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Review

New role of silent information regulator 1 in cerebral ischemia

Yang Yang [a,1], Weixun Duan [a,1], Yue Li [b,1], Juanjuan Yan [c], Wei Yi [a], Zhenxing Liang [a], Ning Wang [a], Dinghua Yi [a,*], Zhenxiao Jin [a,**]

[a] Department of Cardiovascular Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China
[b] Team 10, School of Stomatology, The Fourth Military Medical University, Xi'an, China
[c] Department of Prosthodontics, School of Stomatology, The Fourth Military Medical University, Xi'an, China

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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

* Corresponding author at: Department of Cardiovascular Surgery, Xijing Hospital, Fourth Military Medical University, 169 Changle West Road, Xi'an 710032, China. Tel.: +86 29 84775311; fax: +86 29 83210092.
** Alternate corresponding author at: Department of Cardiovascular Surgery, Xijing Hospital, Fourth Military Medical University, 169 Changle West Road, Xi'an 710032, China. Tel.: +86 29 84775311; fax: +86 29 83210092.
E-mail addresses: dinghuayi210@126.com (D. Yi), jinzx1026cn@yahoo.com.cn (Z. Jin).
[1] These authors contributed equally to this work.

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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-