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Protective effects and mechanisms of sirtuins in the nervous system

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ABSTRACT

Silent information regulator two proteins (sirtuins or SIRTs) are a group of histone deacetylases whose activities are dependent on and regulated by nicotinamide adenine dinucleotide (NAD^+). They suppress genome-wide transcription, yet upregulate a select set of proteins related to energy metabolism and pro-survival mechanisms, and therefore play a key role in the longevity effects elicited by calorie restriction. Recently, a neuroprotective effect of sirtuins has been reported for both acute and chronic neurological diseases. The focus of this review is to summarize the latest progress regarding the protective effects of sirtuins, with a focus on SIRT1. We first introduce the distribution of sirtuins in the brain and how their expression and activity are regulated. We then highlight their protective effects against common neurological disorders, such as cerebral ischemia, axonal injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Finally, we analyze the mechanisms underlying sirtuin-mediated neuroprotection, centering on their non-histone substrates such as DNA repair enzymes, protein kinases, transcription factors, and coactivators. Collectively, the information compiled here will serve as a comprehensive reference for the actions of sirtuins in the nervous system to date, and will hopefully help to design further experimental research and expand sirtuins as therapeutic targets in the future.

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Abbreviations: 4-HNE, 4-hydroxynonenal; Aβ, beta-amyloid; AD, Alzheimer's disease; ADPR, ADP-ribose; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; APE1, apurinic/apyrimidinic endonuclease-1; APP, amyloid precursor protein; AROS, active regulator of SIRT1; Bax, Bcl-2 associated X protein; BDNF, brain-derived neurotrophic factor; CREB, cAMP response binding protein; DBC1, deleted in breast cancer 1; CHK1, cycle checkpoint kinase 1; CK2, casein kinase II; DYRK, dual specificity tyrosine phosphorylation-regulated kinase; E2F1, E2F transcription factor 1; eNOS, endothelial nitric oxide synthase; FOXO, forkhead box protein O; HD, Huntington's disease; HIC1, hypermethylated in cancer 1; HuR, Hu family of RNA-binding proteins; IRES, internal ribosomal entry sequence; JNK1, c-jun N-terminal kinase 1; LXR, liver X receptor; miR, microRNA; MST1, mammalian sterile 20-like kinase 1; MRPL10, mitochondrial ribosomal protein L10; NAD^+, nicotinamide adenine dinucleotide; NADH, NAD^+ reduced; NDUFA9, NADH dehydrogenase 1 alpha subcomplex subunit 9; NAMPT, nicotinamide phosphoribosyltransferase; NBS1, Nijmegen breakage syndrome protein 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NMNAT-1, nicotinamide mononucleotide adenylyltransferase 1; NO, nitric oxide; Nrf2, nuclear factor (erythroid-derived 2)-like 2; OA-ADPR, 2′-O-acetyl-ADP ribose; PARP-1, poly(ADP-ribose)polymerase 1; PD, Parkinson's disease; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PPARs, peroxisome proliferator-activated receptors; PTEN, phosphatase and tensin homologue deleted in chromosome 10; RAR, retinoic acid receptor; ROS, reactive oxygen species; SdhA, succinate dehydrogenase subunit A; sir2, silent information regulator 2; SIRT, sirtuin; sirtuins, silent information regulator 2 proteins; SODs, superoxide dismutases; SUMO, small ubiquitin-like modifier; Wlds, Wallerian degeneration slow; XP, xeroderma pigmentosum.

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1. Introduction

1.1. Histone deacetylases

Proteins undergo many posttranslational modifications to alter their function. One such modification is that certain proteins are acetylated on their lysine residues, a reaction mediated by acetyltransferases (Mellert and McMahon, 2009). Removal of these acetyl groups is facilitated by another family of enzymes – deacetylases (Mellert and McMahon, 2009; Yang and Seto, 2007). The prototypical proteins that exemplify the effects of acetylation are histones, as acetylated histones are unbound to DNA and allow transcription, while deacetylated histones bind tightly to DNA and restrict transcription (for a more detailed description see Section 5.1).

There are four classes of deacetylases in mammals; among them, class III is unique because its members require nicotinamide adenine dinucleotide (NAD^+) for catalysis. Therefore, they are also known as the NAD^+-dependent class III histone deacetylases (Imai et al., 2000; Mellert and McMahon, 2009; Yang and Seto, 2007). More commonly, they are referred to as *s*ilent *i*nformation *r*egulator *t*wo prote*ins* (*sir*tuins or SIRTs), named after their yeast homologue, silent information regulator 2 (sir2) (Afshar and Murnane, 1999). To date, seven sirtuins have been identified, and they are known as sirtuin 1 (SIRT1) through SIRT 7 (Fig. 1) (Michan and Sinclair, 2007). Structurally, they share significant sequence homology, and they all contain a conserved catalytic domain and a NAD^+-binding domain (Finnin et al., 2001; Sherman et al., 1999; Yamamoto et al., 2007).

1.2. SIRT1 mediates longevity under calorie restriction

SIRT1 is the best-characterized sirtuin among the seven. It contains 747 amino acids in human, with a predicted molecular weight of 81 kDa and a measured one of 120 kDa. In addition to histones, SIRT1 also deacetylates a number of non-histone substrates, such as p53 (Luo et al., 2001) and peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) (Nemoto et al., 2005). SIRT1 is drawing even more attention since it is considered to be one of the determining factors in lifespan elongation induced by calorie restriction, a phenomenon observed in phylogenetically diverse organisms including yeast,