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SIRT2 (Sirtuin2) – An Emerging Regulator of Neuronal Degeneration

Tatsuro Koike*, Kazuhiko Suzuki and Tomohiro Kawahata
Hokkaido University Graduate School of Life Science, Sapporo, Japan

1. Introduction

SIRT2(sirtuin 2) is one of the mammalian orthologs (sirtuins) of yeast silent information regulator 2 (Sir2) proteins that regulate cell differentiation and calorie restriction (Gan and Mucke, 2008; Nakagawa and Guarente, 2011 for review). In contrast to other family members of sirtuins, SIRT2 is mostly localized in the cytoplasm, and regulates post-translational modifications of proteins such as microtubules via tubulin deacetylation (North et al., 2003)(Fig. 1). The enzyme catalyzes the hydrolysis of NAD^+ and transfer of the acetyl moiety of acetylated alpha-tubulin to the resultant ADP-ribose, thus yielding free alpha-tubulin, 2'-O-acetylated ADP-ribose, and niconinamide. This stoichiometry indicates that its activities are modulated by the status of energy metabolism, and nicotinamide serves as an inhibitor. It has well been appreciated that SIRT2 plays a crucial role in cellular functions including oligodendrocyte differentiation (Li et al., 2007; Ji et al., 2011) and cell cycle (Dryden et al., 2003; Inoue et al., 2007) in non-neuronal cells. So far very few studies have ever addressed the question as to whether its expression in neurons shows any functional significance. We will briefly summarize our results on its functional involvement in axon degeneration, and discuss some of recent findings, highlighting an emerging role of SIRT2 in the regulation of neuronal degeneration and plasticity.

2. Tubulin acetylation and axon stability

2.1 Acetylation and deactylation of tubulin

With long axons and elaborated dendrites, neurons establish the circuitry that receives, stores and transmits information to perform neuronal functions (Horton and Ehlers, 2003). The establishment and maintenance of this circuitry requires a coordinated and widespread regulation of the cytoskeleton and membrane trafficking system. Microtubles, whose building block is a heterodimer of alpha- and beta- tublins, play a pivotal role in this function (Fig. 1). There are multiple pathways through which microtubules are stabilized. For instance, acetylation is mostly observed in stable microtubules in neurons as revealed by their low sensitivity to drug-induced depolymerization (Black and Greene, 1982) or upregulation of acetylated alpha-tubulin in response to trophic factor (Black and Keyser,

*Corresponding Author

1987). These findings support a correlate between axon stability and acetylation of alpha-tubulin, but still pose a yet unresolved question regarding the causal relationship between the two (Westermann and Weber, 2003). Acetylation, the major post-translational modification of alpha-tubulin, occurs at the epsilon-amino moiety of Lys40 in the amino terminal region of alpha-tubulin (MacRae,1997). The level of acetylation will be regulated by a balance of tubulin acetyltransferase and tubulin deacetylase activities (Laurent and Fleury, 1996). Although tubulin acetyltransferase (alpha-TAT/MEC-17) has recently been into focus, its regulation is still unknown. Both microtubles and, to a lesser extent, tublins may serve as the substrate for this enzyme (Maruta et al., 1986). The mechanism by which this enzyme works in the lumenal space of the microtubules remains a mystery. Recently, histone deacetylase 6 (HDAC6) (Hubbert et al., 2002; Matsuyama, 2002) and SIRT2 (North et al., 2003) have been identified as an enzyme that catalyzes deacetylation of acetylated alpha-tubulin (Fig. 1). Each enzyme is likely to play an independent role in each compartment of axons.

2.2 The *Wld*^{S} gene and axon stability

In a mutant mouse strain (*Wld*^{S} :Wallerian degeneration resistance) axon degeneration, but not cell somal death, is delayed (Coleman, 2005 for review). Researchers found that transected axons from *Wld*^{S} mice are morphologically indistinguishable from intact axons and capable of conducting action potentials for more than 2 weeks, whereas transected axons from wild-type mice rapidly degenerate within 2 days (Lunn et al., 1989), suggesting that the axonal cytoskeleton is highly stabilized in these mutant *Wld*^{S} mice. This model provides evidence that axonal degeneration is an active process intrinsic to axon itself, which is consistent with the notion that axons often undergo degeneration, independently of cell somal apoptosis during development (Koike et al., 2008, for review). The responsible gene for this phenotype has been demonstrated to encode a chimeric protein (Wld^S) of the full-length of Nmnat1 and N-terminal 70 amino acids of Ufd2a (Conforti et al., 2000). Researchers have shown that the overexpression of the chimeric protein or Nmnat1, or NAD treatment delays axonal degeneration (Mack et al., 2001; Araki et al., 2004; Wang et al., 2005). Nmnat1 is a key enzyme for NAD biosynthesis, and hence it has been postulated that NAD-dependent pathways are involved in the mechanisms underlying Wld^S-mediated axonal protection (Araki et al., 2004; Sasaki et al., 2006). However, both Wld^S and Nmnat1 are localized in the nucleus, and NAD level remains unchanged irrespective of Wld^S or Nmnat1 overexpression (Mack et al., 2001; Araki et al., 2004). The precise mechanism of this neuroprotection is still not yet clear, but these findings suggest the involvement of putative downstream target(s) responding to *Wld*^{S} expression in cell soma. Moreover, *Wld*^{S} phenotype shows a substantial resistance to microtubule depolymerizing drugs (Wang et al., 2000; Ikegami and Koike, 2003), suggesting that this system provides a model to examine the correlation between axon stability and microtubule acetylation.

2.3 Involvement of SIRT2 in axon stability

2.3.1 Evidence for SIRT2 involvement in the axon stability in the *Wlds* model

Based on our preliminary finding on the presence of SIRT2 in cerebellar granule neurons (CGNs), we have put forward our hypothesis that SIRT2 may be involved in microtubule stability by regulating the level of tubulin acetylation. If our hypothesis is correct, the level

of acetylated alpha-tubulin of CGN axons from *Wld*^{S} mice should be higher than those from wild-type mice, and lowering the levels should ameliorate the resistance of these mutant axons to degenerative stimuli including colchicine. Westernblot analysis showed that the basal levels of both acetyl microtubule and acetyl alpha-tubulin were indeed higher in cultured CGNs from *Wld*^{S} mice than those from wild-type mice (Suzuki, 2007; Suzuki and Koike, 2007a). This is also the case for in vivo; Fig. 2 shows that the level of acetylated alpha-tubulin per total alpha-tubulin is significantly higher in the *Wld*^{S} cerebellum compared to the wild-type cerebellum at postnatal 21 days (P21).

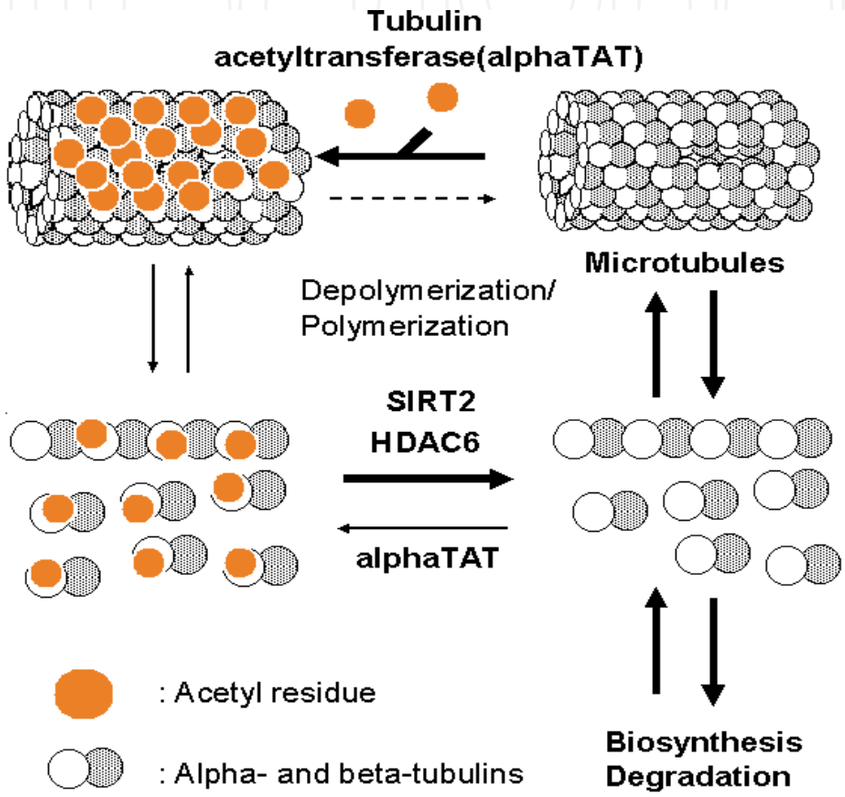

Fig. 1. Acetylation and microtubule dynamics of assembly and disassembly. Microtubules, whose building block is a heterodimer of alpha- and beta- tubulins, are in a dynamic equilibrium of assembly and disassembly. Major acetylation site is at Lys40 of alpha-tubulin. Both microtubles and tublins may serve as the substrate for acetyltransferase (Maruta et al., 1986). Both SIRT2 (North et al., 2003) and histone deacetylase 6 (HDAC6) (Hubbert et al., 2002; Matsuyama, 2002) are known to catalyze the deacetylation of acetylated alpha-tubulin. The level of acetylation will be regulated by a balance of tubulin acetyltransferase and tubulin deacetylase activities.

To further test our hypothesis, CGNs from *Wld*^{S} mice were transfected with the expression vector for GFP or GFP-*sirt2*, and then immunostained with anti-acetylated alpha-tubulin (Suzuki, 2007; Suzuki and Koike, 2007a). The proximal region of the axons was clearly stained in CGNs expressing GFP alone, consistent with the previous reports (Baas and Black, 1990; Shea, 1999), whereas it was markedly reduced in those expressing active GFP-

SIRT2. The results suggest that SIRT2 overexpression is sufficient to substantially reduce the hyperacetylation of CGN axons from *Wld*^{S} mice. Morphologically, changes in the number and length of CGN axons expressing GFP or GFP-*sirt2* were measured overtime after treatment with colchicine: 50% of axons per GFP-positive CGNs from *Wld*^{S} mice still remained alive, whereas in *Wld*^{S} CGNs expressing active *sirt2,* only 10% of axons per GFP-positive cell remained alive at 24 h after colchicine treatment. These results clearly indicate that SIRT2 overexpression downregulated the elevated level of tubulin aceylation and amiliorated the resistance of CGN axons from *Wld*^{S} mice to the degenerative stimulus (Suzuki and Koike, 2007a).

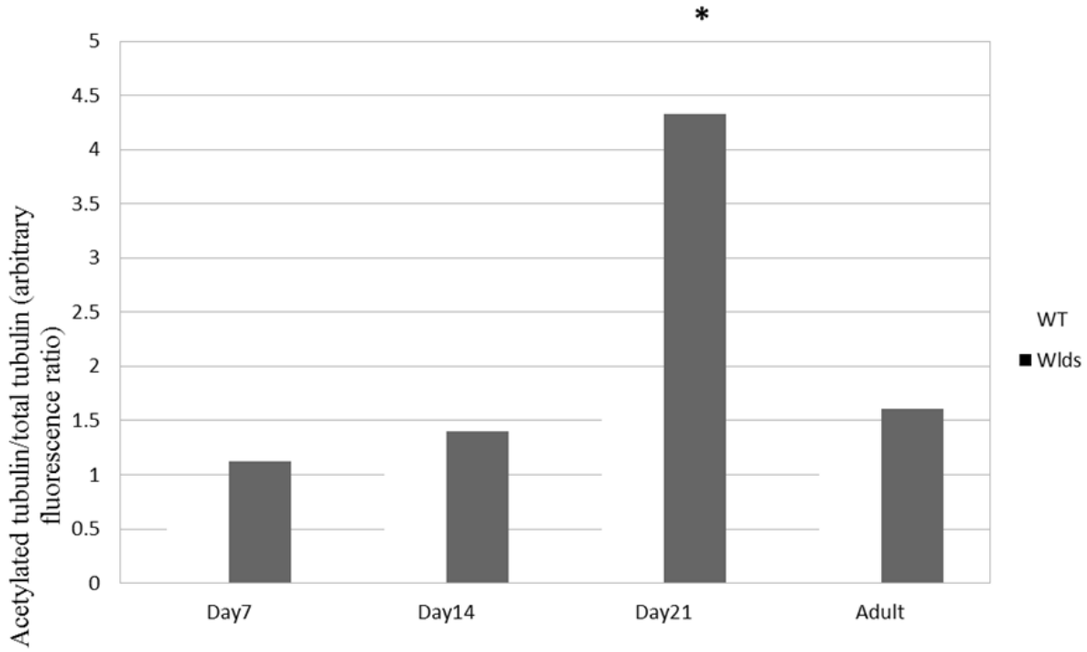

Fig. 2. The level of alpha-tubulin acetylation in the molecular layer of the cerebellum from wild-type (WT) and Wld^S mice during postnatal development. Details of the procedures are previously described (Suzuki and Koike, 2007a). Staining intensities on the sections were measured by using Scion Image software. Relative intensities of total and acetylated alpha-tubulins were calculated by normalizing staining intensities of total and acetylated alpha-tubulins to those of phalloidin, respectively. Tubulin acetylation was determined as a ratio of the intensities of acetylated alpha-tubulin to those of total alpha-tubulin in adjacent sections. The data are shown as mean ± S.D. (n = 3 animals). Statistical significance was detected by Student's t-test (*$p < 0.05$ between groups at wild-type and Wld^S). Data from Suzuki (2007).

2.3.2 Functional correlate between SIRT2 levels and axon resistance against degenerative stimuli

If microtubule hyperacetylation is involved in acquiring resistance of CGN axons from mutant mice to degenerative stimuli, then similar resistance would be attainable for wild-type CGN axons by the use of SIRT2 inhibitors or *sirt2* silencing technology. By exposing

wild-type CGNs from wild-type mice to nicotinamide, the inhibitor of SIRT2, prior to colchicine application, we obtained evidence for enhanced tubulin acetylation and increased resistance to colchicine (Suzuki and Koike, 2007a). Immunoblot analysis shows that the level of alpha-tubulin acetylation increased following treatment with nicotinamide in a concentration- and time-dependent manner (Suzuki, 2007). However, treatment with 3-aminobenzamide(3-AB), an inhibitor for PARP, failed to elevate the level, suggesting that the effect of nicotinamide on tubulin deacetylation is mediated by SIRT2 but not by PARP. On the other hand, trichostatin A (TSA), a specific inhibitor for HDAC6 tubulin deacetylase (Matsuyama et al., 2002), failed to enhance tubulin acetylation. Morphologically, more than 70% of axons were viable, whereas 90% of cell somata were dead when CGNs were treated with 10 mM nicotinamide and then with colchicine for a further 24h. However, it should be noted that nicotinamide was neuroprotective only after its exposure to CGNs for more than 2 days, and that this agent elevated the level of alpha-tubulin acetylation, but not the level of microtubule acetylation.

To eliminate the possibility that nicotinamide acted through other pathways, CGNs were transfected with a lentiviral vector expressing SIRT2 small interfering RNA (siRNA). SIRT2 silencing indeed caused an increase in the level of acetylated alpha-tubulin (Fig. 3). Morphologically, more than 50 % of axons were viable as revealed by calcein-AM staining, whereas more than 90% of cell bodies were dead as revealed by PI staining, after colchicine treatment for 48hr (Suzuki, 2007). These results show that CGN axons form wild-type mice acquired resistance to degenerative stimuli by downregulating *sirt2* expression.

2.3.3 Resveratrol-mediated modulation of axon degeneration

Resveratrol, a natural polyphenol, shows a wide range of interesting biological and pharmacological activities. Besides acting as a general inhibitor against oxidative stress, this agent is known to activate SIRT1, thus providing a potential effect for longevity (Fulda and Debatin, 2006; Buer, 2010 for review). To asses the effect of resveratrol on SIRT2 HEK293 cells were transfected with GFP alone, active GFP-SIRT2, or GFP-SIRT2 N168A, a catalytically inactive mutant (North et al., 2003), and then the cellular lysates were immunoprecipitated by anti-GFP antibody. The resultant immunoprecipitates were used as SIRT2 enzymes for tubulin deacetylation assay. We found that resveratrol decreased the level of acetylated alpha-tubulin in the immunoprecipitates from CGNs transfected with active GFP-SIRT2, but not inactive GFP-SIRT2 or GFP alone, suggesting that resveratrol indeed activates SIRT2 (Suzuki, 2007).

Westernblot analysis showed that resveratrol decreased the level of acetylated alpha-tubulin in the CGN lysates from wild-type mice in a time- and dose-dependent manner (Suzuki, 2007; Suzuki and Koike, 2007b). Moreover, resveratrol decreased the level of tubulin acetylation, and, as a result, reduced the resistance of CGN axons from Wld^S mice to the degenerative stimulus. The effect of resveratrol on cell body degeneration appeared to be minimal, which is consistent with the previous report (De Ruvo et al., 2000). These results suggest that resveratrol amiliorated the resistance of CGN axons from Wld^S mice to colchicine by enhancing tubulin deacetylation. However, it should be noted that resveratrol was neuroprotective after its treatment for more than 2days, suggesting that it may acts indirectly on SIRT2 or other targets including nuclear transcriptional factors that regulate the expression of a variety of genes (Fulda and Debatin, 2006).

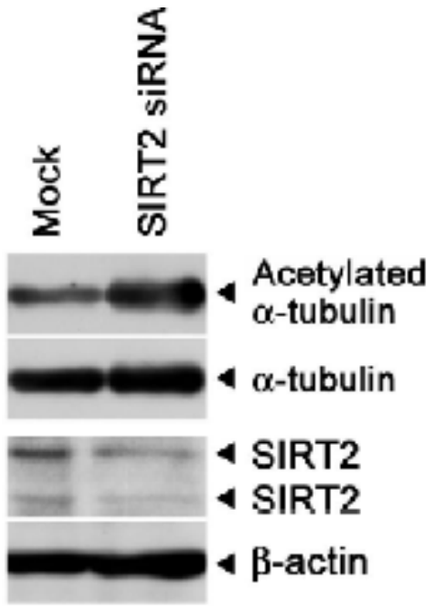

Fig. 3. The enhancement of the level of acetylated alpha-tubulin in wild-type CGNs by silencing of *sirt2*. CGNs from wild-type mice were mock infected or infected with lentivirus expressing SIRT2 siRNA at 1 moi, and cultured for a further 48 h. Five micrograms of total proteins from the cytoskeletal fraction (microtubules fraction) of both cultures were applied on a gel, and analyzed by immunoblotting with anti-acetylated alpha-tubulin antibody. Equal loading was confirmed by reprobing the same blot with anti-alpha-tubulin antibody (upper 2 blots). For immunoblotting with anti-SIRT2 antibody, twenty micrograms of total proteins from the total cellular fraction were analyzed. Equal loading was confirmed by the same blot with anti-beta-actin antibody (lower 2 blots). Each experiment was repeated three times with similar results. Note that both long (43kDa) and short (39kDa) forms of the SIRT2 proteins are detected. Data from Suzuki (2007).

3. Evidence for neuronal distribution of acetyl alpha-tubulin and SIRT2: An immunoreactivity study during postnatal development of mouse cerebellum

In the mouse brain, the expression of alpha-tubulin is high during early postnatal days, and subsequently decrease upon maturation (Burgoyne and Cambray-Deakin, 1988), whereas tubulin acetylation in vivo is known to occur concomitantly with maturation (Black and Keyser, 1987), indicative of its association with microtubule stability (Westermann and Weber, 2003). Immunohistochemistry using the monoclonal antibody specific for acetylated alpha-tubulin showed intense particulate staining in the molecular layer of postnatally developing and adult mouse cerebellum (Suzuki, 2007; Kawahara, 2007). Bergmann glial fibers and Purkinje cell dendrites were not stained, whereas Purkinje cell bodies were intensely stained in developing mouse cerebellum (Suzuki, 2007; Kawahara, 2007), consistent with the previous findings (Cambray-Deakin and Burgoyne, 1987). During postnatal development the external granular layer becomes thinner, while the molecular layer becomes enlarged (Burgoyne and Cambray-Deakin, 1988). Along with this, intense staining was observed in the molecular layer from wild-type and *Wld*^{S} mice. The level of

microtubule acetylation in *Wld*^{S} cerebellum was increased at P14-21 (Suzuki, 2007; Kawahara, 2007), which corresponds to the stage when granule cells migrate into the internal granule layer (IGL) along extending parallel fiber axons, and form short dendrites (Burgoyne and Cambray-Deakin, 1988). These findings suggest that microtubule acetylation occurs in a manner that depends on developmental stages. In vitro, Wallerian degeneration of transected axons is further delayed by extending culture period of time prior to axotomy in cerebellar explant cultures from Wld^S mice (Buckmaster et al., 1995).

Fig. 4 shows the immunostaining patterns of SIRT2 of wild-type and *Wld*^{S} mouse cerebella during development; intense immunostaining was observed in the EGL, the IGL and the Purkinje cell layer at P1, and the EGL and the Purkinje cell layer at P7, and then gradually declined in both cerebella, although the intensity was lower in the *Wld*^{S} cerebellum. At P21 and, to a lesser extent, in adult, clear and distinct staining was observed for the Purkinje cell layer. Fig. 4 clearly shows that SIRT2 immunoreactivity is localized in the cytoplasm of Purkinje cells; though less clearly, the staining of CGNs were rather uniform. In the molecular layer of both adult wild-type and *Wld*^{S} cerebella immunostaining was far less intense, consistent with the recent report (Li et al., 2007). Our findings clearly show that both CGNs and Purkinje neurons are positively stained with the antibodies against SIRT2 at the critical period of time when these neurons are undergoing differentiation and migration (Suzuki and Koike, 1997; Powell et al., 1997). SIRT2 immostaining clearly showed the localization of SIRT2 in developing CGNs and Purkinje neurons in contrast to the previous finding on its distribution in non-neuronal cells. Recent study has revealed a widespread distribution of SIRT2 in CNS neurons (Maxsell et al., 2011).

4. Possible roles of SIRT2 in neurodegeneration

4.1 Acetylated alpha-tubulin as a marker of stable microtubules

We have showed that alpha-tubulins and microtubules are hyperacetylated in CGNs from wld^s mutant mice, and the resistance of these CGN axons to degenerative stimuli is ameliorated by downregulating the level of acetylation by multiple methods including silencing of *sirt2*. Similarly, CGN axons from wild-type mice acquired resistance to colchicine by *sirt2* silencing, which was associated with reduced levels of tubulin deacetylation, but not enhanced levels of microtubule acetylation. The reason for this is unclear, since both acetylated and non-acetylated alpha-tubulins are known to be a good substrate for tubulin acetylatransferase in vitro. It is likely that the degeneration pathway may play a role in the regulation of axon stability given the fact that deacetylated tublin is rapidly degradated (Black et al., 1989; Ren et al., 2003) as shown in Fig. 5, and therefore, if this step is blocked, acetylated microtubules are metabolically stabilized (but not accumulated). Consistently, the level of acetylated alpha-tubulin is a signal for fine-tuning microtubule dynamics by modulating alpha-tubulin turnover (Solinger et. al., 2010). It has been shown that microtubules were stabilized and the level of acetylated alpha-tubulin was elevated in the cells transfected with microtubule-associated proteins tau or other associated proteins (Takemura et al., 1998), suggesting these microtubule associated proteins influence microtubule stability by modulating tubulin acetylase activities; Fig. 5 shows that the association of alpha-tubulin with tau stabilizes microtubules via a yet unknown mechanism.

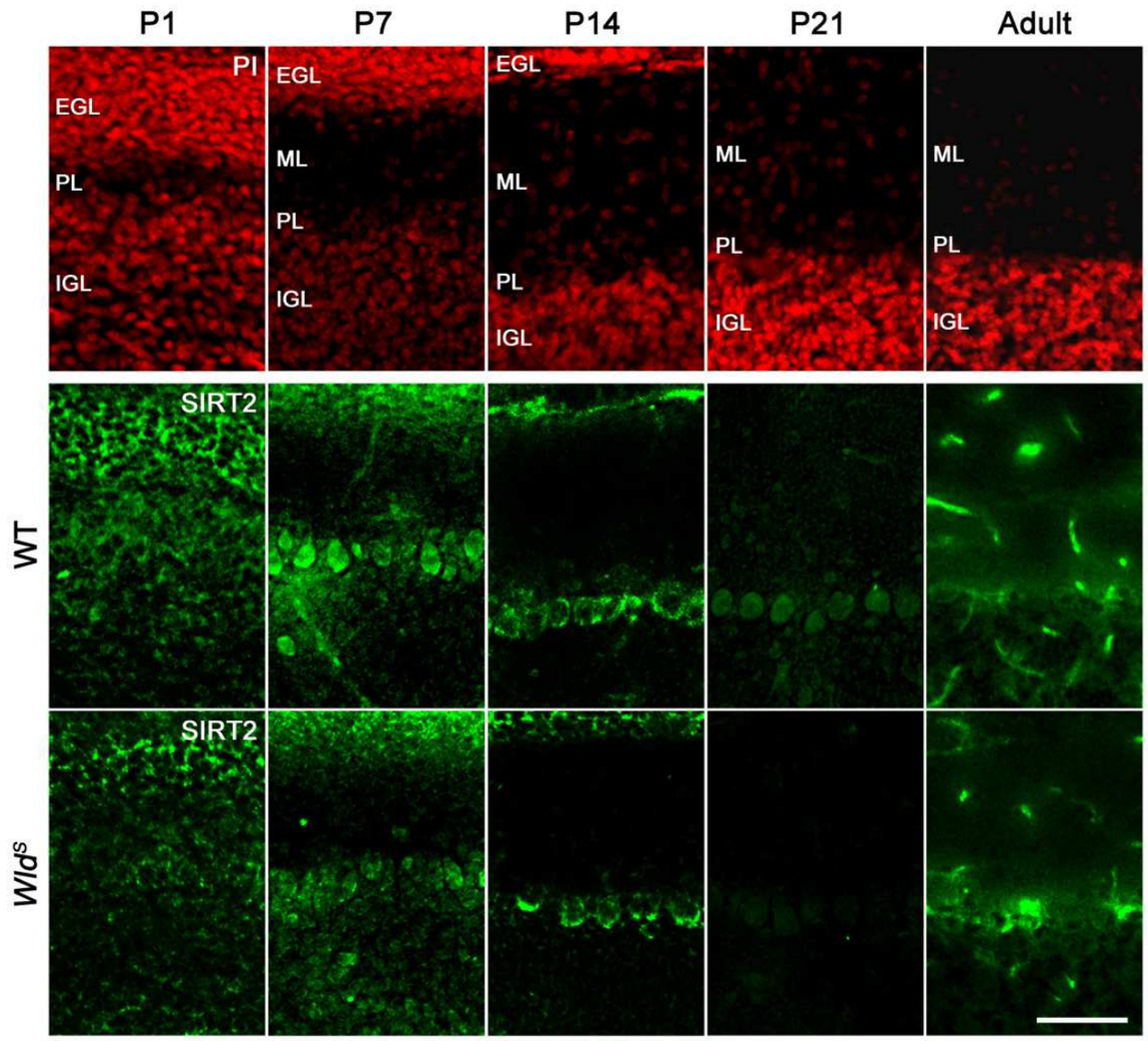

Fig. 4. Immunohistochemical staining patterns of SIRT2 during postnatal development of the cerebellum from wild-type and WldS mutant mice. Coronal crysections from cerebella from each mouse were immunostained with anti-SIRT2 antibody (green). As a reference, nuclear stainings with PI (red) in wild-type cerebellum are shown. Details of this method have been described (Suzuki and Koike, 2007a). Note that oligodendrosites are intensely stained in the adult cerebellum (Li et al., 2007). EGL, the external granular layer; ML, the molecular layer; PL, the Purkinje cell layer; the IGL, internal granular layer. Scale bar represents 25 microm. Data from Suzuki (2007) and Kawahara (2007).

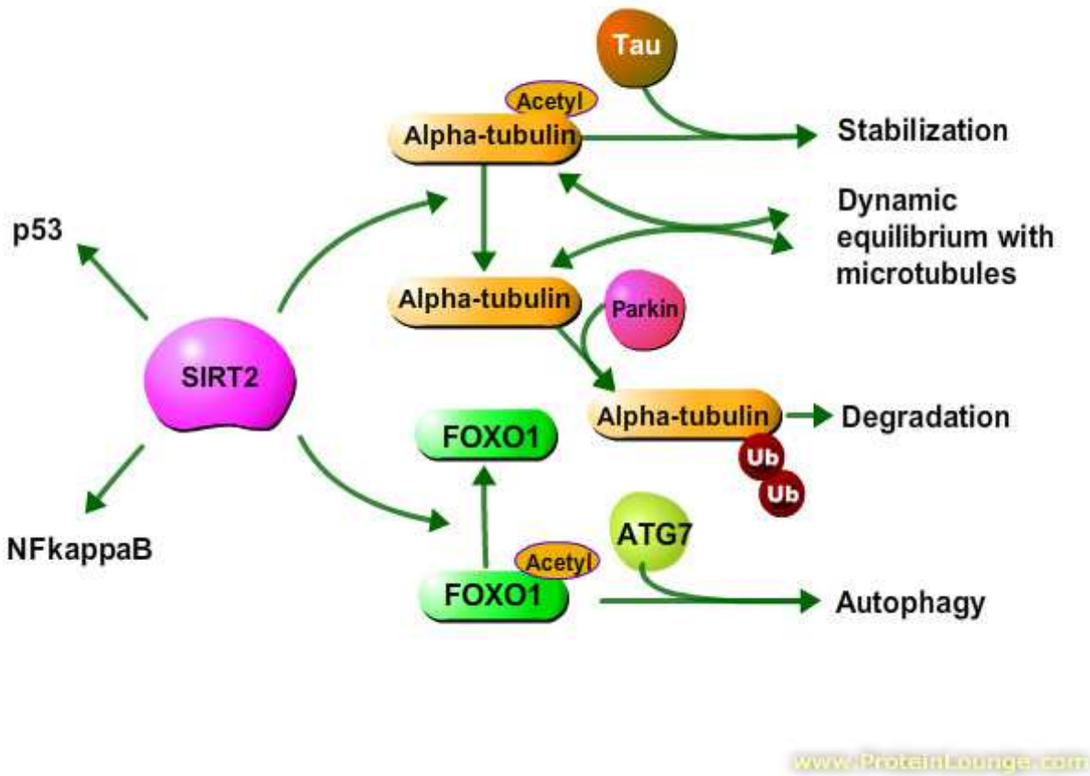

Fig. 5. SIRT2 targets and its functions. Targets of SIRT2 include a number of transcription factors including p.53, p.300, 14-3-3, p.65, Foxo's, NFkappaB, SREBP-2 and others, only two of which are shown in this figure. Besides these transcription factors, SIRT2 is known to act on FOXO1 and tubulins. FOXO-1 in the cytoplasm plays a crucial role in autophagic mechanisms, although its neuronal distribution is not currently available. Alpha-tubulin is shown to bind to Parkin, and is thereby ubiquitinated and quickly degradated. On the other hand, acetylated-tubulin is able to bind to tau and is involved in microtubule stabilization. The plus ends of Microtubules are in a dynamic equilibrium of assembly and disassembly and their minus ends with extensive acetylation and association with tau are relatively stable.

4.2 Multiforms of SIRT2

Previous reports have shown that SIRT2 is localized mainly in the cytoplasm (North et al., 2003; Dryden et al., 2003). For CGNs, SIRT2 immunoreactivity was observed throughout the cells. Westernblot analysis shows two different isoforms of SIRT2 proteins. Interestingly, the long isoform (43 kDa) was barely detectable in the cytoplasmic fraction in both WT and *Wld*^{S} granule cells (Suzuki, 2007). The short form (39 kDa) lacks the corresponding N-terminal 37 amino acids in the long isoform (Voelter-Mahlknecht et al., 2005) and may be located in the cytoplasm and the nucleus. Recent study shows that there is a *sirt2* transcript expressed preferentially in aging CNS (Maxsell et al., 2011). Further experiments should be needed to delineate the precise roles of these nuclear, cytoplasmic, age-specific forms of the *Sirt2* transcripts.

4.3 Degradation pathways of SIRT2

Dryden et al. (2003) reported that SIRT2 is dephosphorylated by the phosphatase CDC14B and then degradated via the ubiquitin-proteasome pathway. This finding suggests that the level of SIRT2 proteins could be regulated by phosphorylation in the nucleus where this phosphatase is located, and ubiquitination in the cytoplasm. CDC14B overexpression promotes microtubule acetylation and stabilization, indicative of the involvement of the nucleo-cytoplasmic shuttling in the degadation pathway of SIRT2 (Cho et al., 2005). Parkin, an ubiquitin E3 ligase linked to Parkinson's disease, is also shown to bind to alpha- and beta-tubulins and enhance their ubiquitination and degradation (Ren et al., 2003)(Fig. 5). Regulation by phosphorylation has also been shown for HDAC6, another tubulin deacetylase.

Recently, researchers have shown that FOXO (Forkhead box, class O) transcription factors are clearly involved in the degradation pathway in a number of important ways. SIRT2 facilitates FOXO3 deacetylation, promotes its ubiquitination and subsequent proteosomal degradation (Wang et al., 2011). Fig. 5 shows various targets of SIRT2 in which there are number of transcription factors. including NFkappaB (Rothgieser at al., 2010). On the other hand, cytosolic FOXO1 acts independently of its capability as being a transcription factor and is shown to be essential for the induction of autophagy in response to stress (Zhao et al., 2010). Fig. 5 shows that FOXO1 is acetylated by dissociation from SIRT2, and the acetylated FOXO1 forms a complex with Atg7, an E1-like protein, in the autophagy signaling pathway (Zhao et al., 2010). As shown previously, autophagic degradation processes play a key role in the survival and degeneration of axons and dendrites (Koike et al., 2008).

4.4 SIRT2 versus HDAC6

SIRT2 is shown to be localized in the proximal region of CGN axons (Suzuki, 2007), whereas HDAC6 tubulin deacetylate distributes in the distal region of axons of Hipocampal neurons (Black et al., 1998), suggesting each tubulin acetylase may have different regulatory roles in microtubule stability and the protein-protein interaction along axons. Previous studies have shown that HDAC6 inhibition or suppression regulates the interaction of ankyrinG or similar axonal domain-interacting proteins with voltage gated sodium channels that diffuse along the axon (Black et al., 1998). Thus, the distribution of SIRT2 in the proximal region of the axon and its absence from the distal region of the axon may regulate the formation of different microtubules domains in the axon. HDAC6 regulated activity at the distal axon can promote axonal growth (Tapia et al., 2010), while microtubules at the proximal region of the axon can be more acetylated and allow the maintenance of the axon initial segment, necessary for polarized axonal transport, tethering of ankyrin proteins and generation of neuronal action potentials. It is interesting to point out that both the protein-protein interactions along axons and the protein degradation pathway are regulated through the acetylation/deacetylation pathway. Therefore, its switching is a key event for the regulation of microtubule degradation and hence stability of various axonal domains. Further experiments will be necessary to understand how SIRT2 or HDAC6 deacetylase activities are locally regulated and involved in the axon stability and degeneration.

5. Conclusion & future issues

SIRT2, a NAD-dependent protein deacetylase, is mostly localized in the cytoplasm and regulates post-translational modifications of proteins such as microtubules via tubulin deacetylation. We have shown evidence that SIRT2 could modulate hyperacetylation of alpha-tubulin in cerebellar granule axons and thereby abrogate their resistance to degenerative stimuli in a mutant mouse strain where axon degeneration, but not cell somal death, is markedly delayed. We have provided evidence for its functional involvement in axon stability, and discuss some of recent findings, highlighting the emergence of SIRT2 as a novel regulator of neuronal degeneration and plasticity.

Recently, the suppression of SIRT2 effectively ameliorates neurotoxicity in a variety of neuronal disease models including Drosophila model of Huntington disease (Pallos et al., 2008), mutant huntingtin neurotoxicity (Luthi-Cortea et al., 2010), alpha-synuclein-mediated toxicity in models of Parkinson's disease (Outeiro et al., 2007). It has been proposed that the SIRT2 inhibitors or SIRT2 suppression may function by promoting the formation of enlarged inclusion bodies, and thereby provide neuroprotection. Nicotinamide is also shown to increase the level of acetylated alpha-tubulin, tau stability, and restore memory loss in a transgenic mouse model of Alzheimer's disease (Green et al., 2008). The mechanisms of neuroprotection found in these disease models are still unknown. These findings should be discussed in the light of the functional diversity of SIRT2 subtypes and their localization in axonal domains.

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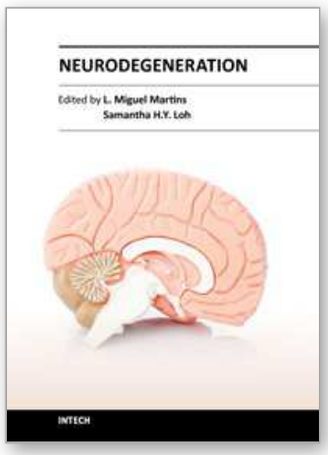

Neurodegeneration

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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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