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Review

New role of silent information regulator 1 in cerebral ischemia

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ABSTRACT

Silent information regulator 1 (SIRT1) is a type of histone deacetylase whose activity is dependent on nicotinamide adenine dinucleotide. SIRT1 plays a key role in the longevity effects elicited by calorie restriction. Recently, a neuroprotective effect of SIRT1 was reported for neurological diseases. The focus of this review is to summarize the protective effects of SIRT1 in cerebral ischemia. First, the post-translational modifications of SIRT1 are illustrated; then, we discuss the roles of SIRT1 in cerebral immune homeostasis. Next, we introduce the deacetylase activity of SIRT1 in cerebral ischemia and provide some examples of relevant studies. In addition, we discuss several activated mediators of SIRT1, such as resveratrol, caloric restriction, ischemic preconditioning, and other proteins and compounds. Finally, we highlight a few SIRT1-related signaling pathways, such as the peroxisome proliferator-activated receptor γ coactivator 1α, nuclear transcription factor κB, uncoupling protein 2, and forkhead box O pathways. Taken together, the information compiled in this article will serve as a comprehensive reference for the actions of SIRT1 in the nervous system and will help in the design of future experimental research and promote SIRT1 as a new therapeutic target.

1. Introduction

Cerebral ischemia is a common neurological disease caused by the sudden reduction or cessation of blood flow to the brain, which leads to infarction. Cerebral ischemic injury is considered to be 1 of the leading causes of death and adult disability because of its high mortality rate in many countries. A transient or permanent reduction of cerebral blood flow often initiates brain ischemia and usually leads to neuronal cell death in the central ischemic core and penumbra. The clinical management of brain ischemia is difficult and often ineffective because the only method of rescuing ischemic brain tissue involves the restoration of blood flow (Wang et al., 2009b). To develop effective treatments for cerebral ischemia, researchers have focused on testing neuroprotective drugs, and these experiments have proven important for current and future studies (Stroke Therapy Academic Industry Roundtable [STAIR], 1999). Currently, several promising alternative candidate neuroprotective strategies have been investigated, including resveratrol treatment, ischemic preconditioning (IPC), caloric restriction (CR), and the use of chemical and biological compounds that target the critical molecular mediators of neuronal death and survival. These strategies exert their neuroprotection through silent information regulator 1 (SIRT1)-related pathways (Wang et al., 2009b; Zhang et al., 2011).

The neuroprotective effect of SIRT1 was first reported by Raval et al. (2006). Using an in vitro model of cerebral ischemia (the organotypic hippocampal slice culture), they reported that resveratrol pretreatment mimics IPC via the SIRT1 pathway. Morris and colleagues also showed that increased SIRT1 activity is a common mechanism for the protective effects of IPC and resveratrol against ischemia (Morris et al., 2011). The neuroprotective role of SIRT1 is further supported by Della-Morte et al. (2009), who showed that SIRT1 activation reduces ischemic neuronal injuries. All of these studies suggest that SIRT1 might serve as a new target in the treatment of cerebral ischemia.

The focus of this review is to summarize the latest progress regarding the protective effects of SIRT1 in cerebral ischemia. First, the posttranslational modifications of SIRT1 are outlined. Next, we

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discuss the roles of SIRT1 in cerebral immune homeostasis. Then, we introduce the deacetylase activity of SIRT1 in cerebral ischemia and provide some examples of relevant studies. In addition, we discuss several activated mediators of SIRT1, such as resveratrol, CR, IPC, and other proteins and compounds. Finally, we highlight a few SIRT1-related signaling pathways, such as the peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α), nuclear transcription factor κB (NF-κB), uncoupling protein 2 (UCP2), and forkhead box O (FOXO) pathways. Taken together, the information compiled in this report will serve as a comprehensive reference for the actions of SIRT1 in the nervous system and will hopefully help in the design of future experimental research and promote SIRT1 as a therapeutic target.

2. SIRT1 posttranslational modifications

As observed in other enzymes, SIRT1 enzymatic activity is also altered by posttranslational modifications (Chung et al., 2010; Tang, 2009). The most common posttranslational modifications for SIRT1 are sumoylation and phosphorylation.

2.1. Sumoylation

The small ubiquitin-like modifiers (SUMO) are a group of proteins that are covalently attached to lysine residues of targeted proteins via the sumoylation process. Distinct from the degradation function of ubiquitination, sumoylation exerts a regulatory function on its target proteins, and those regulations include subcellular translocation and altered enzymatic activity (Verger et al., 2003; Zschoernig and Mahlknecht, 2008). SIRT1 is 1 target of sumoylation (Yang et al., 2007b). Sumoylation of Lys734 significantly increases the enzymatic activity of SIRT1, and the abrogation of sumoylation by site-directed mutagenesis impairs the deacetylase activity of SIRT1 on p53 and histones. The desumoylation of SIRT1 occurs after genotoxic stresses, thereby leading to increased cell death (Yang et al., 2007b; Zschoernig and Mahlknecht, 2008). These results suggest that the sumoylation and desumoylation of SIRT1 can function as a molecular switch to regulate SIRT1 activity in response to cellular stresses.

2.2. Phosphorylation

Reversible phosphorylation of proteins is the most common posttranslational modification that functions as a "molecular switch" in the concerted control of biological systems. There are at least 13 candidate sites for phosphorylation in SIRT1 (Sasaki et al., 2008), including Ser27 and Ser47 in its N-terminus (Beausoleil et al., 2004, 2006). Indeed, it was reported that the c-Jun N-terminal kinase (JNK) 1 phosphorylates these 2 serine residues in addition to Thr530 of SIRT1 (Nasrin et al., 2009). The phosphorylation of SIRT1 occurs in conditions of oxidative stress and increases the nuclear translocation and enzymatic activity of SIRT1 specifically toward histone H3 but not p53 (Nasrin et al., 2009), suggesting that the phosphorylation of SIRT1 might play a role in a stress-protective pathway.

The cell cycle checkpoint kinases are a group of kinases that also phosphorylate SIRT1. Checkpoint kinase 1 catalyzes the phosphorylation of Thr530 and Thr540 of SIRT1, which increases SIRT1 activity; accordingly, the dephosphorylation of SIRT1 results in decreased enzymatic activity (Sasaki et al., 2008).

Another family of protein kinases, the dual specificity tyrosine phosphorylation-regulated kinases (DYRKs), has also been reported to phosphorylate SIRT1. DYRKs are important in the embryonic development of the brain and play a special role in the pathogenesis of Down syndrome (Guo et al., 2010; Tejedor and Hammerle, 2011). One of their roles is regulation of apoptosis. Among its 7 members, DYRK1A and DYRK3 inhibit apoptosis in various cell types, whereas DYRK2 induces apoptosis by activating p53 (Guo et al., 2010; Taira et al., 2007). Two of the DYRK members, namely the prosurvival DYRK1a and DYRK3, directly phosphorylate SIRT1 at its Thr522 and activate it, leading to increased p53 deacetylation (Guo et al., 2010). The most recently identified kinase that increases SIRT1 activity is casein kinase II (CK2), which is a eukaryotic protein kinase with more than 100 known substrates. CK2 is recruited to SIRT1 after cellular stresses and phosphorylates multiple conserved serine and threonine residues of SIRT1, including Ser154, 649, 651, and 683 (Kang et al., 2009), and Ser659 and Ser661 (Zschoernig and Mahlknecht, 2009). The phosphorylation of SIRT1 by CK2 increases its substrate-binding affinity and deacetylation rate, especially with regard to p53 (Kang et al., 2009; Sasaki et al., 2008; Zschoernig and Mahlknecht, 2009).

Phosphorylation does not only amplify the activity of SIRT1. Mammalian sterile 20-like kinase 1 (MST1) is a serine/threonine kinase, and its overexpression induces apoptosis via the activation of p53 (Lin et al., 2002; Yuan et al., 2011). A recent study showed that SIRT1 is phosphorylated by MST1 at its C-terminus (at 489–747) after DNA damage, leading to reduced activity of SIRT1 and increased acetylation of p53, ultimately causing cell death (Yuan et al., 2011). Taken together, these results show that SIRT1 is phosphorylated at multiple sites by several protein kinases, which together with sumoylation, play important roles in the functional regulation of SIRT1.

3. The roles of SIRT1 in cerebral immune homeostasis

Recent studies indicate that SIRT1 is a critical regulator of the immune response, and its altered functions are likely involved in some immune diseases in the brain and other organs (Kong et al., 2012). Here, we provide a brief report focusing on the functions of SIRT1 in the immune system.

Studies reveal that SIRT1 exerts effects on the immune system by regulating the activity of T cells. Kwon et al. (2008) reported that blocking SIRT1 induces T cell hyperactivation, suggesting that SIRT1 acts as a negative regulator of T cell activation. Zhang et al. (2009) also found that the loss of SIRT1 functionality resulted in abnormally increased T cell activation and a breakdown of CD4+ T cell tolerance and that conversely, the upregulation of SIRT1 expression led to T cell anergy. Lee et al. (2011, 2012) found that SIRT1 plays a pivotal role in the host immune defense system in human dental pulp cells and periodontal ligament cells. Additionally, Singh et al. (2010) reported that resveratrol might protect against colitis via the upregulation of SIRT1 in immune cells.

Most importantly, researchers found that SIRT1 might provide neuroprotection by regulating the immune system. The rising epidemic of obesity is associated with cognitive decline and is considered to be 1 of the major risk factors for neurodegenerative diseases. Neuroinflammation is a critical component in the progression of several neurological and neurodegenerative diseases. Increased metabolic flux to the brain in response to overnutrition and obesity can induce stress responses, blood–brain barrier disruption, recruitment of inflammatory immune cells from peripheral blood, and microglial cell activation, thus leading to neuroinflammation. Nerurkar et al. (2011) reported that high-fat, diet-induced brain inflammation and oxidative stress were significantly reduced by bitter melon supplementation with a concomitant reduction in FOXO and normalization of SIRT1 protein expression. Nimmagadda et al. (2013) reported that the treatment of experimental autoimmune encephalomyelitis (EAE) with resveratrol, an activator of SIRT1, reduces the disease severity. This finding suggests that activators of SIRT1 might have immune-

modulating or neuroprotective therapeutic effects in EAE. The authors also examined the potential neuroprotective and immunomodulatory effects of SIRT1 overexpression in chronic EAE induced by immunizing C57BL/6 mice with myelin oligodendrocyte glycoprotein peptide 35–55. The results of this study suggested that SIRT1 reduces neuronal loss in this chronic demyelinating disease model and that this effect is associated with a reduction in inflammation. Additionally, Matarese et al. (2013) found that SIRT1 might be involved in the functions of the hypothalamus by regulating T cell activation. All of these observations reveal a previously unsuspected role of SIRT1 in the regulation of the cerebral immune response.

4. Deacetylase activity of SIRT1 in cerebral ischemia

SIRT1 is a member of the class III group of histone deacetylases. The deacetylase activity of SIRT1 is dependent on the nicotinamide adenine dinucleotide (NAD)-to-β-nicotinamide adenine dinucleotide reduced disodium salt hydrate (NADH) ratio of the cell. In cerebral ischemia, the deacetylase activity of SIRT1 plays a key role in neuroprotection. For example, hypoxia-inducible factors (HIFs) are a family of transcription factors that also function as oxygen sensors. When activated, HIFs upregulate proteins involved in oxygen transport, angiogenesis, cell survival, and glycolysis. Notable proteins in these categories include the neuroprotective proteins, erythropoietin (Sakanaka et al., 1998; Zhang et al., 2006, 2010) and vascular endothelial growth factor (Wang et al., 2007b; Wick et al., 2002). Thus, the HIFs play protective roles against hypoxia and ischemia (Correia and Moreira, 2010). SIRT1 was first linked with HIF activity in hepatoma cells, in which HIF2 was acetylated at its C-terminus during hypoxia, leading to the decreased transcriptional activity of HIF2 (Dioum et al., 2009). SIRT1 activation reverses the acetylation of HIF2, increases HIF2 transcription, and increases erythropoietin production (Dioum et al., 2009), which exerts important neuroprotective effects. Moreover, SIRT1 also affects the liver X receptors (LXRs), a group of nuclear receptors with oxysterols as ligands. LXRs are expressed in the brain and demonstrate a protective role against cerebral ischemia, traumatic brain injury, and amyloid toxicity (Cheng et al., 2010; Fitz et al., 2010). LXRs are acetylated at Lys432, blunting its response to agonists in the liver (Li et al., 2007). SIRT1 deacetylates LXRs. In SIRT1 knockout animals, LXR acetylation increases, but the expression of LXR target genes decreases (Li et al., 2007), suggesting that SIRT1 might protect the brain by enhancing LXR activity.

Meanwhile, SIRT1 is involved in the repair of some brain-related DNA damage. This type of repair requires several enzymes, including poly [adenosine diphosphate (ADP)-ribose] polymerase 1 (PARP-1) and Ku70. PARP-1 binds to DNA breaks and transfers ADP-ribose units from the metabolism of NAD+ to its substrates, a process known as ADP-ribosylation. When overactivated, however, PARP-1 is fatal to host cells because of the severe depletion of NAD+ and the consequent release and translocation of apoptosis-inducing factor from the mitochondria to the nucleus (Moroni, 2008). In neurons, PARP-1 is highly activated because of cerebral ischemia and in Parkinson's disease, thus contributing to neuronal apoptosis. Additionally, the inhibition of PARP-1 protects the brain from neuronal death (Moroni, 2008; Outeiro et al., 2007; Zhang et al., 2005). In cardiomyocytes, PARP-1 is acetylated after physical stress; this acetylation is an indicator of increased enzyme activity and is further enhanced in SIRT1 knockout mice (Rajamohan et al., 2009). SIRT1 directly binds and deacetylates PARP-1 in a SIRT1 catalytic site-dependent manner, which consequently reduces the enzyme activity of PARP-1 and ultimately promotes cell survival (Kolthur-Seetharam et al., 2006; Rajamohan et al., 2009). Ku70 is a 70-kDa nuclear protein that helps repair double-strand DNA breaks by binding to the broken ends. Ku70 also has a distinct anti-apoptotic role, binding to Bax and inhibiting its mitochondrial translocation (Sawada et al., 2003). After cerebral ischemia in mice, the levels of Ku70 in the ischemic region decrease as early as 4 hours and remain low thereafter. This decrease is accompanied by DNA fragmentation and neuronal death (Kim et al., 2001). However, IPC upregulates the expression of Ku70 in the CA1 region of the rat hippocampus, indicating that Ku70 plays a protective role against stroke (Sugawara et al., 2001). SIRT1 deacetylates Ku70 at Lys539 and Lys543 of its C-terminus (Cohen et al., 2004) and increases the DNA repair activity of Ku70 after cellular exposure to radiation (Jeong et al., 2007). These results suggest the possibility that the deacetylase activity of SIRT1 might play a role in protecting the brain against ischemic injury.

5. Resveratrol-mediated activation of SIRT1 in cerebral ischemia

Resveratrol, a polyphenol found in red wine, is considered to be a potential drug in the treatment of cardiovascular disease, diabetes, cancer, and neurological diseases, including ischemic brain disease. When administered before or after ischemia in rodent models, resveratrol reduces the size of brain lesions. The neuroprotective mechanisms of resveratrol might include antioxidation, anti-inflammation, and antiapoptosis. Considering these diverse actions, it is likely that multiple signaling pathways are involved in the neuroprotection mediated by resveratrol. Resveratrol is known as the most efficacious SIRT1 activator, and SIRT1 activity is necessary for resveratrol-mediated neuroprotection in models of neurological disorders (Shin et al., 2012). By upregulating the activity of SIRT1, resveratrol exerts neuroprotective effects. Raval et al. (2006) found that resveratrol mimics IPC in the brain. IPC can increase the resistance of cells to ischemia and can reduce necrosis and apoptosis in cerebral ischemia. Those authors indicated that resveratrol and IPC mediated neuroprotection via SIRT1 enzyme activation. However, the time course for the activation of SIRT1 was different between the 2 paradigms. As expected, resveratrol rapidly and transiently increased SIRT1 activity, whereas the IPC-induced increase in SIRT1 activity was only observed 48 hours after IPC exposure. SIRT1 activity increased rapidly in response to resveratrol stimulation (Raval et al., 2006), thus activating PGC1α expression (Nemoto et al., 2005). Resveratrol also increased the phosphorylation of Akt and p38 but inhibited the increase in phosphorylation of extracellular signal-regulated kinase 1/2. Additionally, the messenger RNA (mRNA) levels of 1 of PGC1α's target genes, antioxidative superoxide dismutase 2, were elevated. These changes resulted in an antioxidative effect on ischemic injury (Shin et al., 2012). In addition, resveratrol plays a role in the SIRT1-UCP2 pathway. Della-Morte et al. (2009) reported that resveratrol significantly decreased UCP2 levels by 35% compared with sham-treated rats. The SIRT1-specific inhibitor sirtinol abolished the neuroprotection mediated by the resveratrol preconditioning and the decrease in UCP2 levels. The authors also observed that resveratrol preconditioning significantly increased the ratio of moles of ADP phosphorylated per moles of oxygen consumed in hippocampal mitochondria, reflecting enhanced adenosine triphosphate (ATP) synthesis efficiency. Their findings indicate that resveratrol induces tolerance to brain injury.

Furthermore, resveratrol provides neuronal protection to brain cells in Alzheimer's disease (AD). Resveratrol-induced SIRT1 has been found to deacetylate and repress the p53 activity of neurons, prevent the apoptotic death of these neurons, suppress the apoptotic activities of FOXO proteins, and promote neuronal survival. In a recent study with mixed neuron/glia cultures from a Sprague-Dawley rat, resveratrol-induced SIRT1 inhibited NF-κB signaling in microglia and astrocytes and protected AD neurons

against amyloid beta (Aβ)-induced toxicity (Chen et al., 2006). According to that study, a nonfibrillar form of Aβ first binds to an unknown cell surface receptor that stimulates NF-κB signaling in microglia and astrocytes. In turn, this NF-κB signaling controls the expression of induced nitric oxide synthase (iNOS) and cathespin B, which are 2 toxic factors that mediate apoptosis and that lead to neurodegeneration. These studies suggest that the resveratrol-induced SIRT1 pathway mediates significant neuroprotection.

Although SIRT1 has been shown to be crucial for resveratrol-mediated protection during ischemia (Chen et al., 2009; Raval et al., 2006), the role of SIRT1 in many resveratrol pathways has not been identified. For example, the resveratrol activation of adenine mononucleotide-activated protein kinase (AMPK) and the stimulation of neurite outgrowth in neuronal cultures were not altered by the inhibition of SIRT1 (Dasgupta and Milbrandt, 2007). Therefore, resveratrol might activate the SIRT1-dependent pathways that provide protection against ischemic injury.

6. CR-mediated activation of SIRT1 in cerebral ischemia

CR has been associated with increased lifespan in many animal models. The idea that restricting diet can increase longevity is not new. In fact, "longevity" mechanisms and genes have been studied in detail for many decades. Changes in genetic and transcriptional regulation during CR affect processes that are intimately involved in the aging process, such as energy metabolism, stress signaling pathways, and reactive oxygen species (ROS) production (Anderson and Weindruch, 2010). Of recent significant interest is SIRT1, an NAD+-dependent deacetylase that modulates longevity in response to CR.

In the liver extracts of CR mice, Rodgers et al. (2005) found that the absence of NAD+ decreased CR-associated SIRT1 deacetylase activity, which further suggests that increases in NAD+ availability induced by CR-mediated changes in redox potential might be a major factor in stimulating SIRT1 activity. SIRT1 depleted NAD+ and activated FOXO transcription factors, thereby inducing the genes that code for antioxidant enzymes. During CR, an increase in the NAD+ ratio could upregulate SIRT1 expression to protect brain cells against ischemic injury. Moreover, it was found that nicotinamide phosphoribosyltransferase (NAMPT) is upregulated by CR (Yang et al., 2007a) and is also a mediator of longevity and activator of SIRT1 (Van der Veer et al., 2007). The AMPK activation by CR (Greer et al., 2007; Palacios et al., 2009) has been shown to stimulate SIRT1 through NAMPT regulation (Fulco et al., 2008). This finding suggests that NAMPT might also be important in CR-mediated longevity.

In contrast to the view that SIRT1 increases lifespan, Herranz et al. (2010) found that although increased expression of the related SIRT1 protein in mice suppresses metabolic dysfunction and the development of certain types of cancer, it did not increase overall lifespan. However, it has been demonstrated that the indirect activation of SIRT1 by resveratrol protects against metabolic and age-related diseases (Lagouge et al., 2006), curbing the reduction in lifespan induced by high-calorie diets (Baur et al., 2006), even though it has no effect on lifespan in mice fed regular chow (Pearson et al., 2008). Conversely, outbred mice lacking SIRT1 show deficiencies in metabolism and cannot respond properly to the lifespan-increasing effects of calorie restriction (Herranz and Serrano, 2010). These findings highlight how the metabolic adaptations that SIRT1 induces might indirectly influence mammalian lifespan. However, further research is needed to clarify this controversial point.

7. IPC-mediated activation of SIRT1 in cerebral ischemia

IPC is an innate protective mechanism, whereby a sublethal ischemic insult protects against a subsequent potentially lethal ischemic attack. IPC has been shown to significantly improve survival and functional recovery after severe ischemic episodes in the heart and the brain by activating signaling pathways that maintain mitochondrial function, suppress ROS production, and reduce infarct size (Dave et al., 2008; Saurin et al., 2002). The specific mechanism that leads to ischemic tolerance by IPC is complex; however, researchers have identified several mediators of IPC-mediated protection.

Centeno et al. (1999) discovered that there was an increase in NAD+/nicotinamide adenine dinucleotide levels in hippocampal slices after preconditioning, similar to that observed for CR. Therefore, it was proposed that IPC could potentially activate SIRT1, leading to neuroprotective pathways similar to those previously shown for CR (Morris et al., 2011). Exposing organotypic hippocampal slices to IPC increased SIRT1 enzymatic activity (Raval et al., 2006). Furthermore, SIRT1 activation was found to be neuroprotective against oxygen-glucose deprivation (OGD)-induced cell death because blocking SIRT1 with sirtinol abrogated IPC-induced neuroprotection (Raval et al., 2006). Similarly, IPC increased the hippocampal SIRT1 enzymatic activity and neuroprotection after the global ischemia induced by cardiac arrest (Della-Morte et al., 2009). Other studies have also shown an important role for SIRT1 in IPC-mediated cardioprotection. Hypoxic preconditioning in cardiac myocytes upregulated SIRT1 expression, which was associated with the induction of hypoxic preconditioning protection (Rane et al., 2009). Pharmacological inhibition of SIRT1, or the suppression of the SIRT1 activator NAMPT, abolished the IPC-mediated protein deacetylation and cardioprotection after prolonged coronary artery occlusion (Nadtochiy et al., 2011). Xu et al. (2012) found that the levels of SIRT1 protein, the putative target of miR-199a and a known mediator of the neuroprotective effect in brain ischemic tolerance, decreased significantly in hippocampal neurons via the overexpression of miR-199a. In contrast, SIRT1 protein levels increased with the knockdown of miR-199a. Based on these results, the authors hypothesized that miR-199a might play a role in the formation of cerebral ischemic tolerance.

Although these studies in the heart and brain show an important role for SIRT1 in IPC-mediated protection, the specific SIRT1 pathways activated during IPC have not yet been identified.

8. Effects of several proteins and compounds on the expression of SIRT1

In this section, we describe several proteins and compounds that can affect the expression of SIRT1 in cerebral ischemia.

8.1. Nicotinamide

SIRT1 is a type of NAD+-dependent enzyme. SIRT1 enzyme activity requires a sufficient amount of NAD+. Therefore, it is possible that the activation of SIRT1 causes energy depletion, exposing the neural cells to the excitotoxic and ischemic injury. Liu et al. (2009) found that nicotinamide, an NAD+ precursor and an inhibitor of SIRT1 and PARP-1, inhibited SIRT1 deacetylase activity without affecting SIRT1 protein levels. Treating neurons with the SIRT1 activator resveratrol did not protect the neurons from glutamate/N-methyl-D-aspartic acid-induced NAD+ depletion and cell death. Administering nicotinamide (200 mg/kg, intraperitoneally) up to 1 hour after the onset of ischemia elevated brain NAD+ levels and reduced the ischemic infarct size. Their findings demonstrate that the NAD+ bioenergetic state is critical for determining whether neurons live or die in excitotoxic and ischemic conditions and suggest a potential therapeutic benefit in stroke patients that is mediated by the agents that preserve cellular NAD+ levels. Their data further suggest that SIRT1 is linked to the bioenergetic state and stress responses in neurons and that under conditions of

reduced cellular energy levels, SIRT1 enzyme activity might consume sufficient NAD+ to nullify any cell survival-promoting effects of its deacetylase action on protein substrates. This result suggests that nicotinamide might protect neurons by preserving cellular NAD+ levels.

8.2. Icariin

Icariin, a flavonoid extracted from the traditional Chinese herb *Epimedium brevicornum Maxim*, has demonstrated a wide range of pharmacological and biological activities, including estrogenic activity, antitumor activity, an antioxidant effect, immunoregulation, and improved sexual functioning (Liang et al., 1997; Makarova et al., 2007; Wang et al., 2007a; Ye and Lou, 2005). Recent studies suggest that icariin protects against OGD-mediated injury in primary cultured neurons, contributes to the antiapoptotic effect, reduces oxidative stress, and induces the differentiation of stem cells into neuronal cells (Li et al., 2005). Icariin protects neural cells against ischemic injury. Wang et al. (2009a) found that icariin facilitates neuronal viability after OGD by increasing the expression of SIRT1 and that SIRT1 inhibitor III partially blocks the effect of icariin. Further research indicated that the neuroprotection mediated by icariin must be induced by SIRT1. Icariin regulates SIRT1 expression via the mitogen-activated protein kinase/P38 pathway. Through this pathway, SIRT1 is increased, and SIRT1 protects brain cells by inhibiting p53 and other factors. Zhu et al. (2010) also found that icariin prevents ischemic injury by mediating the SIRT1-PGC1α pathway. Their findings suggest that icariin might serve as a novel drug in the prevention of stroke-related brain damage.

8.3. Nicotinamidase

In 2008, Chong and Maiese (2008) investigated the role of drosophila nicotinamidase in mammalian SH-SY5Y neuronal cells during oxidative stress. Their findings highlight 3 important points, that demonstrate that there is a relationship between SIRT1 and nicotinamidase. First, the application of resveratrol increased cell survival during oxidative stress either alone or in conjunction with the expression of nicotinamidase to a similar degree, suggesting that nicotinamidase might rely on SIRT1 activation for its neuronal protective effects. Second, the overexpression of either SIRT1 or nicotinamidase in neurons prevented apoptotic injury, specifically in neurons expressing these proteins during oxidative stress. This result supports the hypothesis that nicotinamidase and SIRT1 might mediate neuronal protection via similar pathways. Third, the inhibition of sirtuin activity with sirtinol was detrimental to neuronal survival during oxidative stress and prevented neuronal protection during the overexpression of nicotinamidase or SIRT1, further supporting the idea that SIRT1 activity might be necessary for nicotinamidase neuroprotection during oxidative stress. Further work to elucidate the cellular mechanisms that govern nicotinamidase activity in mammalian cells might reveal novel avenues for the treatment of disorders related to oxidative stress and cellular metabolic dysfunction.

8.4. 2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside

2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside (TSG), an active component of the rhizome extract from *Polygonum multiflorum*, exhibits antioxidative and anti-inflammatory effects. Wang et al. (2009b) used an in vitro ischemic model of OGD followed by reperfusion (OGD-R) and an in vivo ischemic model of middle cerebral artery occlusion (MCAO) to investigate the neuroprotective effects of TSG on ischemia/reperfusion brain injury. The authors demonstrated that OGD-R-induced neuronal injury, intracellular ROS generation, and mitochondrial membrane potential dissipation were reversed by TSG. The elevation of hydrogen peroxide (H_2O_2)-induced free calcium ion concentration was also attenuated by TSG. The inhibition of the JNK and B-cell lymphoma gene 2 family-related apoptotic signaling pathways was involved in the neuroprotection mediated by TSG. In addition, TSG inhibited the iNOS mRNA expression induced by OGD-R, which might be mediated by the activation of SIRT1 and the inhibition of NF-κB activation. In vivo studies further demonstrated that TSG significantly reduced the brain infarct volume and the number of terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cells in the cerebral cortex compared with the MCAO group. Their results showed that the inhibitory effect of TSG on iNOS mRNA expression and NF-κB activation induced by the OGD-R insult was partially reversed by treatment with nicotinamide, an inhibitor of SIRT1. Furthermore, the authors also found that the SIRT1 protein levels were elevated after normal cells were incubated for 3 days with TSG. These results might highlight the mechanism of the inhibitory effects of TSG on iNOS gene expression. Their findings indicate that TSG is a potential protective agent against ischemic injury and that the SIRT1 activation of TSG is similar to that of resveratrol.

8.5. NAMPT

NAMPT, also known as visfatin, the rate-limiting enzyme in mammalian NAD+ biosynthesis, protects against ischemic stroke by inhibiting neuronal apoptosis and necrosis. SIRT1 is involved in the neuroprotection of NAD+. Ying et al. (2007) observed that the intranasal infusion of NAD+ decreased the infarct volume in rats after focal cerebral ischemia. NAMPT, the rate-limiting enzyme of the NAD+ salvage pathway, also demonstrates a protective effect against stroke. NAMPT overexpression reduces ischemic infarct volume, whereas NAMPT inhibition worsens ischemic injuries. The protective effect of NAMPT has been deemed to be SIRT1-dependent because knocking out SIRT1 blocks the protection.

NAMPT also plays a role in autophagy. Wang et al. (2011a, 2011b) determined the involvement of autophagy in the NAMPT-mediated neuroprotection in cerebral ischemia. In their study, MCAO in rats and OGD in cultured cortical neurons were performed. NAMPT was overexpressed or knocked down using lentivirus-mediated gene transfer in vivo and in vitro. Immunochemistry (LC3-II), electron microscopy, and immunoblotting assays (LC3-II, beclin-1, mammalian target of rapamycin [mTOR], ribosomal S6 kinase 1 [S6K1], and tuberous sclerosis complex-2 [TSC2]) were performed to assess the autophagy. The authors found that the overexpression of NAMPT increased the autophagy (LC3 puncta immunochemistry staining, LC3-II/beclin-1 expression and autophagosome number), both in vivo and in vitro, 2 hours after MCAO. At the early stage of OGD, the autophagy inducer, rapamycin, protected against the neuronal injury induced by the NAMPT knockdown, whereas the autophagy inhibitor, 3-methyladenine, partly abolished the neuroprotective effect of NAMPT. The overexpression or knockdown of NAMPT regulated the phosphorylation of the mTOR and S6K1 signaling pathway on OGD by enhancing the phosphorylation of TSC2 at Ser1387 but not at Thr1462. Furthermore, in cultured SIRT1-knockout neurons, the regulation of NAMPT on the autophagic proteins LC3-II and beclin-1 was abolished. Their results demonstrate that NAMPT promotes neuronal survival by inducing autophagy via the regulation of the TSC2-mTOR-S6K1 signaling pathway in an SIRT1-dependent manner during cerebral ischemia. In another study, Wang et al. (2012) found that NAMPT inhibition by a highly specific NAMPT inhibitor, FK866, worsened brain infarction in rats with experimentally induced cerebral ischemia, whereas local overexpression of NAMPT and an NAMPT enzymatic product, nicotinamide mononucleotide, in the brain reduced ischemia-

induced cerebral injuries. In neurons, NAMPT positively modulated NAD+ levels and thereby controlled SIRT1 activity. The NAMPT-induced neuroprotection disappeared in SIRT1-knockout neurons. Their findings reveal that NAMPT protects against ischemic stroke by rescuing neurons from death via the SIRT1-dependent pathway, indicating that NAMPT is a new therapeutic target for stroke.

9. SIRT1 and signaling pathways

In this section, we highlight several SIRT1-related signaling pathways and discuss their mechanisms in cerebral ischemia.

9.1. PGC1α

PGC1α, a master regulator of antioxidative enzymes and mitochondrial biogenesis (St-Pierre et al., 2006), has been identified as a target protein of SIRT1 in models of global ischemia, amyotrophic lateral sclerosis, and Parkinson's disease (Mudo et al., 2012; Wang et al., 2011a, 2011b). Mitochondrial antioxidant enzymes are induced by PGC1α in neurons exposed to oxidative stress, indicating that increasing PGC1α expression protects neurons from oxidative insult (St-Pierre et al., 2006). A study using a focal ischemic stroke model showed that increased SIRT1-dependent PGC1α expression played a crucial role in the neuroprotection induced by the flavonoid icariin (Zhu et al., 2010). The authors found that the enhancement of PGC1α was consistent with that of SIRT1 after stroke in vivo and in vitro, indicating that there was a strong correlation between SIRT1 and PGC1α. Additionally, SIRT1 and PGC1α interact with each other functionally and physically to form a stable complex if the activity and acetylation status of PGC1α are regulated. The overexpression of SIRT1 deacetylase activated the transcriptional activity of PGC1α in neuron metabolism and mitochondrial activity (Canto and Auwerx, 2009; Nemoto et al., 2005; Wareski et al., 2009). Because SIRT1 activates PGC1α directly through deacetylation and increased rates of transcription (Canto and Auwerx, 2009; Rodgers et al., 2008), SIRT1 inhibitor III was used to verify that the enhancement of PGC1α by icariin was SIRT1-dependent. As a result, the expression of PGC1α was suppressed by SIRT1 inhibitor III in the OGD neurons in the presence of icariin. Moreover, the icariin neuroprotection after OGD was inhibited by SIRT1 inhibitor III or PGC1α small interfering RNA. This finding suggested that the PGC1α activity was at least partially regulated by SIRT1. The expression of SIRT1 was upregulated by icariin via the mitogen-activated protein kinase/P38 pathway (Wang et al., 2009a). SIRT1 directly interacts with PGC1α in the 200–400 region and deacetylates PGC1α at more than 12 lysine residues in different domains of the protein to form a transcriptional complex that controls the expression of the metabolic gene (Rodgers et al., 2008). In this way, more energy is produced to supply the ischemia-injured brain. Therefore, it is possible that SIRT1-PGC1α signaling contributes to the resveratrol-mediated antioxidative effects in an ischemic brain.

9.2. NF-κB

NF-κB is the major transcription factor that transcribes proinflammatory mediators in the nervous system, which are known as crucial regulators of cell proliferation, differentiation, apoptosis, oncogenesis, and memory functions (Kucharczak et al., 2003; Meffert and Baltimore, 2005); its activation exacerbates neuronal damage after neurological insults, especially ischemic stroke (Pizzi et al., 2009; Teng and Tang, 2010; Zheng and Yenari, 2004). SIRT1 deacetylates the p65 subunit of NF-κB at Lys310 and reduces its transcriptional activity, protecting cells from apoptosis (Yeung et al., 2004). Chen et al. (2001) also found that NF-κB activation is also modulated by posttranslational modifications, including the reversible acetylation of the p65 subunit. The transcriptional activity of RelA/p65 requires the acetylation of Lys310, which can be deacetylated by SIRT1. The activation of SIRT1 by resveratrol is associated with the inhibition of NF-κB signaling by promoting the deacetylation of Lys310 of RelA/p65 (Howitz et al., 2003). In a recent study using mixed neuron/glia cultures derived from Sprague-Dawley rats, resveratrol-induced SIRT1 inhibited NF-κB signaling in microglia and astrocytes and protected AD neurons against Aβ-induced toxicity (Chen et al., 2006). According to this study, a nonfibrillar form of Aβ first binds to an unknown cell surface receptor that stimulates NF-κB signaling in microglia and astrocytes. This NF-κB signaling then controls the expression of both iNOS and cathespin B, 2 toxic factors that mediate apoptosis and lead to neurodegeneration. In addition, the inhibition of NF-κB by SIRT1 also contributes to the neuroprotection afforded by ginkgo extract or glucosides against AD and ischemia (Longpre et al., 2006; Wang et al., 2009b). These results indicate that the SIRT1–NF-κB pathway contributes to the neuroprotection against ischemic injury.

9.3. UCP2

Previous studies in pancreatic β-cells have established that SIRT1 activity modulates the levels of mitochondrial UCP2 (Bordone et al., 2006). The decrease in UCP2 was blocked by sirtinol. Thus, the regulation of UCP2 levels by in vivo resveratrol pretreatment regulation requires SIRT1 activation. UCP2 is a member of a family of inner mitochondrial membrane proteins capable of driving the ATP synthase pathway via the regulation of the proton electrochemical gradient (Esteves and Brand, 2005). Della-Morte et al. (2009) found that resveratrol pretreatment induced a decrease in UCP2 levels in hippocampal mitochondria and a rapid increase in SIRT1 activity. This condition results in a significant increase in the moles of ADP phosphorylated per moles of oxygen consumed ratio. The neuroprotective role of UCP2 against cerebral ischemia is not clearly defined. Higher UCP2 levels after IPC were shown to play a role in neuroprotection after cardiac and cerebral ischemia (Mattiasson et al., 2003; McLeod et al., 2005). In contrast, De Bilbao et al. (2004) observed a reduction of ischemic brain damage in UCP2 knockout mice after focal cerebral ischemia. In addition, a recent study showed that the overexpression of UCP2 protected thalamic neurons against global cerebral ischemia. Other brain regions, such as the hippocampus, were not protected (Deierborg Olsson et al., 2008). Moreover, another study demonstrated that UCP2 overexpression results in increased cell death after hypoxia-reoxygenation in adult rat cardiomyocytes (Bodyak et al., 2007). UCP2 overexpression led to decreased ROS generation and promoted a shift in H_2O_2 release from an intramitochondrial to an extramitochondrial site (De Bilbao et al., 2004). Thus, UCP2 overexpression altered cellular redox signaling (Arsenijevic et al., 2000; Mattiasson et al., 2003). In contrast, the UCP2-depleted condition led to increased ROS production and an increase in the cellular ROS buffering capacity by increasing the reduced glutathione and mitochondrial manganese superoxide dismutase levels (De Bilbao et al., 2004). The common denominator in the UCP2-overexpressed and UCP2-depleted conditions is decreased ROS. These results suggest that in addition to increasing the ROS buffering capacity, UCP2-depleted conditions also increase the mitochondrial ATP production capacity. Thus, UCP2 might be a new target in cerebral ischemia treatments.

9.4. FOXO

The SIRT1-FOXO pathway plays a neuroprotective role in the AD brain. Resveratrol-induced SIRT1 has been found to deacetylate and

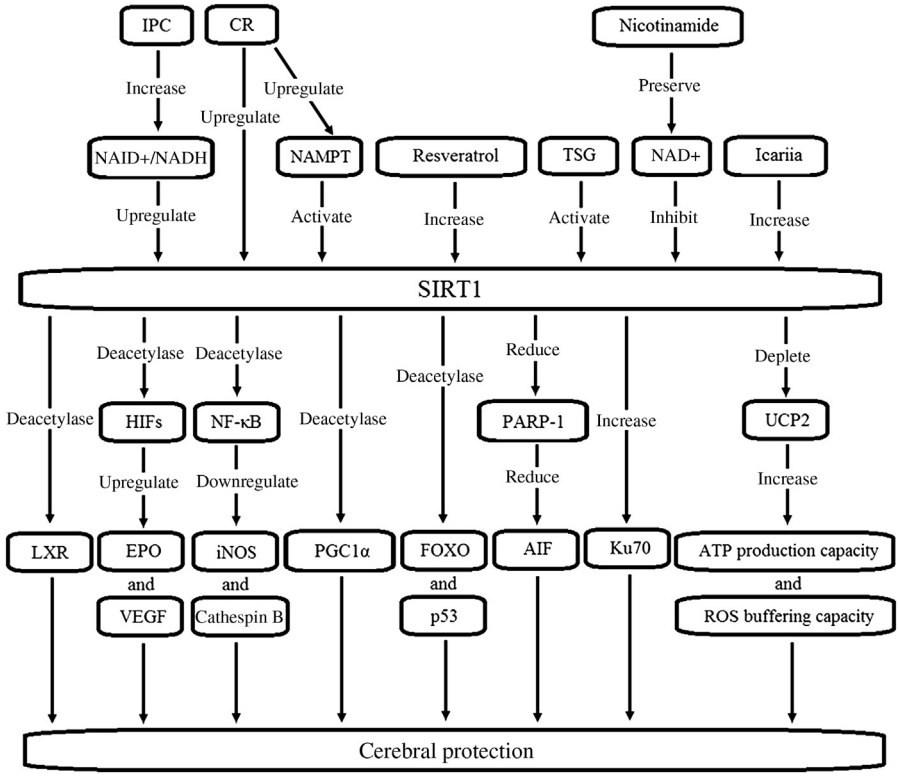

Fig. 1. Schematic diagram of pathways activated by SIRT1 activation. The regulation of gene expression by SIRT1 deacetyltransferase activity allows for the activation and inhibition of signaling pathways involved in numerous cellular functions. SIRT1 regulates gene expression via the deacetylation of histone proteins, thereby leading to a closed chromatin configuration, and by the deacetylation of transcription factors, thereby activating or repressing their activity. Abbreviations: ADP, adenosine diphosphate; AIF, apoptosis-inducing factor; ATP, adenosine triphosphate; CR, caloric restriction; EPO, erythropoietin; FOXO, forkhead box O; HIFs, hypoxia-inducible factors; iNOS, induced nitric oxide synthase; IPC, ischemic preconditioning; LXR, liver X receptor; NAD+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; NF-κB, nuclear transcription factor κB; PARP-1, poly (ADP-ribose) polymerase 1; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1α; ROS, reactive oxygen species; SIRT1, silent information regulator 1 TSG, 2, 3, 5, 4′-tetrahydroxystilbene-2-O-β-D-glucoside; UCP2, uncoupling protein 2; VEGF, vascular endothelial growth factor.

repress the p53 activity of neurons, prevent the apoptotic death of these neurons, suppress the apoptotic activities of FOXO proteins, and promote neuronal survival. FOXOs share functional similarities and participate considerably in cross-talk with p53 (You and Mak, 2005). In motor neurons, FOXO3a induces neuronal death through the Fas pathway, in cooperation with JNK (Barthelemy et al., 2004). FOXO proteins directly induce bim gene expression and cause apoptosis in sympathetic neurons (Gilley et al., 2003). These studies raise the possibility that FOXOs might contribute—either directly or in cooperation with p53—to neuronal death in AD. Because resveratrol is known to trigger SIRT1 overexpression, it seems likely that resveratrol can effectively suppress p53 and FOXOs and can confer neuronal protection in AD brains. This possibility suggests that we can protect neural cells in cerebral ischemia via the regulation of the SIRT1-FOXO pathway.

10. Conclusions

Currently, SIRT1 is a significant target for the investigation of cerebral ischemia treatment, and its multifarious regulators and signaling pathways provide many opportunities for further investigation. Increasing lines of evidence suggest that SIRT1 protects the brain from ischemic injury. SIRT1 appears to be a promising target for reducing the levels of ischemic injury. However, the biological functions of SIRT1 remain only partially characterized. The new frontiers of SIRT1 study will include its roles in autophagy (Kume et al., 2010; Madeo et al., 2010), neurogenesis (Ichi et al., 2011; Prozorovski et al., 2008), and angiogenesis (Lim et al., 2010; Zhao et al., 2010). There are several significant unknowns in its mechanism. For example, it is not known how SIRT1 specifically increases the transcription of beneficial genes while simultaneously suppressing universal transcription. It is known that when protein synthesis is inhibited globally, select chaperone proteins, such as heat shock proteins, are translated either via the use of internal ribosome entry sequences (Jackson, 2005) or by a shunting mechanism (Yueh and Schneider, 2000). It would be worthwhile to investigate whether similar mechanisms exist for genes upregulated by the SIRT1-mediated activation of transcription. Second, the paradoxical effects of SIRT1 on peroxisome proliferator-activated receptor γ (PPARγ) is controversial. For example, SIRT1 directly suppresses PPARγ transcriptional activity (Picard et al., 2004), but SIRT1 also activates PGC1α (Nemoto et al., 2005; Rodgers et al., 2005), which could increase the transcriptional activity of PPARγ (Puigserver et al., 1998). Third, the role of SIRT1 in many resveratrol pathways has not been identified. For example, resveratrol activation of AMPK and stimulation of neurite outgrowth in neuronal cultures were not altered by the inhibition of SIRT1 (Dasgupta and Milbrandt, 2007). Finally, although studies in the heart and brain show an important role for SIRT1 in IPC-mediated protection, the specific SIRT1 pathways activated during IPC have not been elucidated. Further investigations into the targets and functions of SIRT1 will help develop new strategies for protection against and recovery from common neurological diseases. A schematic diagram of pathways activated by SIRT1 activation is provided (Fig. 1).

Disclosure statement

The authors disclose no conflicts of interest.

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