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REVIEW

Role of sirtuins in ischemia-reperfusion injury

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Abstract

Ischemia-reperfusion injury (IRI) remains an unresolved and complicated situation in clinical practice, especially in the case of organ transplantation. Several factors contribute to its complexity; the depletion of energy during ischemia and the induction of oxidative stress during reperfusion initiate a cascade of pathways that lead to cell death and finally to severe organ injury. Recently, the sirtuin family of nicotinamide adenine dinucleotide-dependent deacetylases has gained increasing attention from researchers, due to their involvement in the modulation of a wide variety of cellular functions. There are seven mammalian sirtuins and, among them, the nuclear/cytoplasmic sirtuin 1 (SIRT1) and the mitochondrial sirtuin 3 (SIRT3) are ubiquitously expressed in many tissue types. Sirtuins are known to play major roles in protecting against cellular stress and in controlling metabolic pathways, which are key processes during IRI. In this review, we mainly focus on SIRT1 and SIRT3 and examine their role in modulating pathways against energy depletion during ischemia and their involvement in oxidative stress, apoptosis, microcirculatory stress and inflammation during reperfusion. We present evidence of the beneficial effects of sirtuins against IRI and emphasize the importance of developing new strategies by enhancing their action.

Key words: Sirtuin 1; Sirtuin 3; Ischemia-reperfusion injury; Oxidative stress; Apoptosis

Core tip: Sirtuins are responsible for the regulation of protein activation by deacetylating a range of proteins that play important roles in the pathophysiology of various diseases. The present review summarizes the beneficial effects of sirtuins 1 and 3, the two most prominent sirtuins involved in mammalian energy homeostasis and oxidative stress. We conclude that both sirtuins might be attractive targets for counteracting the detrimental effects of ischemia-reperfusion injury.

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INTRODUCTION

Sirtuins belong to the highly conserved class Ⅲ histone

deacetylases with homology to the yeast silent information regulator 2. To date, seven sirtuins have been described in mammals. They posses nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase activity, with the exception of sirtuin 4 (SIRT4) which has only ADP-ribosyltransferase activity, and SIRT1 and SIRT6 which have not only deacetylase activity but also relatively weak ADP-ribosyltransferase activity[1]. Their enzymatic activity depends on their protein expression levels, the availability of NAD^+ and the presence of proteins that modulate sirtuin enzymatic activity. For instance, SIRT1 expression increases during starvation or when cells are exposed to conditions of oxidative stress and DNA damage[2,3].

Sirtuins are found in several subcellular locations, including the nucleus (SIRT1, SIRT6, and SIRT7), cytosol (SIRT2), and mitochondria (SIRT3-SIRT5). In some studies, however, SIRT1 has been found to possess cytosolic activity, and SIRT2 has been found to be associated with nuclear proteins[4].

Several recent studies have shown that sirtuins regulate a wide variety of cellular processes, such as gene transcription, metabolism and cellular stress response[5-7]. SIRT1, the most studied member of the family, plays an important role in several processes ranging from cell cycle regulation to energy homeostasis[8,9]. SIRT3 has recently been reported to have a considerable impact on mitochondrial energy metabolism and function[10,11]. In this review, we will focus mainly on SIRT1 and SIRT3 functions in ischemia-reperfusion injury (IRI).

IRI is one of the most significant problems in graft injury, contributing to primary graft dysfunction or non-function after organ transplantation[12-14]. Many factors contribute to IRI. First of all, the loss of oxygen supply during ischemia results in the reduction of adenosine triphosphate (ATP) synthesis and subsequent changes in ion influx, acidosis and cell swelling which may eventually lead to cell death. The restoration of blood flow is followed by an excessive acute inflammatory response triggering the reperfusion injury. Although the ischemic insult causes significant damage in cells, the tissue injury generated during reperfusion is much more severe. On reperfusion, oxygen is suddenly available, and metabolism proceeds rapidly, resulting in a sudden production of reactive oxygen species (ROS), cytokines and chemokines which increase the accumulation of inflammatory cells (monocytes, dendritic cells and granulocytes). In combination with excessive nitric oxide (NO), ROS are able to induce DNA damage and activate various types of cell death pathways[15-17].

Understanding the mechanisms involved in the pathogenesis of IRI is the first step to mitigate its adverse effects. Sirtuins are known to regulate many important processes in cell physiology, including those affecting IRI, such as cellular metabolism and stress response. This makes them potentially appealing targets for therapeutic interventions against IR-induced injury.

ROLE OF SIRTUINS IN ISCHEMIA

The low energy state during ischemia results in activation of adenosine monophosphate protein kinase (AMPK), a fuel-sensing enzyme that is positively regulated by an increased ratio of adenosine monophosphate to ATP. When AMPK is activated, it stimulates processes that restore ATP levels (*e.g.*, fatty acid oxidation) and inhibits other processes that consume ATP (*e.g.*, protein synthesis)[18]. The activity of sirtuins is directly related to the metabolic state of the cell due to their dependence on NAD^+. Suchankova and collaborators found that glucose-induced changes in AMPK are linked to alterations in the NAD^+/reduced nicotinamide adenine dinucleotide ratio and SIRT1 abundance and activity[19]. These results may suggest a possible interaction between AMPK and SIRT1 in ischemic conditions. Indeed, an activator of AMPK, 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside, has been found to improve IRI and increase SIRT1 expression in the rat kidney[20]. Furthermore, enhancing the activity of SIRT1 through the application of resveratrol, a SIRT1 activator, has been demonstrated to protect against cerebral ischemia[21].

Another element that plays an essential role in triggering cellular protection and preventing metabolic alterations caused by oxygen deprivation is hypoxia-inducible factors (HIFs). Mammals possess three isoforms of HIFα, of which HIF1α and HIF2α are the most structurally similar and the best characterized. During hypoxia, protein levels of HIF2α increase slightly, but it presents significant activation, which suggests that its activity is regulated by additional post-translational mechanisms. One of these post-translational modulations may be deacetylation, since in hypoxic Hep3B cells SIRT1 deacetylates lysine residues in the HIF2α protein, enhancing its transcriptional activity[22].

Additionally, SIRT1 interacts with HIF1α, but in this case SIRT1 represses HIF1α transcriptional activity[23]. Under hypoxic stress, decreased cellular NAD^+ downregulates SIRT1, increases HIF1α acetylation, and thereby promotes the expression of *HIF1α* target genes[23]. Interestingly, other studies have shown that HIF2α compete with HIF1α for binding to SIRT1[24]. Moreover, it has been demonstrated that SIRT6 is also linked to HIF1α by repressing the transcription of *HIF1α* target genes[25].

Likewise, the effects of SIRT3 appear to be protective in the context of hypoxic stress in human cancer cells. SIRT3 overexpression resulted in decreased ROS production, impediment of HIF1α stabilization and subsequent suppression of tumorigenesis[26,27]. However, the effect of SIRT3 in HIF1α stabilization in IRI has not been reported to date.

One of the most important factors involved in the metabolic control regulated by SIRT1 is peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α), a transcriptional co-activator of many nuclear receptors and transcriptional factors. SIRT1 functionally interacts with PGC1α and deacetylates it, thus inducing the expression of mitochondrial proteins involved in ATP-generating pathways[28]. Increased PGC1α activity is also associated with lower levels of oxidative damage during

ischemia, as shown by the decrease ROS scavenging in rodents lacking PGC1α subjected to global ischemia[29]. Furthermore, the uncoupling protein 2 (UCP2), an inner mitochondrial membrane protein, regulates the proton electrochemical gradient and in neuronal cells PGC1α is required for the induction of UCP2 and subsequent protection against oxidative stress[30]. It has also been shown that enhanced activity of SIRT1 during ischemic preconditioning (IPC) or resveratrol preconditioning confers protection against cerebral ischemia by reducing UCP2 levels, which results in increased ATP levels[21]. However, a more recent study associated the protective effect of resveratrol against oxidative stress in cerebral ischemia with increased levels of SIRT1/PGC1α and UCP2[31]. Moreover, the exact role of UCP2 during ischemia is not fully understood, as studies of its effects have produced conflicting results[32-35].

ROLE OF SIRTUINS IN REPERFUSION

Deprivation of oxygen to the grafts during ischemia induces severe lesions, but the most important damage is caused during reperfusion, when oxygen entry to the organ is restored. During reperfusion, the cellular metabolism returns to aerobic pathways, which results in the generation of a wide variety of ROS, including superoxide, hydrogen peroxide and reactive nitrogen species, such as peroxynitrite. ROS are mainly produced in mitochondria and trigger several phenomena, including accumulation of Ca^{2+}, caspase activation, cytokine upregulation, lipid, protein and DNA damage[36-38]. ROS can be eliminated by enzymatic pathways including manganese superoxide dismutase (MnSOD), catalase (Cat) and peroxidases. Imbalance between ROS generation and elimination produces oxidative stress[15,16].

Various reports in cardiomyocytes have demonstrated the protective role of SIRT1 against oxidative stress[39,40]. Hearts overexpressing SIRT1 were more resistant to oxidative stress in response to IRI, as SIRT1 upregulated the expression of anti-oxidants like MnSOD and thioredoxin 1[41]. SIRT1 also deacetylated Forkhead box-containing protein O (FoxO) 1 transcription factor, inducing its nuclear translocation and subsequent transcription of anti-oxidant molecules[41,42]. Moreover, the question of whether SIRT1 can induce the transcription of other FoxO transcription factors, like FoxO3α, has not yet been investigated. However, the levels of SIRT1 activation are decisive for its protective role, as very high cardiac SIRT1 expression induces mitochondrial dysfunction and increases oxidative stress[39]. Furthermore, in a model of kidney IRI, the protective effect of SIRT1 against oxidative stress has also been demonstrated since SIRT1 upregulated Cat levels and maintained peroxisome number and function[43].

Although mitochondrial sirtuins (SIRT3-SIRT5) have not been studied as extensively as SIRT1, an increasing body of evidence indicates the importance of SIRT3 in mitochondrial biology and function. Lombard *et al*[44] demonstrated that SIRT3 is the dominant mitochondrial deacetylase, as a significant number of mitochondrial proteins are hyperacetylated in $SIRT3^{-/-}$ mice. SIRT3 deacetylates and thus enhances the activity of various proteins that appear to be an important part of the anti-oxidative defense mechanisms of mitochondria, such as MnSOD[45,46], regulatory proteins of the glutathione[47-49] and thioredoxin system[50].

Transcriptional upregulation of the antioxidant enzymes MnSOD, Cat and peroxiredoxin can also be achieved by FoxO3α transcription factor, which is translocated to the nucleus after being deacetylated by SIRT3[51,52]. Furthermore, SIRT3 is necessary for the enhanced expression of cytochrome c, which presents peroxidase- and superoxidase-scavenging capacity[47,49,53]. However, a similar anti-oxidant effect of SIRT3 in models of IRI has not yet been established.

A wide array of functional alterations develop in mitochondria during reperfusion injury[36,54]. In healthy cells, their primary function is the provision of ATP through oxidative phosphorylation in order to meet the high energy demands. There is increasing evidence of the involvement of a multi-protein complex called the mitochondrial permeability transition pore (mPTP) in the decline in mitochondrial function, which is a common finding during reperfusion injury[55-57]. SIRT3 is known to deacetylate the regulatory component of the mPTP, cyclophilin D, and thereby reduce its activity and the subsequent mitochondrial swelling in the heart[58]. It has also been shown that SIRT4 interacts with the adenine nucleotide translocator, another component of mPTP, and that SIRT5 deacetylates cytochrome c, but the physiological importance of these interactions has not yet been established[59,60], especially in models of IRI.

Microcirculatory alterations play an important part in IRI. During the ischemic period, vascular hypoxia can cause increased vascular permeability. After reperfusion, complement system activation, leukocyte-endothelial cell adhesion and platelet-leukocyte aggregation further aggravate microvascular dysfunction[61].

NO produced by endothelial NO synthase (eNOS) is a key regulator of endothelial function, as it opposes the vasoconstrictive actions of endothelins and provokes vasodilatation. Thus, it can abrogate the microcirculatory stress generated during reperfusion[62]. However, NO produced by inducible NO synthase (iNOS) exacerbates IRI through the NOS-derived superoxide production or the generation of peroxynitrite[12]. There is a large body of evidence in favor of the relationship between eNOS and SIRT1; SIRT1 interacts and modifies the acetylation state of eNOS, resulting in the activation of the enzyme[63-65]. In $SIRT1^{+/+}$ hearts subjected to IRI SIRT1 was associated with eNOS activation[66]. SIRT1 activation by resveratrol protected against subacute intestinal IRI by reducing the NO production through iNOS[67] Moreover, various experimental models showed that resveratrol inhibits endothelin-1 levels, providing better regulation of vascular tone[68-70]. However, a recent study in human umbilical vein endothelial cells

has shown that the inhibitory effects of resveratrol on endothelin-1 levels are SIRT1-independent[71].

ROLE OF SIRTUINS IN IRI-ASSOCIATED INFLAMMATION

IRI results in a profound inflammatory tissue reaction with immune cells infiltrating the tissue. The damage is mediated by various cytokines, chemokines, adhesion molecules, and compounds of the extracellular matrix. The expression of these factors is regulated by specific transcription factors with nuclear factor kappa B (NF-κB) being one of the key modulators of inflammation. After activation, the transcription factor migrates to the nucleus and enhances the transcription of pro-inflammatory genes potentiating the inflammatory response. This is followed by an infiltration of lymphocytes, mononuclear cells/macrophages, and granulocytes into the injured tissue[72-74].

In this way, SIRT1 plays an important role in neuroprotection against brain ischemia by deacetylation and subsequent inhibition of p53 and NF-κB pathways[75]. In $SIRT1^{+/+}$ hearts subjected to IRI SIRT1 was correlated with decreased acetylation of NF-κB and possible prevention of inflammation[66]. Moreover, the anti-inflammatory action of SIRT1 by deacetylating NF-κB and thus inhibiting the expression of endothelial adhesion molecules has also been demonstrated in human aortic endothelial cells[74].

SIRTUINS: CELL SURVIVAL OR DEATH?

Apoptotic cell death is a well known mechanism involved in IRI which occurs *via* activation of caspases that cleave DNA and other cellular components[16,17,76]. There is evidence that SIRT1 is associated with longevity in mammals and enhances mammalian cell survival under stress conditions *via* regulating the specific substrates[77-79]. In fact, several studies have mentioned the anti-apoptotic effect of SIRT1 in IRI. SIRT1 deacetylates known mediators of apoptosis, such as the tumor-suppressor p53, resulting in inhibition of its transcriptional activity[80,81]. SIRT1 also deacetylates the DNA repair factor Ku70[2,82,83]; thus Ku70 prevents the translocation of Bax, a pro-apoptotic B cell lymphoma-2 (Bcl-2) family protein, to the mitochondria. In ischemic kidney and brain SIRT1 has been identified as an important survival mediator, given that increased SIRT1 was associated with reduced p53 expression and apoptosis[75,84]. SIRT1 also modulates apoptosis-related molecules through the deacetylation of the FoxO family of transcription factors. During IRI in heart-specific $SIRT1^{+/+}$ transgenic mice, SIRT1 induces nuclear translocation of FoxO1, which upregulates the anti-apoptotic factors Bcl-2 and Bcl-like X and downregulates Bax[41]. As regards other members of the FoxO family, Brunet *et al*[85] revealed a dual role of SIRT1 in the cell cycle depending on stress conditions; SIRT1 inhibited the ability of FoxO3 to induce cell death, thus promoting cell survival and, surprisingly, it also increased the ability of FoxO3 to induce cell cycle arrest and resistance to oxidative stress.

A possible pro-apoptotic role of SIRT1 in IRI has not been reported previously. However, studies in human embryonic kidney cells have revealed that SIRT1 can promote cell death by inhibiting NF-κB in response to tumor necrosis factor alpha[86]. Further investigation is required to define the conditions under which SIRT1 may promote apoptosis.

Apoptotic pathways are known to be initiated during reperfusion upon the opening of the mPTP which leads to the release of caspase-activating molecules[87,88]. Since SIRT3 is located in the mitochondria, it may be involved in anti-apoptotic pathways. In this regard, SIRT3 protects various types of cells from apoptotic cell death triggered by genotoxic or oxidative stress[89-92]. The pro-apoptotic role of SIRT3 has also been associated with tumor suppression and restraint of ROS[93]. However, SIRT3 has also been reported to contribute to Bcl-2- and JNK-related apoptotic pathways in human colorectal carcinoma cells[94]. In any case, the potential anti-apoptotic mechanisms of SIRT3 during IRI are yet to be elucidated.

CONCLUSIONS AND PERSPECTIVES

A wide range of pathological processes contribute to IRI. Particularly during organ transplantation, IRI contributes to early graft dysfunction. For this reason, it is important to gain additional mechanistic insight into the molecular mechanisms underlying this injury. In the past few years, sirtuins have emerged as critical modulators of various cellular processes, including those that contribute to the pathogenesis of IRI.

In this paper, we have reviewed the signaling pathways of SIRT1 and SIRT3 protection in IRI. SIRT1 has been shown to exert its beneficial effect against oxidative stress, hypoxic injury or inflammation associated with IRI by activating FoxO1, PGC1α and HIF2α or by inhibiting NF-κB transcription factors (Figures 1 and 2). SIRT3's protective role in IRI is mainly mediated by activating FoxO3α and mitochondrial anti-oxidant enzymes (Figure 2). Investigations that can further determine other intracellular signaling, trafficking and post-translational modifications by SIRT1 and SIRT3 in a variety of cell systems and environments will allow us to translate this knowledge into effective treatment strategies that will be applicable in multiple disorders.

Numerous studies have demonstrated key roles for SIRT1 and SIRT3 in brain, heart and kidney IRI. However, the protective effect of these sirtuins against ischemic processes in other organs such as the liver has not yet been demonstrated. The relevance of SIRT3 in the hepatic metabolism has been confirmed in a study showing that its overexpression in hepatocytes decreased the accumulation of lipids *via* AMPK activation[95]. Furthermore, deletion of hepatic SIRT1 resulted in hepatic steatosis, hepatic inflammation and endoplasmatic reticulum stress[96]. Since SIRT1 and SIRT3 have been shown

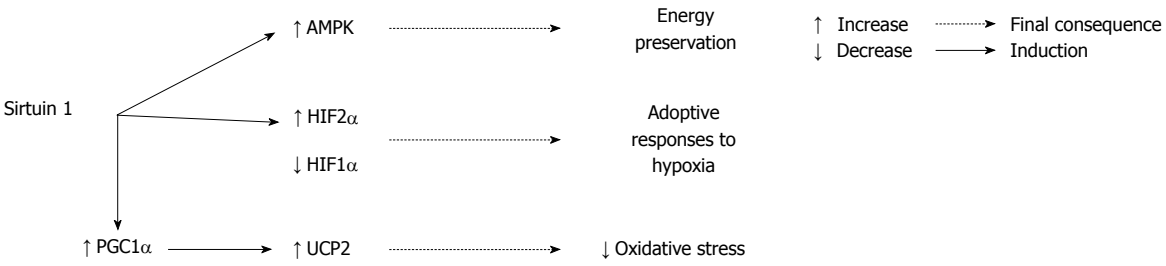

Figure 1 Protective role of sirtuin 1 during ischemia. Sirtuin 1 (SIRT1) activates adenosine monophosphate protein kinase (AMPK) as a cell response to counteract the energy deficiency. SIRT1 upregulates hypoxia-inducible factor 2α (HIF2α) and downregulates HIF1α to increase their transcriptional activity. SIRT1 upregulates peroxisome proliferator-activated receptor-γ coactivator, leading to enhancement of anti-oxidant capacity of uncoupling protein 2 (UCP2). PGC1α: Peroxisome proliferator-activated receptor-γ coactivator.

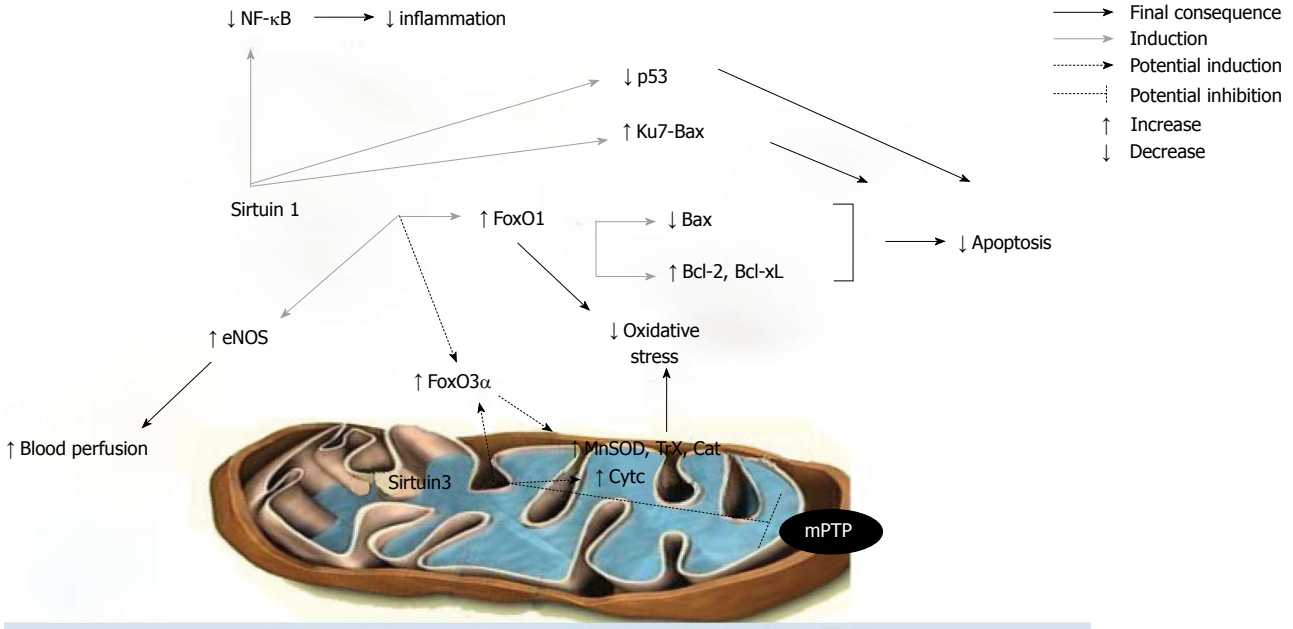

Figure 2 Protective role of sirtuin 1 and suggestive role of sirtuin 3 during reperfusion. Sirtuin 1 (SIRT1) inhibits inflammation through inhibition of nuclear factor kappa B and activates endothelial nitric oxide synthase for a better microcirculation. SIRT1 downregulates apoptosis through multiple pathways, for example, inhibiting p53 transcriptional activity or favoring the binding between Ku70 and Bax. SIRT1 also enhances forkhead box-containing protein O 1 (FoxO1) transcriptional activity, resulting in Bax downregulation and in the upregulation of B cell lymphoma-2 and Bcl-like X. Deacetylation of FoxO1 by SIRT1 also results in lessening oxidative stress, whereas the same effect may be achieved by deacetylation of forkhead box-containing protein 3 alpha (FoxO3α). Sirtuin 3 (SIRT3) is suggested to contribute to decrease in oxidative stress either by a direct interaction with mitochondrial anti-oxidant enzymes [manganese superoxide dismutase (MnSOD), thioredoxin system (Trx), cytochrome (Cyt)] or by enhancing FoxO3α to transcribe MnSOD and Cat. Mitochondrial permeability transition pore (mPTP) may also be inhibited by SIRT3 and result in less production of oxidative stress. NF-κB: Nuclear factor kappa B; eNOS: Endothelial nitric oxide synthase; Bcl-2: B cell lymphoma-2; Bcl-xL: Bcl-like X; Bax: Bcl-2-associated X; Cat: Catalase.

to exert a beneficial effect in regulating hepatic fatty acid metabolism, it would be interesting to investigate their role in the context of liver transplantation. Currently, the shortage of organs for transplantation has obliged physicians to utilize marginal grafts, including grafts with moderate steatosis. Steatotic livers exhibit a more severe inflammatory reaction and more exacerbated oxidative stress and consequently a higher vulnerability to IRI[12]. Thus, activating SIRT1 and SIRT3 might be a potential strategy to protect steatotic livers from IRI as well as to expand the donor pool for liver transplantation. In fact, in preliminary studies our group observed that SIRT1 is involved in the protective mechanisms against IRI elicited by IPC in fatty livers.

For this reason, both surgical and pharmacological strategies should be developed to enhance the activity of sirtuins and thus mitigate the detrimental effect of IRI. Recent studies have highlighted the important role of SIRT1 in IPC-mediated protection in the heart and brain; in IPC brain, SIRT1 prevents neuronal death[97], whereas during cardiac IPC, SIRT1 regulates HIF1α protein levels[98,99]. A recent review has also associated SIRT1 with the protective effects of hyperbaric oxygen preconditioning against apoptosis in the rat brain[100]. However, it is still to be established whether SIRT1 contributes to the protective effects of preconditioning through the regulation of other signalling pathways. Furthermore, its possible implication in IPC related mechanisms in other organs, including the liver or kidney, remains to be elucidated.

Nor has the potential role of sirtuins in cold ischemia

and reperfusion yet been established. In the context of liver IRI, a previous study by our group demonstrated that during normoxic reperfusion, after cold ischemia, the presence of NO favors HIF1α accumulation, also promoting the activation of other cytoprotective proteins, such as heme oxygenase-1[101]. Among these cytoprotective proteins, SIRT1 may be ideally suited to enhance the protective effect.

This review summarizes the basic mediators of IRI influenced by the action of SIRT1 and SIRT3 and highlights the importance of their regulation. Future research should aim to elucidate the complete action of all members of the sirtuins family in IRI, and to develop pharmacological strategies that can allow their action to be modulated.

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