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REVIEW

The forkhead box O3 (FOXO3): a key player in the regulation of ischemia and reperfusion injury

Moussa Omorou[1] · Yiwei Huang[1] · Meng Gao[1] · Chenxi Mu[1] · Weijing Xu[2] · Yuchun Han[1] · Hui Xu[1,3]

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Abstract

Forkhead box O3 is a protein encoded by the FOXO3 gene expressed throughout the body. FOXO3 could play a crucial role in longevity and many other pathologies, such as Alzheimer's disease, glioblastoma, and stroke. This study is a comprehensive review of the expression of FOXO3 under ischemia and reperfusion (IR) and the molecular mechanisms of its regulation and function. We found that the expression level of FOXO3 under ischemia and IR is tissue-specific. Specifically, the expression level of FOXO3 is increased in the lung and intestinal epithelial cells after IR. However, FOXO3 is downregulated in the kidney after IR and in the skeletal muscles following ischemia. Interestingly, both increased and decreased FOXO3 expression have been reported in the brain, liver, and heart following IR. Nevertheless, these contribute to stimulating ischemia and reperfusion injury via the induction of inflammatory response, apoptosis, autophagy, mitophagy, pyroptosis, and oxidative damage. These results suggest that FOXO3 could play protective effects in some organs and detrimental effects in others against IR injury. Most importantly, these findings indicate that controlling FOXO3 expression, genetically or pharmacologically, could contribute to preventing or treating ischemia and reperfusion damage.

Keywords Oxidative stress · Apoptosis · Blood flow · Inflammation · Autophagy

Introduction

Ischemia is defined as a condition in which oxygen delivery to tissues or organs is compromised due to vascular obstruction or blood flow disruption [1]. Depending on the duration of ischemia and the location of affected tissue, the pathophysiological consequences can vary significantly. During ischemia, ATP production is reduced, leading to increased production of reactive oxygen species (ROS) and inflammation. This can further cause damage to cytoskeletal proteins, cell membranes, organelles, and mitochondria, contributing to cell death. Ischemia–Reperfusion (IR), on the other hand, is a pathological condition resulting from the recovery of oxygen supply to the ischemic tissue or organ. This can cause a burst of ROS production induced by both inflammatory and metabolic processes, leading to tissue damage and cell death. Additionally, immune cells in ischemic tissue can further exacerbate inflammation. The main difference between ischemia and IR is the presence of reperfusion in the latter and its associated exaggerated inflammatory response—due to the increased permeability of the blood–brain barrier (BBB)—which can amplify tissue damage [1–3].

The FoxO (forkhead box, class O) proteins are a member of the FOX (forkhead box) transcription factors family that contains a conserved DNA-binding motif of ~ 100 amino acids [4–8]. The FoxO proteins are expressed in most tissues; however, their expression level, function, and targets are tissue-dependent [9]. Four FoxO transcription factors have been identified, including FoxO1, FOXO3 (FOXO3a or FKHRL1), FoxO4, and FoxO6 [10]. They regulate a plethora of biological processes, including inflammation, apoptosis, stress resistance, autophagy, aging, longevity, metabolism,

✉ Hui Xu
xuhui19782003@163.com

1 Department of Biochemistry and Molecular Biology, Jiamusi University School of Basic Medical Sciences, Jiamusi 154000, Heilongjiang, People's Republic of China

2 Department Epidemiology and Health Statistics, Jiamusi University School of Public Health, Jiamusi 154000, Heilongjiang, People's Republic of China

3 Key Laboratory of Microecology-Immune Regulatory Network and Related Diseases, School of Basic Medicine, Jiamusi University, Jiamusi 154000, Heilongjiang, People's Republic of China

stem cell production, DNA repair, bone structure, immunity, and cancer [11–20].

FOXO3 is expressed throughout the body [21]. It is phosphorylated and inactivated by the PI3K/AKT3 pathway [22]. The phosphorylated and inactive form of FOXO3 is localized in the cytoplasm, but it is translocated into the nucleus after dephosphorylation and activation, where it exerts its transcription function [5, 23–30]. Besides its pivotal role in longevity, FOXO3 has been found to be involved in a plethora of biological disorders and diseases, such as Alzheimer's disease [31], myocardial infarction [32], glioblastoma [33, 34], and stroke [35]; during which it regulates the expression of numerous genes involved in various cellular processes, including metabolism, survival, differentiation, proliferation, aging, autophagy, apoptosis, oxidative stress, and inflammatory response [36–40].

Several studies have reported dynamic changes in the expression levels of FOXO3 in various organs of rats and mice and cells subjected to IR. These variations in FOXO3 levels contribute to IR injury. FOXO3 could play as an inducer or an alleviator of IR injury in different organs [41–49]. Therefore, the present study aimed to summarize the expression level of FOXO3 in various organs and to provide more understanding of the molecular mechanisms underlying its role and regulation to contribute to the strategies to prevent or treat IR injury.

Cerebral ischemia and reperfusion

The brain is the most vulnerable organ to blood flow; it accounts for approximately 25% of total body oxygen consumption. Therefore, the risk of low blood flow——Ischemic stroke——is high [2]. Ischemic stroke is the second leading cause of death worldwide [3]. The damage caused in the brain after ischemia directly depends on the duration of the ischemic period, but it can also be aggravated after reperfusion [1]. Many pathways involved in pathological changes, such as inflammation and neural cell death, are significantly deregulated after cerebral IR [3, 50, 51]. Several studies established FOXO3 as a key player in the pathophysiological mechanisms of cerebral IR.

An extensive number of studies indicate that a large spectrum of biomolecules, including Long non-coding RNAs(lncRNAs), microRNAs (miRNAs), transcription factors, and inflammatory cytokines, are involved in the pathophysiological mechanisms of Cerebral IR [35, 41, 42, 52–57]. In both in vivo and in vitro models of cerebral IR, FOXO3 has been associated with pathological changes. During cerebral ischemia, FOXO3 is downregulated [58], but after reperfusion, its protein expression is increased, which induces its nuclear translocation and increases its transcription activity [35, 41, 42, 52–57, 59]. Deregulation in the expression of many molecules has been suggested to contribute to this upregulation in FOXO3 transcription activity. Evidence shows that lncRNAs could play crucial roles in the pathogenesis of cerebral IR by boosting FOXO3 expression and activity by regulating miRNAs or protein expression. LncRNAs GAS5, TUG1, and XIST respectively inhibit miR-9, miR-410, and miR-27a-3p expression, three miRNAs that play as upstream targets of the FOXO3 pathway, activating FOXO3 activity [52, 53, 56, 57]. This could aggravate the injury after IR through activation of the inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and the apoptotic pathway by increasing Bax/Bcl2 ratio and cleaved-caspase-3 expression as well as ROS production [52, 53, 56, 57]. Meanwhile, overexpression of the lncRNA SNHG12 inhibits the expression of SIRT1 to activate FOXO3 activity, which induces LC3 II expression and reduces that of LC3 I to cause autophagy and increase MDA content and decrease SOD activity to exacerbate oxidative stress in the brain tissue [60].

Other miRNAs involved in the regulation of FOXO3 in the brain after IR are miR-122, miR-200a, and miR-19a/b-3p. Potassium voltage-gated channel subfamily Q member 1 opposite strand 1 (KCNQ10T1)-induced inhibition of miR-200a and downregulation of miR-122 as well as upregulation of miR-19a/b-3p and its inhibition of SIRT1, contribute to increasing FOXO3 activity [41, 42, 55] after cerebral IR. Nevertheless, the effects remain detrimental as this conduces to an increase in the expression of autophagic proteins [55]. Besides, FOXO3 could downregulate Heat Shock Protein 70 (HSP70) expression but upregulate SPHK1, both of which conduce to the upregulation of NF-kB expression. The latter evoke apoptosis by inducing caspase-3 and ROS expression and decrease Bcl2 expression and inflammation by increasing the expression of IL-1β, IL-6, and TNF-α [41, 42].

Many events have been shown to converge on the dephosphorylation and deactivation of AKT——a well-known FOXO3 upstream target——in the brain tissue after IR; these include the hypoxia-inducible factor 1 alpha (HIF-1α)-mediated upregulation of the CXC motif chemokine ligand 6 (CXCL6) expression [61], AMPK-mediated inhibition of mTOR expression [62], overexpression of the FK506 binding protein 5 (FKBP5) [63], and downregulation of PTEN [43] and SIRT2 [35]. The inhibition of AKT activity releases FOXO3 expression and activity to exacerbate the brain damage via activation of apoptotic proteins Bim, Bad, and caspase-3 as well as Bax/Bcl2 ratio [35, 43, 59, 62, 64], inflammatory response by inducing NF-kBp65, IL-β, IL-6, and TNF-α [59][59], cell permeability by inhibiting SIRT3 expression [61], oxidative stress by increasing MDA content and decreasing SOD and GSH activity [59], and autophagy by increasing Beclin-1 and LC3 II expression and reducing sequestosome-1 (SQSTM1) expression [63, 64, 66].

The overexpression of FOXO3 and increase in its activity are also attributed to the overexpression of general control nonderepressible 2 (GCN2) and SRY-box transcription factor 9 (SOX9) and downregulation of Methyl CpG binding protein 2 (MeCP2) in the brain after IR [54, 67, 68]. Following its activation by SOX9, FOXO3 increases the transcription of Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2) and IKKα expression, both of which are involved in the inflammatory response and the programmed cell death [54]. On the other hand, after its activation by SOX9 expression and MeCP2 inhibition, FOXO3 promotes the expression of proapoptotic proteins such as SPRY2, ZEB1, caspase-3, and Bax/Bcl2 ratio, and inflammatory cytokines such as IL-β, IL-6, and TNF-α [54, 68]. GCN2-mediated activation of FOXO3 could also induce ROS expression to promote Endoplasmic reticulum stress (ERS) [67]. These studies confer FOXO3 a detrimental role in the brain after cerebral IR, suggesting its participation in many pathological processes, such as apoptosis, inflammation, autophagy, ERS, and cell permeability (Fig. 1). This was confirmed as inhibition of FOXO3, genetically or using pharmacological treatments such as glutathione (GSH), Syringin, rosuvastatin, or Coenzyme Q10 (CoQ10) significantly reduced brain damage after cerebral IR [42, 52, 53, 55, 57, 59, 60, 62, 65, 66, 69].

However, according to the findings of recent studies, FOXO3 expression and its activity could be decreased in the brain after cerebral IR, probably due to the overexpression of IFN-γ and the phosphorylated JNK (p-JNK) [70, 71]. But intriguingly, the deactivation of FOXO3 has been associated with the elevations in NF-kB expression as well as its downstream targets, including caspase-3, Bim, Bax/Bcl2 in the apoptotic pathway, the inflammatory cytokines IL-1β, IL-6, and TNF-α, and oxidative biomarkers MDA and ROS with a decreased SOD activity [70]. In this line, deactivated FOXO3 was found to release ROS, caspase-1, IL-1β, and IL-18 expression to induce pyroptosis via inhibition of mitophagy [71]. These studies attributed a beneficial function to FOXO3, as its overexpression through pharmacological treatment with melatonin [70] or mesenchymal stem cell-derived exosomes (MSC-exos) [71] contributed to a decrease in the damage previously caused by IR. However, the mechanism leading to FOXO3 decrease is unclear; ultimately, as more research is conducted, the exact role of FOXO3 in the brain after stroke will hopefully become clearer.

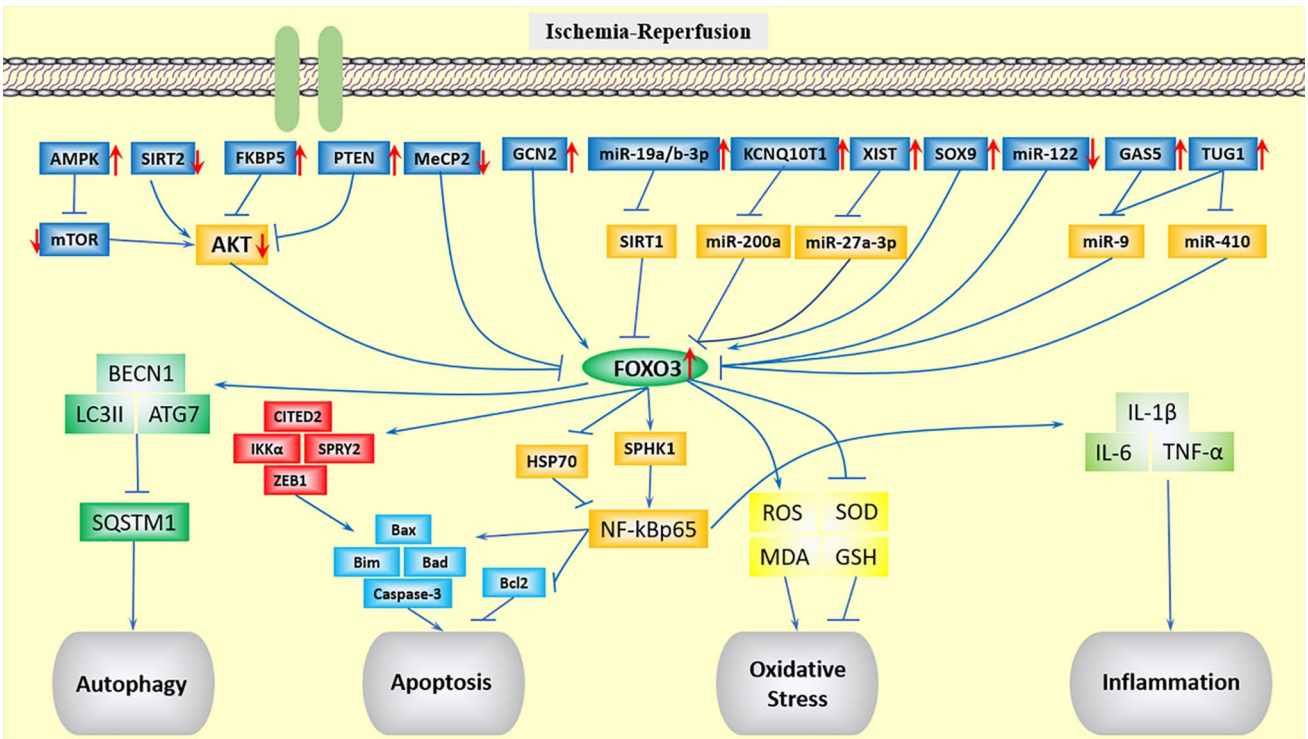

Fig. 1 The expression level of FOXO3 is stimulated by variations in the expression of its several upstream genes in the brain after IR, including SIRT2, GAS5, SOX9, AMPK, PTEN, mTOR, FKBP5, GCN2, KCNQ10T1, XIST, TUG1, AKT, SIRT1, miR-19a/b-3p, miR-200a, miR-27a-3p, miR-122, miR-9, and miR-410 to induce autophagy, apoptosis, oxidative stress, and inflammation-related genes. *FKBP5* FK506-binding protein 51, *GCN2* general control nonderepressible 2, *TUG1* taurine up-regulated 1, *CITED2* Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2, *HSP70* Heat Shock Protein 70

Myocardial ischemia and reperfusion

Myocardial ischemia and reperfusion (MIR) is a common medical concern worldwide [72]. It is a medical condition that occurs when the heart muscle is deprived of oxygen due to either a reduced (ischemia) or completely blocked (infarction) blood supply, usually caused by a clot or plaque [73]. This causes damage to the heart muscle and leads to a risk of serious complications, including death. It is believed that timely restoring adequate blood flow to the affected area is the effective way to relieve the myocardial damage induced by ischemia; however, reperfusion could induce supplementary damage—reperfusion injury [74]. Accumulating evidence revealed that FOXO3 could play a crucial role in the development of ischemia and reperfusion injury in the myocardium [44, 45, 75].

It is well known that FOXO3 promotes cardiomyocyte survival by modulating calcium homeostasis and inducing the expression of antiapoptotic molecules such as CITED2 and PTEN-induced kinase 1 (PINK1) after IR [76, 77]. Therefore, the downregulation of FOXO3 in the myocardium after IR could contribute to harmful consequences, including apoptosis, pyroptosis, and mitophagy [78, 79]. This mechanism involves non-coding RNAs (ncRNAs) such as lncRNAs and miRNAs that have been shown to play a potentially pivotal role in the development of MIR injury. Investigators suggested that overexpression of miR-149, miR-200c, miR-302a-3p, and miR-29b could directly contribute to the inhibition of FOXO3 expression in cardiomyocytes after MIR [78, 80–82]. On the other hand, the inhibition of FOXO3 could drive the downregulation of lncRNA-LINC00261, which in turn could release the expression of miR-23b-3p to inhibit NRF2 [83], an antioxidant transcription factor known to protect cardiomyocytes against IR injury [84]. In line with this, FOXO3 downregulation could provoke cardiomyocyte death through the release of caspase-3 and p53 expression and increase in Bax/Bcl2 ratio, mitophagy by increasing LC3 II, p62, Parkin, Beclin-1, and BCL2-interacting protein 3-like (BNIP3L, commonly called NIX) expression, and pyroptosis by inducing the overexpression of pyroptotic markers caspase-1, IL-1β, and IL-18 [78–82, 85, 86]. Besides the role of ncRNAs, other mechanisms have been identified as a possible cause of FOXO3 inhibition after MIR; these include the downregulation of SITR3 and hyperphosphorylation of AMPK [79, 85, 87]. Furthermore, apart from apoptosis, mitophagy, and pyroptosis, the inhibition of FOXO3 also contributes to exacerbating the oxidative stress resulting from MIR by remarkably inducing the ROS and MDA production, and reducing SOD, catalase (CAT), and GSH activities [75, 79, 85, 86]. Additionally, these studies reported that forced overexpression of FOXO3, whether genetically or pharmacologically, markedly contributed to alleviating the MIR-induced injury [75, 78–83, 86]. It has also been found that FOXO3 could mediate the potential SIRT6-induced cardio-protection after MIR [88]. These results indicate that FOXO3 may play a beneficial role in the heart tissue after IR.

However, recent evidence revealed an enhanced increase in FOXO3 expression in both in vitro and in vivo models of MIR [44, 45, 89–92]. This suggests a controversial role of FOXO3 in the pathophysiological process of MIR. Several mechanisms involving the AKT pathway contribute to the overexpression of FOXO3 in the MIR models. In males, it has been shown that testosterone could reduce the phosphorylation of AKT, inducing its deactivation [93]. Besides, the reduction in mTORC2 in the myocardium after IR contributed to decreased AKT expression and activity [89]. Following these events, the deactivation of AKT caused the dephosphorylation and inhibition of GSK-3β activity [89]. Inhibition of AKT and GSK-3β facilitates the upregulation of FOXO3 expression and activity. Subsequently, FOXO3, per se or through activation of HIF-1α and Bnip3, could exacerbate the MIR injury by increasing the expression of proapoptotic proteins caspase-3, Bad, Bim, $p27^{kip1}$, and Bax and reducing Bcl2 expression, autophagic protein LC3 II, and oxidative stress-related ROS and MDA in the infarct area [45, 89, 91, 93, 94]. On the other hand, inhibition of miR-221 induced by circPAN3 overexpression, inhibition of miR-23a, and downregulation of SIRT1 after MIR could also contribute to the overexpression of FOXO3 to play the same role mentioned above, inducing cardiomyocyte death through Bim, caspase-3, Bax activation, and autophagy via Beclin-1, ATG7, p62, and LC3 II expression [44, 90, 95]. Evidence shows that FOXO3 could also mediate the IL-18-induced cardiac inflammation and dysfunctions by promoting CXCL16 expression [96]. Further investigations found that genetical or pharmacological inhibition of FOXO3 could contribute to relieve the MIR injury [89, 91, 92, 94, 95, 97–99]. These results indicate that FOXO3 may play a detrimental role in the cardiomyocytes after MIR. The mechanisms explaining this controversial role of FOXO3 in the heart after IR are still not well understood; this may provide good insights for future studies to clarify the role of FOXO3 in this injury. (See Fig. 2).

Renal ischemia and reperfusion

Acute kidney injury (AKI), also known as acute renal failure (ARF), is a disorder in which the kidneys become acutely and rapidly damaged and stop working. Renal IR constitutes one of the major causes of AKI in many clinical settings [100]. It is believed that IR could cause various pathophysiological changes in the kidney by promoting

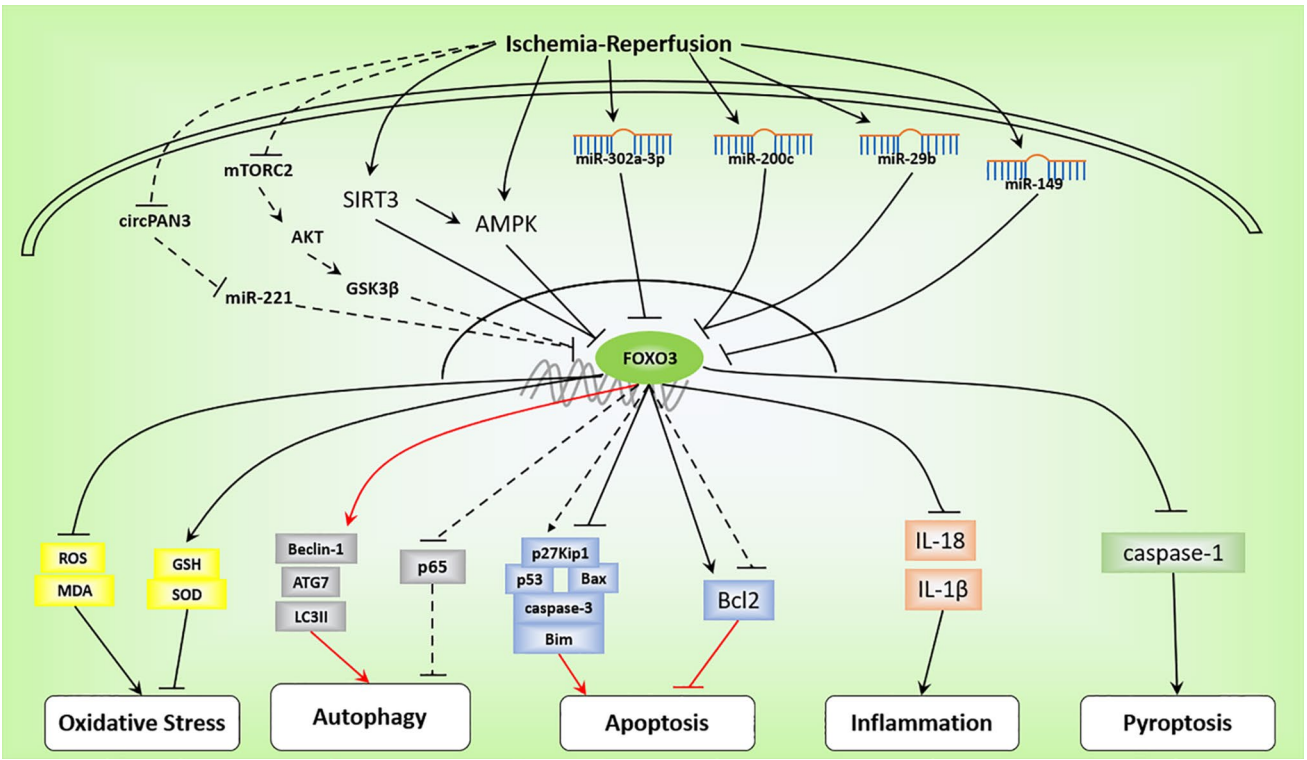

Fig. 2 The expression level of FOXO3 is downregulated by SIRT3, AMPK, miR-149, miR200c, miR-29b, and miR-302a-p in the myocardium after IR. In contrast, downregulation of mTORC2/AKT/GSK3β pathway and circPAN3 stimulate the expression of FOXO3 in the myocardium after IR to contribute to the resulting injury. These contributed to autophagic effects, oxidative stress, apoptosis, inflammation, and pyroptosis by regulating their related respective proteins. Black straight lines indicate pathways with decreased FOXO3. Black dashed lines indicate pathways with increased FOXO3. Red straight lines indicate common pathways between both decreased and increased FOXO3

tubular apoptosis and inflammation [101]. In recent years, investigators suggested that FOXO3 could play a pivotal role in the pathophysiological mechanisms underlying renal after IR injury. In both in vivo and in vitro models of renal IR injury, it has been found that upregulation of miR-182 [102], miR-155 [46], PI3K/AKT pathway [103], IL-6-induced DNMT1-mediated hypermethylation of FOXO3 promoter [104], and downregulation of the cytochrome P4502J2 (CYP2J2)/ epoxyeicosatrienoic acids (EETs)/SIRT1 cascade [105] could contribute to reduce the expression level and the activity of FOXO3. Down-expressed FOXO3 may release the expression level of cardiotrophin-like cytokine factor 1 (CLCF1) [106]——a member of the IL-6 family of cytokines suggested to play an important role in focal segmental glomerulosclerosis (FSGS) [107]. Meanwhile, the inhibition of FOXO3 expression and activity could provoke diverse harmful consequences leading to autophagy through upregulation of Belclin-1 and LC3 II/LC3 I ratio [105], apoptosis via upregulation of caspase-3 activity and Bax/Bcl2 ratio [102, 105], pyroptosis via upregulation of caspase-1, caspase-11, IL-1β, and IL-18 [46], and renal fibrosis via activation of EMT and Wnt/β-catenin pathway [103, 104] Fig. 3). These results indicate that FOXO3 might play a protective role against IR-induced injury in the kidneys, as it was found that forced overexpression of FOXO3 by treatment with β-hydroxybutyrate (β-OHB) or through genetical processes could reverse the IR-related apoptosis, pyroptosis, autophagy, and fibrosis [46, 103, 105, 108].

However, a study performed by Wang et al. (2017) revealed that FOXO3 might be deacetylated, and its activity increased by the overexpression of SIRT2 after renal IR injury [109]. The study showed that FOXO3 could induce the expression of FasL as well as the activity of caspase-3 and caspase-8 to promote renal cell death after IR. This suggests that FOXO3 could also play deleterious effects on renal cells after IR, indicating a controversial role of FOXO3 after renal IR, which could be clarified by future studies.

Hepatic ischemia and reperfusion

Hepatic IR injury is a pathophysiological process that can occur in a variety of clinical settings, such as resection surgery, transplantation, and trauma. When the blood supply to

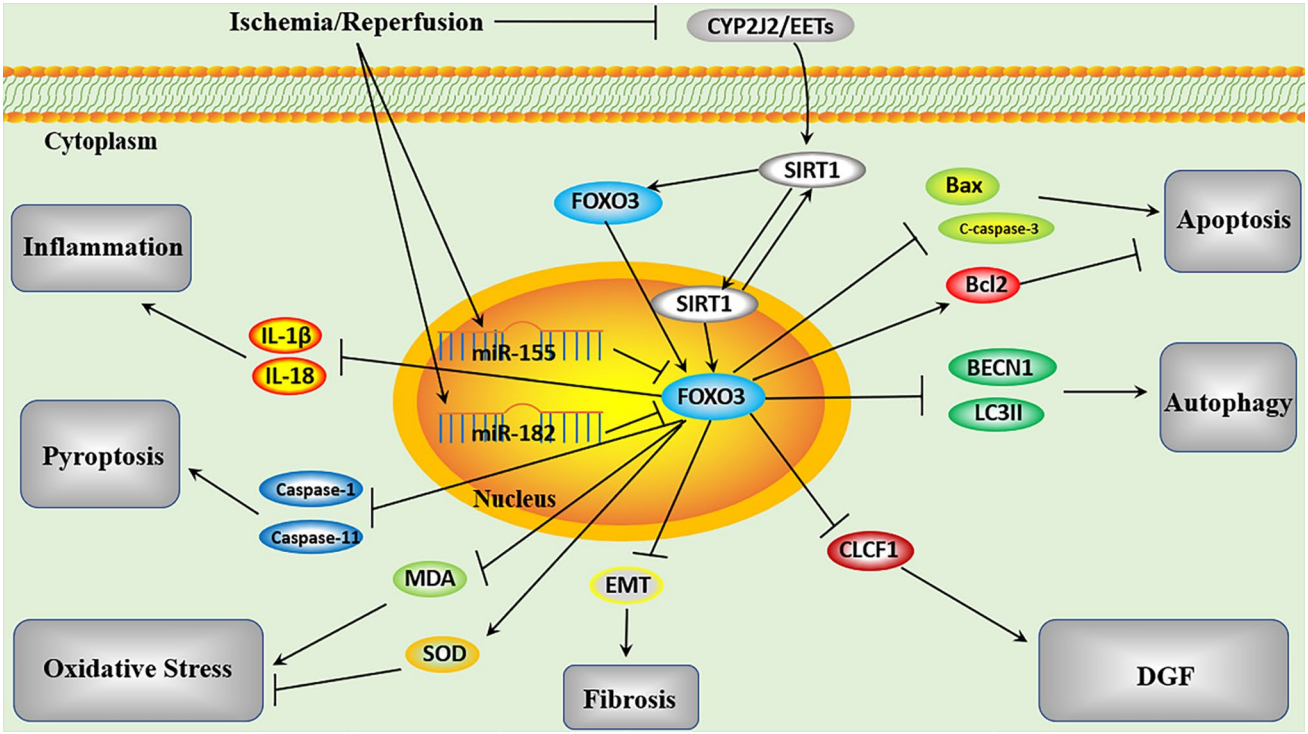

Fig. 3 The expression of FOXO3 is reduced in the kidney following IR. This may be caused by the downregulation of CYP2J2/EETs and SIRT1. The increase in FOXO3 levels leads to the regulation of many genes involved in fibrosis, autophagy, apoptosis, inflammation, pyroptosis, oxidative stress, and delayed graft function

the liver is reduced, followed by reperfusion, the tissue can suffer from acute liver failure, graft rejection, and chronic hepatic dysfunction [110, 111]. These issues increase the rate of morbidity and mortality in those affected by hepatic IR injury. Common effects of hepatic IR injury include elevated levels of liver enzymes, inflammatory cytokines, oxidative stress, autophagy, and apoptosis. Findings of many researches show that FOXO3 may play an important role in these adverse effects [47, 112, 113]. Some studies have suggested that upregulation of SIRT1 [114] and TGR5/SIRT3 axis [115] and downregulation of Wnt3a/β-catenin and AKT pathways [113] contribute to increasing FOXO3 expression. Thereafter, FOXO3 contributed to aggravating the IR-induced damage in the liver by inducing hepatocellular inflammation, autophagy, oxidative stress, and apoptosis (Fig. 4) [113–115]. These studies indicate that FOXO3 might play a detrimental role in the liver after IR, as forced FOXO3 inhibition contributed to alleviating the damage caused by FOXO3 expression.

Controversially, studies showed that FOXO3 could play beneficial effects on the liver after IR. The overexpression of the AKT pathway and downregulation of SIRT1 and Nrf-2 contribute to reducing FOXO3 expression and activity. This significantly induced hepatocellular apoptosis, autophagy, and oxidative stress (Fig. 5) [47, 116, 117]. Further investigations show that stimulation of FOXO3 expression could contribute to attenuating the IR-induced damage in the liver. These studies indicate that FOXO3 could play beneficial effects after hepatic IR. Future studies will be required to elucidate FOXO3 function after hepatic IR.

Intestinal ischemia and reperfusion

Intestinal IR injury is a common clinical condition caused by interruption of normal blood supply to the intestine, followed by reperfusion. It is associated with a variety of pathologic changes, including cellular damage and inflammatory responses [118, 119]. Clinically, it is often characterized by abdominal pain, nausea, vomiting, and diarrhea; and it can lead to multi-organ dysfunction, infections due to the release of pro-inflammatory molecules, and high mortality and mortality rates [120, 121]. The exact mechanisms underlying intestinal IR injury are not well-understood. However, it is known to be associated with ischemia-induced cellular damage and inflammatory response as well as acute lung injury (ALI) resulting from intestinal IR [122]. Upon reperfusion, it has been shown that FOXO3 expression and activity could be increased, possibly due to the inhibition of its upstream SIRT1[48, 123] and overexpression of TNF-α and JNK [124]. Once active, FOXO3 can cause lung cell death and trigger an inflammatory response in the intestinal epithelial

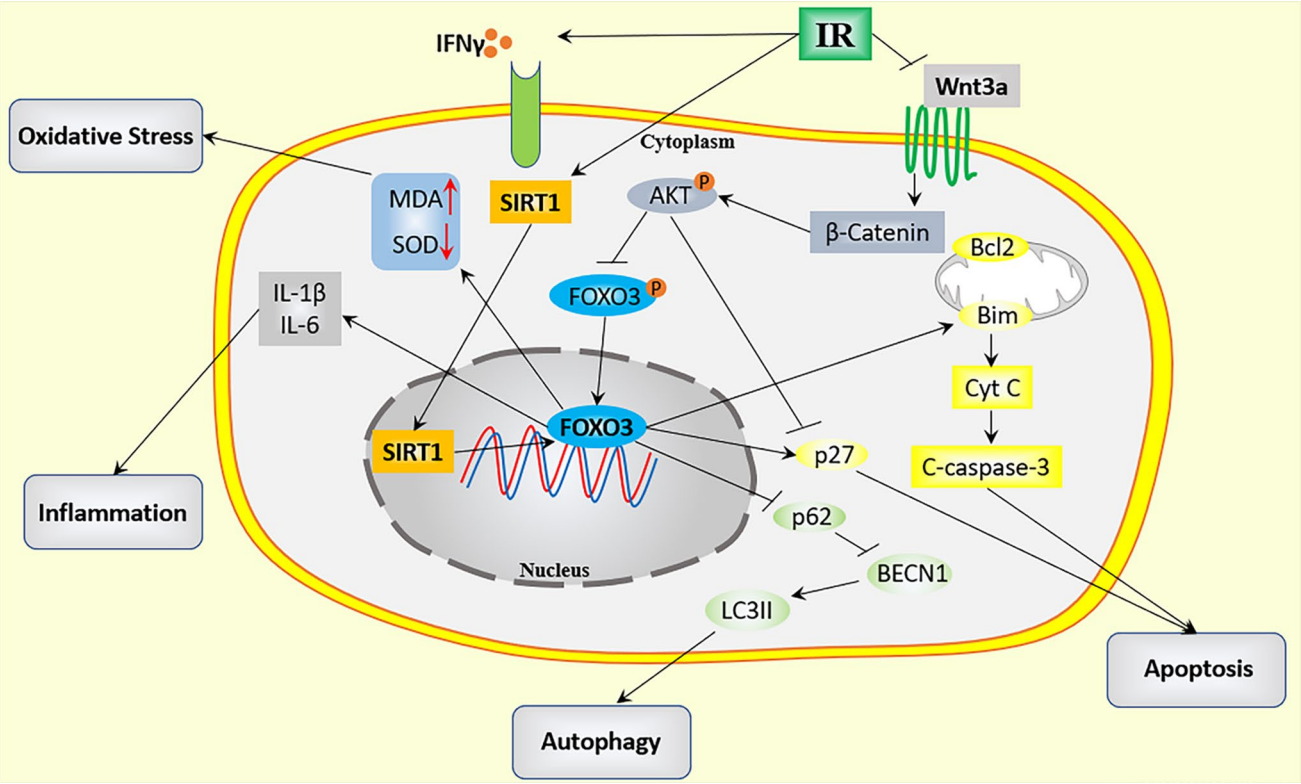

Fig. 4 The expression level of FOXO3 is released following Wnt3a/β-Catenin/AKT reduction and SIRT1 and IFNγ induction in the liver after IR. This conduces to activating the apoptotic, autophagic, inflammatory, and oxidative stress pathways

cells by inducing the expression of pro-inflammatory molecules such as cytokines, which can lead to cellular injury, edema, and organ failure [48, 123, 124]. In addition, FOXO3 could mediate the IR-induced influx of neutrophils into the intestine to further contribute to tissue damage by releasing inflammatory and apoptotic mediators [124] (Fig. 6). These indicate that FOXO3 may play a detrimental function in the intestinal epithelial cells and lung tissue after intestinal IR.

Hind limb ischemia

Hind Limb Ischemia (HLI) is the most common and severe form of peripheral vascular disease that can cause severe symptoms such as pain and disability, leading to limb amputation and even death [125–127]. In addition, this condition significantly contributes to mobility loss, likely due to impairments in skeletal muscle homeostasis, such as impaired contractility, altered innervation, increased fat infiltration, fiber wasting, and disruptions in mitochondrial energy production [128–130]. However, the molecular mechanisms underlying this decrease in muscle function are not yet fully understood. A recent study by Yan et al. (2020) has suggested the involvement of FOXO3 in this process [49]. It was suggested that circHIPK3 downregulation could release the expression of miR-421, which inhibits the expression and activity of FOXO3, leading to aberrant expression of pyroptotic proteins. This indicates that FOXO3 could contribute to hind limb ischemic injury by inducing pyroptosis in the ischemic muscle (Fig. 7). In-depth studies are required to elucidate the exact role of FOXO3 in the ischemic muscle.

Conclusion

The expression levels of FOXO3 show dynamic changes in different organs following ischemia and reperfusion. These changes in FOXO3 expression influenced the expression levels of various proteins related to various damages, such as oxidative stress, inflammation, autophagy, pyroptosis, mitophagy, and apoptosis. The present study revealed that FOXO3 is markedly upregulated in the lung tissue and intestinal epithelial cells following ischemia and reperfusion, where it substantially contributes to ischemia and reperfusion injury. In contrast, FOXO3 is significantly downregulated in the renal tissue after ischemia and reperfusion and in the ischemic hindlimb muscle; nevertheless, the low level of FOXO3 was associated with the ischemic and reperfusion injury, suggesting that FOXO3 could also contribute to the alleviation of the ischemic and reperfusion injury in the

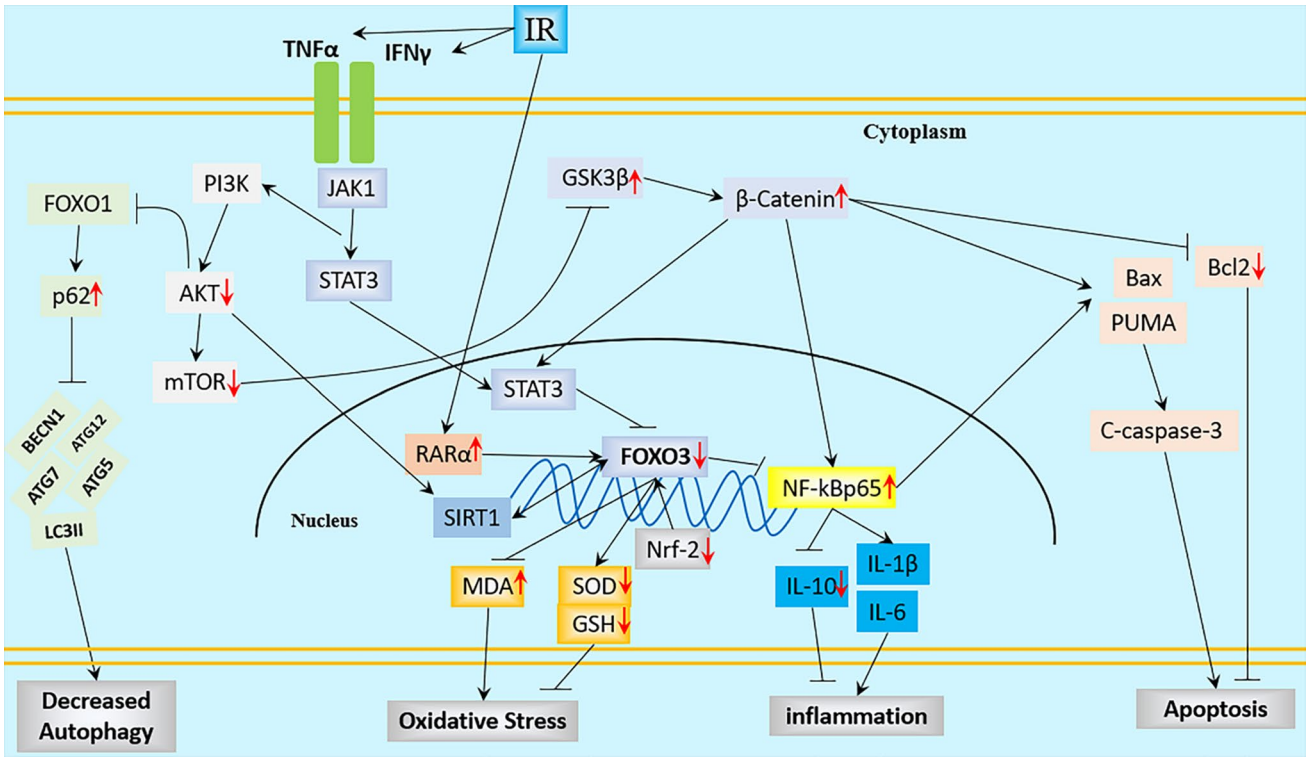

Fig. 5 FOXO3 expression in the liver is decreased after IR. FOXO3 decrease followed JAK1/STAT3, RARα, GSK3β/β-Catenin, IFNγ, TNFα, and Nrf-2 activation and PI3K/AKT/mTOR and SIRT1 deactivation. This activates the anti-autophagic FOXO1 and p62 and the expression of oxidative stress-related MDA, inflammatory IL-1β and IL-6, and apoptotic Bax, PUMA, and caspase-3

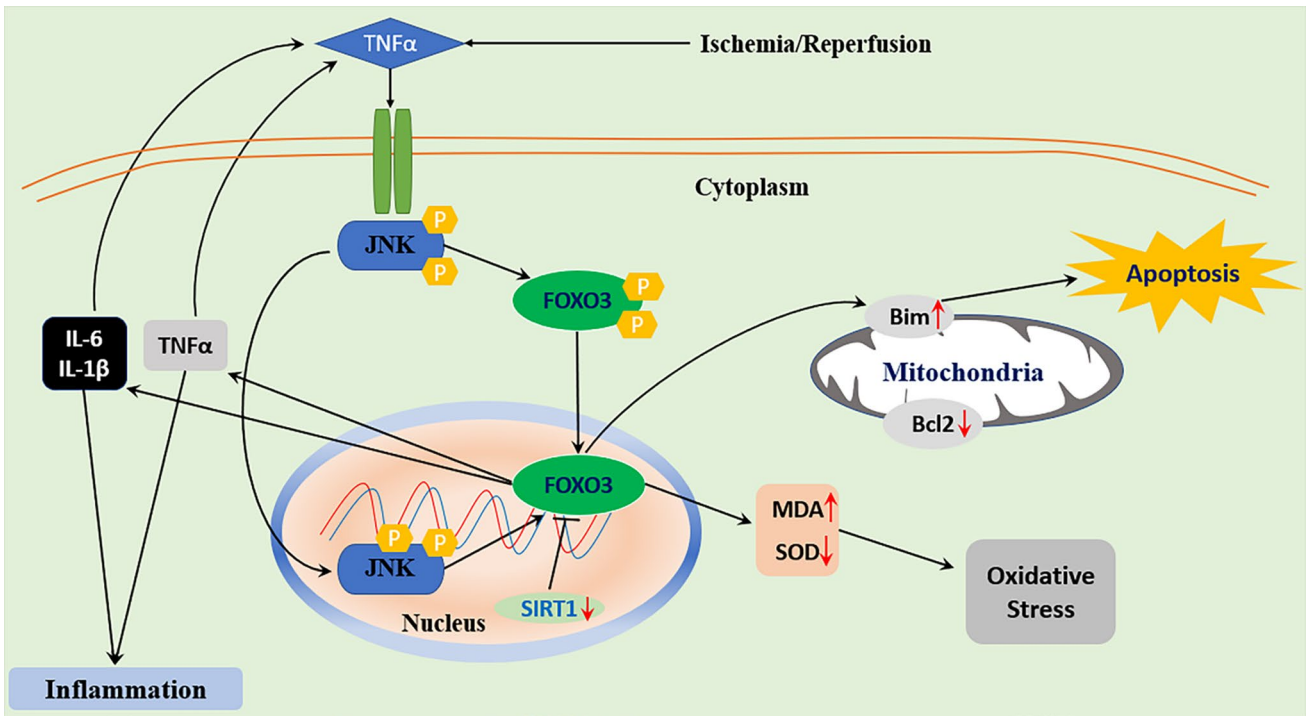

Fig. 6 The expression of FOXO3 is increased in the lung tissue and the intestinal epithelial cells after intestinal IR. The upregulation of FOXO3 is induced by the overexpression of TNFα and JNK and the downregulation of SIRT1. This conduced to overexpressing IL-1β and IL-6 in the inflammatory pathway, Bim in the apoptotic pathway, and MDA in the oxidative stress pathway

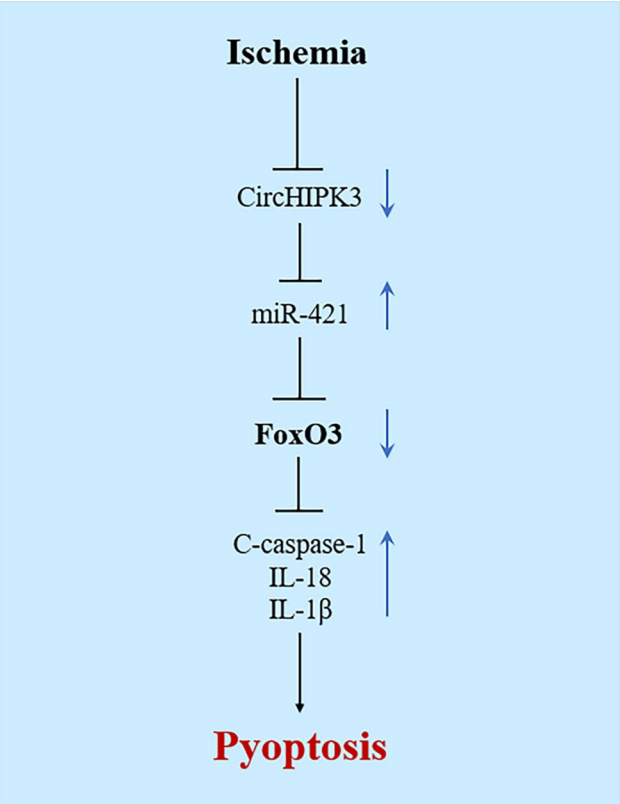

Fig. 7 FOXO3 is down-expressed in the skeletal muscle subjected to ischemia. This resulted from the downregulation of circHIPK3 and the upregulation of miR-421. FOXO3 stimulates caspase-1 activation and IL-18 and IL-1β expression to induce pyroptosis in the skeletal muscle

kidney and hind limb muscle. Intriguingly, studies reported upregulation and downregulation of FOXO3 expression in the brain, myocardium, and liver following ischemia and reperfusion, where it could play both stimulation or inhibition effects on the induced injury. Therefore, in-depth studies are required to elucidate the role of FOXO3 in the brain, cardiac, and liver tissues after ischemia and reperfusion. FOXO3 deserves to be considered in diagnosing ischemia and reperfusion injury. Ultimately, as studies showed, maintaining FOXO3 expression level, whether genetically or through the administration of exogenous molecules, could be a great approach to control or treat the ischemia and reperfusion-induced damages.

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Author contributions MO wrote the manuscript. YH, MG, CM, WX, and YH proofread the manuscript. HX supervised and revised the manuscript. All authors reviewed and approved the final manuscript.

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Data availability All data generated or analyzed during the present study are included in the present article.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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