependent phosphorylation of FOXO1 suppresses FOXO1 transcriptional activity in the nucleus, leading to its concentration in

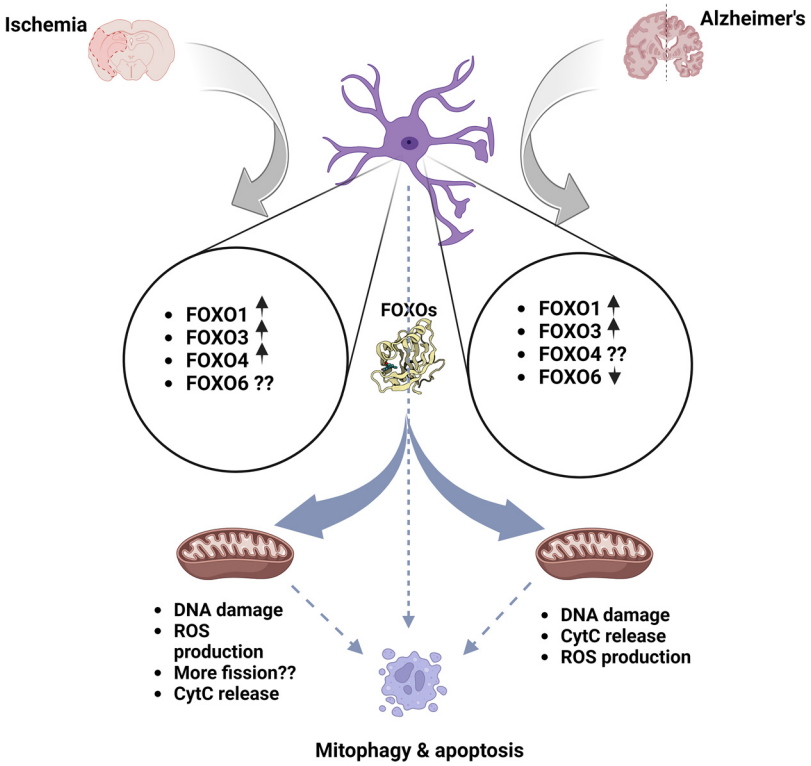

Figure 2. FOXOs regulate neuronal injury in the ischemic brain and Alzheimer's disease

In the condition of ischemic brain injury and Alzheimer's disease, the level and post-translational modifications of FOXO proteins are altered, thereby causing changes to mitochondrial structure and function, which lead to cell death.

the cytoplasm. This process hinders the expression of proapoptotic proteins, contributing to cancer progression[85,86]. The multifaceted roles of FOXO proteins in cellular processes make them intriguing targets for therapeutic strategies across diverse pathological conditions[87], emphasizing the need for continued research to fully unlock their therapeutic potential.

In addition, FOXO proteins also crosstalk with other signaling pathways at various levels, influencing regulation, downstream cascades, and cellular biological functions. Numerous nuclear proteins involved in mitochondrial homeostasis are potential participants in the FOXO pathway, contributing to the intricate network of cellular regulation[88]. Acetylation and phosphorylation, for instance, conjoin FOXO1 and P53 to express common genes related to cell cycle arrest and mitochondrial-induced apoptosis[89]. Nuclear respiratory factor-1 and -2 (NRF-1/2) interact with PGC-1α, resulting in antioxidative and protective effects after ischemia-reperfusion injury, and evidence suggests interactions with the FOXO pathway[90]. The role of mitochondrial biogenesis in renal injury has been shown in other studies[91]. Moreover, OXPHOS complex proteins, encoded by both mitochondrial and nuclear genomes, are influenced by FOXO3, or activated by AMPK and ERK, to regulate oxidative phosphorylation[34]. Conversely, the OXPHOS complex is controlled by PGC-1α and nuclear steroid receptors (ERs and PRs)[92,93]. Understanding the crosstalk of FOXO proteins with these pathways would provide insights that can aid in developing more effective pharmaceutical compounds targeting processes such as autophagy and apoptosis, particularly in the context of various acute and chronic neurological diseases, such as ischemic stroke and AD. This nuanced understanding of interconnected pathways enhances the potential for targeted therapeutic interventions.

CONCLUSIONS AND FUTURE DIRECTIONS

Mammalian FOXO proteins represent a crucial transcription factor family with significant physiological expression and a key role in cell function. The intricate relationship between FOXO proteins and mitochondria, the primary organelle that is involved, leads to transcriptional effects culminating in processes such as apoptosis, autophagy, and mitophagy[48]. The regulation of mitochondrial function and structure is highly dependent on the localization of FOXO proteins, a process determined by phosphorylation, acetylation, and ubiquitination[38]. The regulatory role of FOXO proteins extends to mitochondrial biogenesis, dynamics, and quality control[16]. Owing to the diverse and tissue-specific roles of FOXO proteins, FOXOs are potential targets for both acute and chronic neurological diseases[77,94].

In connection with the role of FOXO proteins in cells and tissues, there are many questions that need to be addressed in future research. For example, how does the function of each of these proteins in a specific tissue and cell in physiological conditions compare to conditions such as cancer in those tissues or organs? Continued research is crucial to unravel the intricacies of FOXO signaling and to develop targeted pharmacological interventions for various pathological conditions. By exploring these interactions, we hope to shed light on the dynamic interplay between the nucleus and mitochondria, unveiling their collective impact on cellular processes and the manifestation of various health and disease conditions.

In summary, FOXOs are important transcriptional factors either indirectly or directly regulating various cellular functions, including cell survival and death, through modulating mitochondrial structure and function. A better understanding of their role in brain cells in some pathological conditions, such as in ischemic stroke and Alzheimer's disease, will facilitate identification of therapeutic agents in treating these diseases.

AUTHOR CONTRIBUTIONS

YA wrote the first draft of the manuscript; HW edited the work. Both YA and HW contributed to preparing the figures.

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