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Class II HDACs and Neuronal Regeneration

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ABSTRACT

The vastly more superior regenerative capacity of the axons of peripheral nerves over central nervous system (CNS) neurons has been partly attributed to the former's intrinsic capacity to initiate and sustain the functionality of a new growth cone. Growth cone generation involves a myriad of processes that centers around the organization of microtubule bundles. Histone deacetylases (HDACs) modulate a wide range of key neuronal processes such as neural progenitor differentiation, learning and memory, neuronal death, and degeneration. HDAC inhibitors have been shown to be beneficial in attenuating neuronal death and promoting neurite outgrowth and axonal regeneration. Recent advances have provided insights on how manipulating HDAC activities, particularly the type II HDACs 5 and 6, which deacetylate tubulin, may benefit axonal regeneration. These advances are discussed herein. J. Cell. Biochem. 115: 1225–1233, 2014.

KEY WORDS: AXONAL REGENERATION; HDAC5; HDAC6; HISTONE DEACETYLASES (HDACs); NEURITE OUTGROWTH

Central nervous system (CNS) neurons and peripheral nerves differ greatly in their ability to regenerate severed axons. While lesioned tips of peripheral nerves could form a growth cone [Bradke et al., 2012], axotomy of CNS neurons invariably result in the formation of characteristic swellings known as retraction bulbs [Ertürk et al., 2007]. In general, there are two main reasons why CNS neurons are normally regeneration incompetent. The first pertains to the inhibitory CNS environment, where a number of myelin-associated inhibitors and extracellular matrix proteins transduce signals that inhibit axonal growth and promotes growth cone collapse [Yiu and He, 2006; Lee and Zheng, 2012]. The second is down to the diminished intrinsic regenerative capacity of adult CNS neurons [Liu et al., 2011]. The "intrinsic regenerative capacity" is a broad term encompassing many factors, including responses to neuronal survival and growth factors [Lykissas et al., 2007], the ability to perform local protein synthesis [Willis and Twiss, 2006], as well as the ability to stabilize the microtubule bundle to form a growth cone [Hellal et al., 2011]. Post-translational modifications of tubulin affects microtubule stability and functions [Hammond et al., 2008]. One such modification is acetylation/deacetylation of lys-40 of α-tubulin, which impacts on cell motility, cell differentiation, and intracellular trafficking and signaling [Janke and Kneussel, 2010; Perdiz et al., 2011].

Lysine acetylation is a key post-translational modification of many proteins, and which underlie many aspects of gene transcription, cellular signaling, cellular transport, and metabolic changes [Arif et al., 2010; Patel et al., 2011; Scott, 2012]. Acetylation of nuclear histone and a myriad of nuclear and cytoplasmic proteins are mediated by the histone acetyltransferases (HATs) [Roth et al., 2001]. The acetyl moiety is in turn removed by a large family of protein deacetylases, which are divided phylogenetically into four classes [Yang and Seto, 2007]. The Rpd/Hda1 family comprises classes I, II, and IV, and consist of 11 histone deacetylases (HDACs), 1–11 in mammals [Yang and Seto, 2008]. The class III deacetylases consist of members of the sirtuin family (Sirt1–6), which are enzymatically distinct from the other HDACs because of their dependence on the cofactor nicotinamide adenine dinucleotide (NAD^+) [Haigis and Sinclair, 2010]. Class I HDACs are primarily nuclear proteins that function as essential modulators of transcriptional and epigenetic landscaping, and are often found in association with nuclear repressor/co-repressor complexes [Grzenda et al., 2009]. The class II HDACs, however, shuttle between the cytoplasm and the nucleus, and could therefore act as cytoplasmic-nuclear signal transducers, as well as acting on cytoplasmic substrates. Although termed histone deacetylases, the HDACs and sirtuins have a wide range of non-histone nuclear and cytoplasmic

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substrates [Yang and Seto, 2008; Haigis and Sinclair, 2010]. Acetylated tubulin, for example, is one major cytoplasmic substrate for HDAC6 [Zhang et al., 2003] and Sirt2 [North et al., 2003].

HDACs play key regulatory roles during embryonic development and postnatal function, and HDAC inhibitors have shown therapeutic promises in human diseases ranging from cancer [Minucci and Pelicci, 2006] to neurodegenerative disorders [Dietz and Casaccia, 2010]. Pertaining to neuronal function and survival, two common findings are that HDAC inhibition improves neuronal survival [Uo et al., 2009; Brochier et al., 2013], and promotes recovery of cognitive deficits [Fischer et al., 2007; Vecsey et al., 2007; Covington et al., 2009; Foley et al., 2012; Gräff et al., 2012; Morris et al., 2013]. The former may, at least partly, be due to suppression of p53-induced cell death by the class I HDACs 1, 2, and 3 [Juan et al., 2000]. On the other hand, recovery of learning/memory capacity and cognitive ability have been shown to involve HDAC2 [Guan et al., 2009], whereas HDAC3 inhibition have been implicated in enhancing the memory processes involved in the extinction of drug-seeking behavior [Malvaez et al., 2013]. HDAC4 represses genes encoding proteins functioning at the synapses, and a truncated form of HDAC4 encoded by a human allele associated with mental retardation was shown to impair learning and memory in mice carrying a similar mutation [Sando et al., 2012]. Class II HDACs have also been implicated indirectly in learning and memory. For example, HDAC6 reduction improving cognitive deficits in Alzheimer's disease models [Govindarajan et al., 2013]. However, memory functions appear to be impaired by the loss of HDAC5, which may have a role in memory consolidation [Agis-Balboa et al., 2013].

ACETYLATION/DEACETYLATION FACTORS AND THEIR ROLES IN NEURONAL REGENERATION

Upon injury, neurons activate multiple responses to enhance the possibility of survival and recovery [Dancause and Nudo, 2011; Yang and Yang, 2012]. Survival and regeneration are two intertwined responses within injured neurons, and these share overlapping signaling pathways and mechanisms. It has been shown that acetylation/deacetylation processes influence neuronal/axonal outgrowth and regeneration. Histone acetyltransferaces (HATs) such as the CREB-binding protein (CBP)/p300 and the p300/CBP-associated protein (P/CAF), acetylate histone H3K9/K14 and p53, thus generating a transcriptional profile conducive for neuronal outgrowth [Gaub et al., 2010]. Other than its well-known role in neuronal apoptosis [Morrison et al., 2003], p53 in neurons also influences axonal outgrowth and regeneration [Tedeschi and Di Giovanni, 2009]. p53 acetylation has been shown to be specifically involved in the promotion of neurite outgrowth by regulating of the expression of the actin binding protein coronin 1b [Cai et al., 2007] and Rab13 [Sakane et al., 2012], which modulates the actin cytoskeleton [Di Giovanni et al., 2006]. With CBP/p300, p53 forms a transcriptional complex that regulates the expression of axonal growth-associated protein 43 (GAP43). Acetylated p53 could promote GAP-43 expression through the engagement of the neuronal GAP-43 promoter through CBP/p300, thus promoting axon outgrowth [Tedeschi et al., 2009]. In an optic nerve crush model of axonal injury, over-expression of the CBP/p300 can also promote axonal regeneration of the optic nerve [Gaub et al., 2011]. Another newly discovered α-tubulin acetyltransferase, MEC-17, appears to be important in yet another related process in nervous system development, namely neuronal migration. Highly expressed in the cerebral cortex during embryonic development, MEC-17 deficiency causes neuronal migratory and projection defects [Li et al., 2012].

In view of the above, HDAC inhibitors would be expected to have neuroprotective and neurite growth promoting effects. HDAC inhibitors have indeed been shown to attenuate poly-glutamine extension-containing huntingtin-induced neurorodegeneration in *Drosophila* models of Huntington's disease (HD) [Steffan et al., 2001]. HDAC inhibition has been recently shown to modify the acetylation pattern of p53, which decreases its DNA-binding and transcriptional activation of target genes and prevented DNA damage-induced neurodegeneration [Brochier et al., 2013]. Interestingly, although the HDAC1 inhibitor valproic acid delays retinal ganglion cell death and enhances axonal regeneration after optic nerve crush, its neuroprotection and neuroregeneration activity does not appear to be dependent on altered histone-acetylation [Biermann et al., 2010]. Other than being neuroprotective against oxidative stress, pan-HDAC inhibition also promoted neurite outgrowth on non-permissive CNS myelin substrates, an activity that has been attributed to HDAC6 [Rivieccio et al., 2009]. Recent findings have also implicated the involvement of HDAC5 in two modes of action that promotes neuronal regeneration. The first involves axonal injury induced HDAC5 nuclear exit, which changes the transcription profile and activate a pro-regenerative gene-expression program [Cho et al., 2013]. Cytoplasmic HDAC5 also modulates tubulin deacetylation at the lesion site, which promoted neurite outgrowth [Cho and Cavalli, 2012]. In the paragraphs below, we focus on findings associated with the role of class II HDACs in neuronal regeneration, in particular HDAC6 and HDAC5.

THE COMPLEX ROLES OF HDAC6 IN NEURONAL PATHOLOGY

We first look at HDAC6, which is the classical tubulin deacetylating enzyme [Hubbert et al., 2002]. HDAC6 is categorized under histone deacetylase class IIb, together with HDAC10. Its domain structure is distinct from all other HDACs, as it harbors two deacetylase domains and a C-terminal zinc finger domain [Haberland et al., 2009]. The protein is largely cytoplasmic, where it associates with microtubules [Kawaguchi et al., 2003]. HDAC6 is not essential for mouse development, but its absence results in tubulin hyperacetylation in all tissues [Zhang et al., 2008]. In the mammalian brain, HDAC6 is mainly found in neurons [Southwood et al., 2007]. Recent work has implicated HDAC6, which levels are high at the dorsal and median raphe nuclei, in the regulation of emotional expression in mice. HDAC6-deficient mice exhibit antidepressant-like behavior in behavioral tests, which was mimicked by HDAC6-specific inhibitor [Fukada et al., 2012]. This phenomenon is possibly connected to HDAC6's deacetylation of the molecular chaperone heat shock protein 90 (Hsp90), which is required for glucocorticoid receptor (GR)

maturation. The latter process is compromised in HDAC6-deficient cells [Kovacs et al., 2005]. Selective knockout of the highly abundant HDAC6 in serotonin neurons reduced acute anxiety caused by administration of corticosterone, and blocked the expression of social deficits in this mouse model of traumatic stress [Espallergues et al., 2012]. In another report, HDAC6 inhibition or its silencing was shown to block the enhancement of glutamatergic transmission and glutamate receptor trafficking in the prefrontal cortex by both acute stress in vivo and corticosterone treatment in vitro [Lee et al., 2012].

A neuroprotective role for HDAC6 that was discovered early pertains to the clearing of misfolded proteins and associations with the pathologies of several neurodegenerative diseases involving the formation of toxic cellular aggregates [Richter-Landsberg and Leyk, 2013]. Notably, HDAC6 could exert either a beneficial or a deleterious effect depending on the disease context. HDAC6 binds to both polyubiquitinated misfolded proteins and dynein motors, thereby recruiting misfolded proteins to dynein motors for transport to aggresomes [Kawaguchi et al., 2003; Fusco et al., 2012]. HDAC6 also modulates aggresome autophagy [Su et al., 2011] by controlling the fusion of autophagosomes to lysosomes [Lee et al., 2010]. Parkinson's disease (PD), a common movement disorder, is largely idiopathic. However, a small fraction of patients, often with juvenile onset of symptoms, has inherited mutations in several genes [Trinh and Farrer, 2013]. The *PARK2* gene product Parkin, an E3 ligase mutated in juvenile onset PD, mediates K63-linked polyubiquitination of misfolded DJ-1, the *PARK7* gene product [Bonifati et al., 2003], which enhances the latter's interaction with HDAC6. Misfolded DJ-1 could thus be linked to the dynein motor and transported to aggresomes [Olzmann et al., 2007]. HDAC6 is concentrated in Lewy bodies (LBs) in PD and dementia with LBs (DLB) [Kawaguchi et al., 2003; Miki et al., 2011], which consist of aggregates of α-synuclein. *Drosophila* HDAC6 activity thus protects dopaminergic neurons against α-synuclein toxicity by promoting the formation of inclusion bodies [Du et al., 2010]. HDAC6 also appears to be a critical link between macroautophagy and the ubiquitin–proteasome system (UPS), particularly for the former to be induced to compensate for the impairment of the latter. It is essential for autophagy in mutations affecting the proteasome and in response to UPS impairment in a *Drosophila* model of spinobulbar muscular atrophy (SMA) [Pandey et al., 2007]. HDAC6 interacts with tau, the microtubule-associated protein that is hyperphosphorylated and forms the pathological hallmark of neurofibrillary tangles in Alzheimer's disease (AD) [Ding et al., 2008], and HDAC6 levels were shown to be elevated in Alzheimic brains [Zhang et al., 2013]. Excess tau inhibits HDAC6 activity and attenuates autophagy, which may contribute to AD pathology [Perez et al., 2009]. Over-expression of HDAC6 enhanced deacetylation of microtubule, and could protect against microtubule disintegration by the microtubule-severing protein katanin, resulting from loss of functional tau [Sudo and Baas, 2011].

On the other hand, HDAC6 activity could also exacerbate certain neurodegenerative diseases. HDAC6 deacetylation of tubulin underlies the finding that HDAC inhibitors could alleviate axonal microtubule-based transport defects in an HD model by promoting tubulin acetylation [Dompierre et al., 2007]. In another neurodegenerative disease model of amyotrophic lateral sclerosis (ALS) induced by transgenic expression of mutant superoxide dismutase 1 (SOD1G93A), HDAC6 deletion was shown to significantly extended the survival of these mice via increase in tubulin acetylation [Taes et al., 2013]. HDAC6 could in fact interact with mutant SOD1 and affects its transport and aggregation [Gal et al., 2013]. In a neuronal culture model of AD, inhibition of HDAC6 rescues hippocampal neurons from amyloid-beta (Aβ)-induced impairment of mitochondrial axonal transport [Kim et al., 2012]. HDAC6 is a substrate of the E3 ubiquitin ligase carboxyl terminus of Hsp70-interacting protein (CHIP) [Cook et al., 2012], and the latter also ubiquitinates and aids in the clearing of tau [Petrucelli et al., 2004; Shimura et al., 2004; Dickey et al., 2007, 2008]. Together with Hsp90, CHIP and HDAC6 form a network of chaperone complexes that modulates tau levels, and consequently, AD pathology [Cook and Petrucelli, 2013]. As pointed out in the paragraph above, tau could attenuate HDAC6-induce autophagy, which might be deleterious in terms of AD progression. However, a decrease in HDAC6 activity or expression was on the other hand shown to promote tau clearance [Cook et al., 2012].

The transactive response DNA binding protein of 43 kDa (TDP-43) is a major neurodegenerative disease pathology-associated protein whose cleaved form is concentrated in ubiquitin-positive inclusions of frontotemporal dementia (FTD) and some forms of ALS [Neumann et al., 2006]. TDP-43's exact physiological roles is not yet particularly clear, but the protein is predominantly nuclear, is a RNA binding protein, and it regulates transcript of CNS genes. One of the proteins which expression is positively regulated by TDP-43 is HDAC6 [Fiesel et al., 2010], and TDP-43 binds to HDAC6 mRNA in association with another ALS-associated gene product fused in sarcoma/translated in liposarcoma (FUS/TLS) [Kim et al., 2010]. Interestingly, TDP-43 expression increases Parkin mRNA and protein levels. The latter could mediate TDP-43 ubiquitination at Lys-48 and Lys-63 [Hebron et al., 2013]. Both TDP-43 and Parkin formed a protein complex with HDAC6 in the cytoplasm, which may mediate TDP-43 cytoplasmic translocation and retention. It therefore appears that HDAC6 interacts physically and functionally with multiple neurodegenerative disease gene products and modulates their pathology. HDAC6's role in this regard is apparently not limited to CNS neurons, as HDAC6 inhibitors also alleviates axonal transport defects induced by mutant 27-kDa small heat-shock protein gene (HSPB1) induced type II Charcot-Marie-Tooth disease (CMT) [d'Ydewalle et al., 2011], the latter a common multigenic inherited disorder of the peripheral nervous system [Vallat et al., 2013].

DOES HDAC6 HAVE A POSITIVE ROLE IN AXONAL REGENERATION?

HDAC6's implicated and complex role in neuroprotection and neurodegenerative disease is well known [d'Ydewalle et al., 2012]. In terms of neuritogenesis, centrosome-associated HDAC6 promotes ubiquitination of Cdc20, which stimulates the anaphase promoting complex/cyclosome (APC/C) in postmitotic neurons to drive dendritic outgrowth [Kim et al., 2009]. A role for HDAC6 in neuronal or axonal regeneration could also be speculated from its

enzymatic activity as a major tubulin deacetylase, and apparent effects of its manipulations on axonal transport. Superficial thoughts suggest that as tubulin deacetylation destabilizes microtubules, and microtubule stabilization is critical for formation of growth cone in lesioned axonal tips, HDAC6 activities in severed axons would inhibit regeneration, while HDAC6 inhibition would aid regeneration. These simple assumptions are indeed supported by the observations that HDAC6 is elevated by oxidative injury, and both HDAC6-silencing and specific pharmacological inhibition promoted neurite outgrowth [Rivieccio et al., 2009]. How does HDAC6 function in axonal transport, which is critical for neurite outgrowth, affects regeneration could be a more complicated issue. On one hand HDAC6 levels could be an important determinant that facilitate aggresome formation and clearance, on the other blockage of axonal transport resulting from pathological aggregates in multiple disease models have been shown to be alleviated by HDAC6 inhibition [Dompierre et al., 2007; d'Ydewalle et al., 2011; Kim et al., 2012].

Axonal regeneration, and for that matter neuritogenesis in general, is a process that requires extensive morphological changes which likely requires varying degrees microtubule deacetylation at some point in time. The binding of HDAC6 to the scaffolding septins, for example, could negatively regulate microtubule stability during axonal and dendritic outgrowth during development [Ageta-Ishihara et al., 2013]. It has in fact been reported that for culture hippocampal neurons, HDAC6 localizes to axons and it is distributed in the distal region of axons during axonal elongation [Tapia et al., 2010]. Both inhibition of HDAC6 activity or suppression of HDAC6 levels slows axonal growth, impairs the concentration of voltage gated sodium channels and ankyrin G at the axon initial segment [Bender and Trussell, 2012], as well as altering the distribution of the kinesin family motor protein, KIF5C along the polarized domains of the neuron. These results cautioned against ruling out a positive role for HDAC6 during axonal regeneration.

HDAC5's ROLE IN AXONAL REGENERATION

We now turn to HDAC5, which is a relatively new player recently found to play critical roles in axonal regeneration of peripheral nerves. HDAC5 is grouped under histone deacetylase class IIa. Its deletion does not critically affect mouse development, but HDAC5 deficient mice are sensitized to cardiac stress and develop profoundly enlarged hearts in response to pressure overload, a phenotype it shares with deficiency of HDAC9 [Chang et al., 2004]. Earlier work had implicated HDAC5 in mediating CREB2-dependent histone deacetylation that underlies long-term-memory-related synaptic plasticity in *Aplysia* [Guan et al., 2002]. In culture hippocampal neurons, HDAC5 is primarily nuclear but could translocate to the cytoplasm when the neurons are stimulated by calcium flux through synaptic NMDA receptors or L-type calcium channels [Chawla et al., 2003]. Its nuclear localization in neurons fits its role in mediating epigenetic changes that are associated with stress adaptation and cocaine addiction. Chronic exposure to cocaine or stress decreases HDAC5 activity in the nucleus accumbens (NAc), a major brain reward region, and this loss of HDAC5 causes hypersensitive responses to chronic cocaine or stress [Renthal et al., 2007]. In another recent report, it was shown that cocaine and cAMP signaling induce the transient nuclear accumulation of HDAC5 in rodent striatum. This nuclear import involves a protein phosphatase 2 A (PP2A)-dependent dephosphorylation of a Cdk5 phosphorylation site (S279) within the HDAC5 nuclear localization sequence. Dephosphorylation of HDAC5 S279 in the NAc could suppress the development of cocaine addiction in mice [Taniguchi et al., 2012].

With the above in mind, it may have come as a mild surprise when Cavalli and coworkers' elegant experiments first demonstrated a role for HDAC5 in axonal regeneration [Cho and Cavalli, 2012]. The authors found that injury to axons of peripheral (but not CNS) neurons (mouse sciatic nerves) generated a gradient of decrease microtubule acetylation and increase tyrosination, which indicates an increase in dynamic microtubules [Janke and Kneussel, 2010], proximal to the lesion tip. This increased deacetylation is blocked by the HDAC inhibitor scriptaid. Silencing of class I HDACs and HDAC4 did not attenuate deacetylation, whereas silencing of HDAC6 did. Surprisingly, silencing of HDAC5 had an even greater effect on tubulin deacetylation, as well as markedly suppressed axon regeneration and growth cone dynamics. The injury increased HDAC5 phosphorylation and a HDAC5 gradient, with its highest concentration at the lesioned tip, was observed. It appears that although acetylated tubulin is not a substrate of HDAC5 under basal conditions, phosphorylated HDAC5 could become a major mediator of tubulin deacetylation upon injury. HDAC5 phosphorylation was apparently induced by a calcium flux at the injury site, which generated a wave that travels back to the cell soma and initiated a wave of calcium mediated response, prominently protein kinase C (PKC) activation. PKC phosphorylation of HDAC5 have been previously associated with its translocation to the cytosol [Vega et al., 2004; Peng et al., 2009; Zhang et al., 2011]. PKC phosphorylated HDAC5 has apparently an increased tubulin deacetylase activity, as well as increased interaction with the anterograde microtubule motor protein kinesin 1 that would explain its accumulation at the lesion tip.

Is the above observation merely a reflection of a moonlighting function of nuclear HDAC5, whose main basal deacetylase activity must be on substrates in the nucleus? In follow up studies the same authors showed that in dorsal root ganglion (DRG) neurons, injury-induced calcium back-propagation activates PKCμ/PKD, which correlated with the latter's translocation from the cytoplasm to the nucleus [Cho et al., 2013]. PKCμ phosphorylation of HDAC5 promotes its nuclear-cytoplasmic translocation, and subsequent transport from the cell soma to the axon tip. Tubulin deacetylation aside, another consequence of HDAC5 nuclear exit is histone H3 acetylation. The authors found that HDAC5 nuclear exit is required for axonal regeneration, as mutant HDAC5 that is unable to exit the nucleus strongly suppressed axon regeneration. In HDAC5 knock-down cells which are also impaired in axonal regeneration, a cytosol-trapped mutant (but not the nuclear-trapped mutant) could rescue axon regrowth to control levels.

What exactly is the consequence of HDAC5 nuclear exit induced by axonal injury? Comparative transcript profiling of cells expressing the nuclear-trapped HDAC5 and control cells revealed

that a set of HDAC5-dependent genes that was differentially expressed upon injury. These genes include transcription factors such as c-Fos and c-Jun [Raivich et al., 2004; Fontana et al., 2012], and the Krueppel-like factors KLF4 and KLF5 [Qin et al., 2013] with known roles in neuronal regeneration, as well as the stress sensor growth arrest DNA damage-inducible (Gadd) 45a that is known to be up-regulated in nerve injury [Befort et al., 2003]. HDAC5 nuclear exit appears therefore to induce a gene expression profile that is presumably more pro-regenerative. The DRG neuron offers a model of injury preconditioning, where neurons exposed to a prior conditioning lesion would lead to an enhanced improvement in axon regeneration compared to that of a naive neuron [Smith and Skene, 1997; Neumann and Woolf, 1999]. Importantly, the authors found that promoting HDAC5 nuclear exit in vivo with a PKC activator generates a gene expression profile that partially mimics an injury preconditioning effect. HDAC5's response to axonal injury thus aid regeneration in two different modes. The first is localized tubulin deacetylation at the lesion tip, of which the exact effect on axonal regeneration is still not clear. The second is a more profound change in epigenetic modification and gene expression profile within the nucleus that collectively enhances the regenerative capacity of the injured neuron.

EPILOGUE

The paragraphs above provide a brief outline of the involvement of class II HDACs in neuronal regeneration. HDAC6 appears to be the predominant cytoplasmic HDAC that modulates basal microtubule dynamics by tubulin deacetylation. The complex effect of manipulation of HDAC6 activity in neuronal regeneration is discussed in light of what is known about the consequences of HDAC6 inhibition in several models of neurodegenerative diseases. HDAC6 may be important in toxic aggregate clearance via its ability to bind ubiquitinated proteins and modulation autophagy (Fig. 1), but on the other hand, inhibiting HDAC6 activity could stabilized microtubules and ease congested axonal transport. HDAC6 also appears to be important for axonal elongation during morphological development of hippocampal neurons in culture [Tapia et al., 2010], although its levels do not appear to change much upon injury to sciatic nerve [Cho and Cavalli, 2012]. The fact that HDAC knockout mice are viable and do not have gross nervous system abnormalities suggest that its role may be compensated for by other tubulin deacetylases. In pathological conditions when toxic aggregates accumulate, HDAC6 may at earlier stages be important for axonal aggregate clearance. However, at a later stage, its concomitant accumulation with ubiquitinated aggregates may destabilize microtubules and affect axonal transport—that's probably when inhibition of its deacetylase activity helps in preserving neuronal survival. It is clear that HDAC6 will likely influence axonal regeneration, but it is difficult at this point to surmise if the influence is critical, or indeed if it's positive or negative.

HDAC5, being mainly nuclear, likely has little or no role in modulating microtubule dynamics in neurons under basal conditions. However, upon injury to peripheral nerves, its PKC mediated phosphorylation and consequential export into the cytoplasm

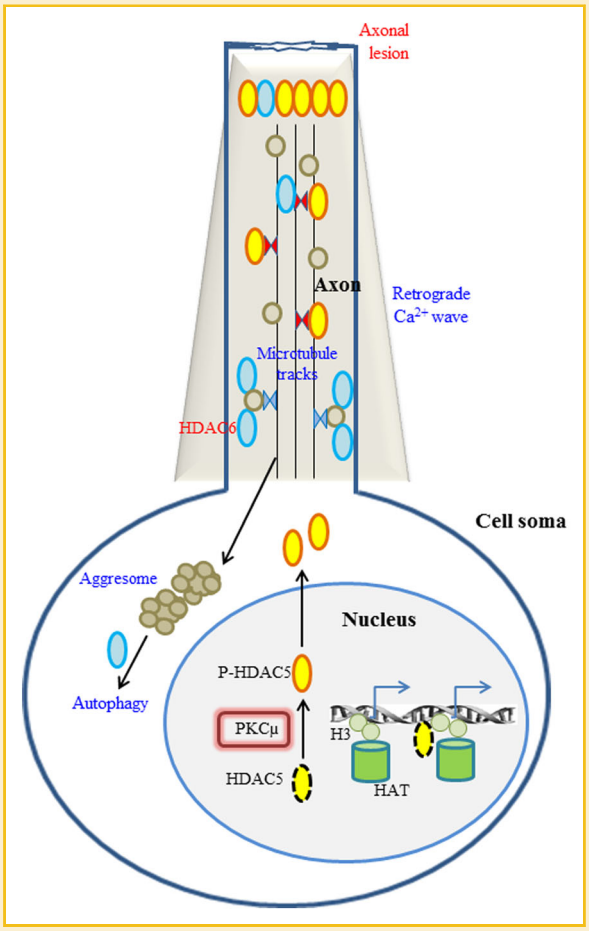

Fig. 1. A schematic diagram illustrating the possible role of class II HDACs during axonal injury. Axonal lesion impairs axonal traffic, and could result in the accumulation of axonal cargo. Cytoplasmic HDAC6 (blue oval) may facilitate transport of cargos and aggregates (gray circles) to aggresomes via dynein (blue triangle pairs), and regulates autophagy. It may thus play a beneficial early role in injured axon that is trafficking-impaired. However, its subsequent accumulation with ubiquitinated aggregates may destabilize microtubule through its deacetylase activity. Nuclear HDAC5 (yellow ovals) is phosphorylated by PKCμ, activated by the retrograde calcium flux from the site of injury to the cell soma. Phosphorylation of HDAC5 facilitates both its nuclear exit and engagement of kinesin, and is transported to the distal tip of the injured axon by kinesin motors (red triangle pairs). Its mode of action at the lesion site in facilitating regeneration is unclear.

induced a more persistent histone H3 acetylation that changes transcriptional profile of genes that are important in regeneration (Fig. 1). The exact consequence of HDAC5 nuclear exit may be context and cell type dependent. Other than PKC, calcium/calmodulin-dependent protein kinase II (CaMKII) could also phosphorylate HDAC5 and mediate its export in myocytes [McKinsey et al., 2000]. In cultured cerebellar granule neurons, CaMKII keeps HDAC5 in the cytoplasm, and HDAC5 nuclear translocation causes apoptosis of depolarization-deprived cerebellar granule neurons [Linseman et al., 2003]. On the other hand, it has been recently shown that prolonged genotoxic stress in some cancer cell lines also leads to HDAC5 nuclear exit, with consequential

increase in Lys 120 acetylation of p53 and selective transactivation of proapoptotic target genes [Sen et al., 2013]. The consequence of prolonged HDAC5 nuclear exit in peripheral nerves is not yet clear.

Once in the cytosol of the cell soma, phosphorylated HDAC5 appears to be able to engage kinesin and be transported in an anterograde manner to axonal tips. Although this accumulation of HDAC5 at the lesion tip appears important for axonal regeneration, exactly what it does to help axonal tip regrowth is unclear. Understanding of the roles for HDAC6 and HDAC5 at the injured axonal tip, and the balance of tubulin and actin dynamics in creating a functional growth cone, would be an important pursuit. Another, equally important point to investigate is why the HDAC5-mediated pro-regenerative mechanism is only operation in peripheral neurons, and if this could be harness or manipulated to aid regeneration of injured CNS axons.

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