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SIRT2-mediated protein deacetylation: An emerging key regulator in brain physiology and pathology

Kai Harting, Bernd Knöll*

Neuronal Gene Expression Laboratory, Department of Molecular Biology, Interfaculty Institute for Cell Biology, Eberhard-Karls-University Tübingen, Auf der Morgenstelle 15, 72076 Tübingen, Germany

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ABSTRACT

Protein function is considerably altered by posttranslational modification. In recent years, cycles of acetylation/deacetylation emerged as fundamental regulators adjusting biological activity of many proteins. Particularly, protein deacetylation by Sirtuins, a family of atypical histone deacetylases (HDACs), was demonstrated to regulate fundamental cell biological processes including gene expression, genome stability, mitosis, nutrient metabolism, aging, mitochondrial function and cell motility. Given this wealth of biological functions, perhaps not unexpectedly then, pharmacological compounds targeting Sirtuin activity are now prime therapeutic agents for alleviating severity of major diseases encompassing diabetes, cancer, cardiovascular and neurodegenerative disorders in many organs. In this review, we will focus on the brain and its physiological and pathological processes governed by Sirtuin-mediated deacetylation. Besides discussing Sirtuin function in neurodegenerative diseases, emphasis will be given on the mounting evidence deciphering key developmental brain functions for Sirtuins in neuronal motility, neuroprotection and oligodendrocyte differentiation. In this respect, we will particularly highlight functions of the unconventional family member SIRT2 in post-mitotic neurons and glial cells.

Introduction

The Sirtuin family of histone deacetylases

The biological activity of most proteins is fine-tuned by reversible posttranslational modifications (Jensen, 2006; Westermann and Weber, 2003). In recent years, protein acetylation at the lysine ε-amino group has attracted considerable attention in the regulation of many key cellular processes (Haberland et al., 2009; Kouzarides, 2000; Polevoda and Sherman, 2002). Originally identified as posttranslational modification to target histones and thereby mainly stimulating gene activity, nowadays many non-histone and non-nuclear substrates are known. Although substrate number has now expanded, enzymes conferring deacetylation are still referred to as histone deacetylases (HDACs), whereas addition of acetyl residues is accomplished by histone acetyltransferases (HATs) (Haberland et al., 2009; Yang and Seto, 2007).

This review will discuss Sirtuins, atypical class III HDACs, in brain function. Sirtuins are atypical HDACs in respect of their dependence on NAD^+ as enzymatic cofactor (Blander and Guarente, 2004; Michan and Sinclair, 2007; Taylor et al., 2008). Mammalian Sirtuins are the homologues of the *Saccharomyces cerevisiae* Sir2 protein (silent information regulator), the Sirtuin family-founding molecule, regulating transcriptional silencing during e.g. yeast mating. In mammals, seven Sirtuins (SIRT1-7) have been identified, each of them sharing a conserved 275-amino-acid catalytic core domain (Fig. 1). Sirtuin-mediated deacetylation creates *O*-acetyl-ADP-ribose (*O*AADPr) as by-product (Fig. 1) (Landry et al., 2000; Sauve et al., 2001). This metabolite has second messenger-like properties by e.g. regulating transient receptor channels (i.e. TRPM2; (Grubisha et al., 2006); see below). In addition, many Sirtuins (like SIRT2) carry a second enzymatic activity, i.e. operating as mono-ADP-ribosyl transferase, the biological significance of which is less well understood (reviewed in e.g. (Michan and Sinclair, 2007)).

SIRTs are heterogeneous with regard to their subcellular localisation: some Sirtuins are constitutively localised to the nucleus (i.e. SIRT6 and 7) or mitochondrion (SIRT3-5), whereas others (i.e. SIRT1 and more pronounced SIRT2) shuttle between nucleus and cytoplasm (Blander and Guarente, 2004; Michan and Sinclair, 2007; Taylor et al., 2008).

Biological functions of Sirtuins

In this review, we will mainly discuss biological functions of SIRT1 and SIRT2.

* Corresponding author. Tel.: +49 7071 297 8843; fax: +49 7071 29 5359.
E-mail address: bernd.knoell@uni-tuebingen.de (B. Knöll).

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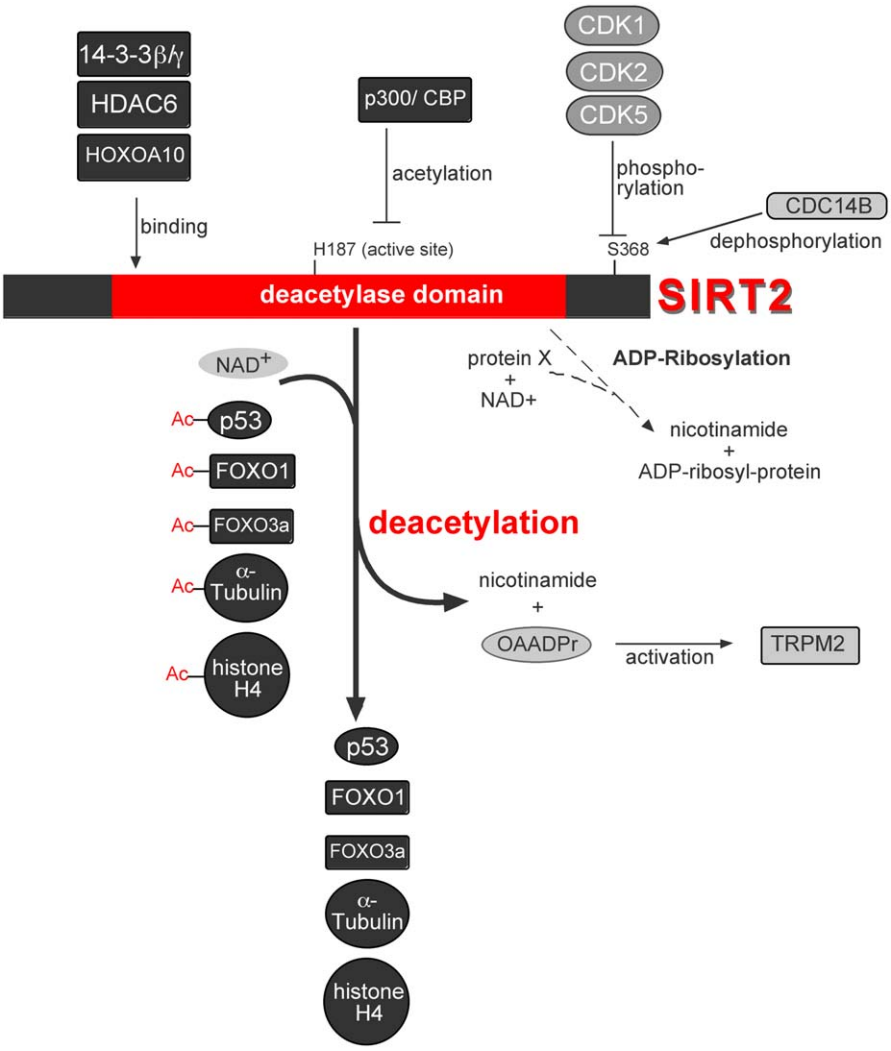

Fig. 1. The SIRT2 regulatory network. SIRT2-interacting partners, of which some are known substrates (p53, FOXO, tubulin, histone H4) and others are binding partners (14-3-3, HDAC6, HOXOA10). SIRT2 is inactivated upon p300/CBP-mediated acetylation or CDK phosphorylation. CDC14B de-phosphorylation of SIRT2 results in decreased SIRT2 protein levels. SIRT2 contains a central deacetylase domain, which in an NAD-dependent manner deacetylates the indicated substrates. As a by-product, nicotinamide and OAADPr are released. The latter functions as signalling intermediate by e.g. regulating the TRPM2 channel. A further reaction mediated by SIRT2 is ADP ribosylation of so far unknown substrates. Note, most components of this SIRT2 regulatory network have so far been described in non-neuronal cells.

Sirtuins in chromosomal stability and gene expression

SIRT1 induces heterochromatin formation, which generally is associated with hypoacetylation and gene repression (Blander and Guarente, 2004; Michan and Sinclair, 2007; Taylor et al., 2008) by deacetylating various histones (histone H1, H3 and H4 (Imai et al., 2000; Vaquero et al., 2004)). In addition, non-histone substrates such as components of the core RNA polymerase I transcriptional machinery and the HAT p300/CBP (Bouras et al., 2005) are deacetylated by SIRT1 and thereby gene expression can be reduced (Muth et al., 2001). Further, mouse mutants lacking SIRT6 revealed impaired DNA repair that correlated with hallmarks of premature aging (Mostoslavsky et al., 2006).

Sirtuins regulate apoptosis versus cell survival

A pro-survival function for SIRT1 has been described (Michan and Sinclair, 2007). For this, key interaction partners for SIRT1 are the tumour suppressors p53 and p73. SIRT1-mediated p53 deacetylation prevents p53 transcriptional activity and counteracts apoptosis in response to oxidative stress and DNA damage (Dai et al., 2007; Luo et al., 2001; Vaziri et al., 2001). Of note, p53 and p73 have recently been attributed various other cellular functions including regulation of neuronal cell migration, nerve fibre outgrowth, growth cone motility and axonal regeneration (Di Giovanni et al., 2006; Tedeschi and Di Giovanni, 2009; Zhang and Chen, 2007). Thus, function of p53 or p73 interacting with Sirtuins is likely not restricted to regulation of apoptosis (see below). Besides blocking apoptosis, Sirtuins increase cell survival through regulation of FOXO transcription factors (Michan and Sinclair, 2007; Wang et al., 2007; Wang and Tong, 2009) (Fig. 1).

Sirtuins as regulators of cell cycle progression and cell proliferation

SIRT2 has been implicated in cell cycle regulation (Inoue et al., 2007a, b, 2009; North and Verdin, 2007a, b; Vaquero et al., 2006). Expression of SIRT2 correlates with cell cycle progression and peaks in mitosis. Functionally, SIRT2 is considered a mitotic exit regulator and given its capacity to suppress glioma colony formation in culture (Hiratsuka et al., 2003) (see also below), SIRT2 was suggested to inhibit (transformed) cell proliferation (Fig. 2). SIRT2 is phosphorylated by various cyclin-CDK complexes (North and Verdin, 2007b; Pandithage et al., 2008) and de-phosphorylated by CDC14B (Dryden et al., 2003), which might down-regulate SIRT2 function. However, there are conflicting results on the role of SIRT2 in cell cycle regulation. SIRT2 overexpression delayed mitotic exit in the presence of