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Acetylation Unleashes Protein Demons of Dementia

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Aberrant posttranslational modifications of proteins can impair synaptic plasticity and may render neurons vulnerable to degeneration during aging. In this issue of *Neuron*, Min et al. show that acetylation of the amino acid lysine in the microtubule-associated protein tau prevents its ubiquitin-mediated degradation, resulting in "tau tangles" similar to those of dementias. Other recent studies suggest that lysine hyperacetylation contributes to the accumulation of amyloid β-peptide in Alzheimer's disease and to impaired cognitive function resulting from a trophic factor deficit.

Learning and memory and associated forms of information processing involve complex neuronal networks distributed throughout the cerebral cortex, hippocampus, and associated structures. Research during the past century has elucidated fundamental requirements for normal cognitive function which include the following: a sufficient number of neurons with axons and dendritic arbors capable of both maintenance and modification of their structure; synapses that transmit electrochemical signals between neurons; and activity-dependent neurotrophic factor-mediated modification of neuroarchitecture and synaptic strength. The biochemical processes that control the structure and function of neuronal networks involve tightly controlled production, placement, and removal of proteins, as well as rapid modulation of protein functions (enzymatic activity, binding to other proteins, conformational change, etc.). In many cases, reversible posttranslational modification of one or more specific amino acids is the key to control of a protein's function. Thus, phosphorylation of serine, threonine, and/or tyrosine residues has been shown to regulate numerous proteins involved in learning and memory, including neurotransmitter receptors and associated proteins, ion channels, and synaptic vesicle-associated proteins (Wayman et al., 2008). In addition, a major mechanism for the removal of spent proteins involves ubiquitination on lysine, a diet-derived amino acid, which targets the protein for degradation in the proteasome (Yang and Seto, 2008). Scientists at the Gladstone Institute and the University of California at San Francisco now report that excessive acetylation of specific lysine residues in the tau protein prevents ubiquitination of those same lysine residues, thereby reducing the degradation of tau (Min et al., 2010). As a result, tau accumulates inside neurons in a manner similar to that seen in Alzheimer's disease (AD), frontotemporal dementia (FTD), and other "tauopathies."

The tau in neurons affected in AD is hyperphosphorylated on amino acids threonine 231 and threonine 181 (p-tau), which may result from increased activity of a protein kinase or decreased activity of a protein phosphatase (Goedert et al., 2006). However, the abnormal aggregation of tau in tauopathies is not readily explained by altered phosphorylation because p-tau is also present in robustly healthy neurons during brain development. Tau is believed to be ubiquitinated and degraded by the proteasome (Petrucelli et al., 2004) and impaired proteasome-mediated clearance of proteins is implicated in the pathogenesis of neurodegenerative disorders: α-synuclein in Parkinson's disease, huntingtin in Huntington's disease, and superoxide dismutase 1 in amyotrophic lateral sclerosis. Besides being ubiquitinated, lysine residues can be acetylated, a process regulated by lysine acetyltransferases and lysine deacetylases (Yang and Seto, 2008). Min et al. (2010) asked whether acetylation of tau might affect its clearance by the proteasome. They developed antibodies that only recognized tau when it was acetylated on specific lysines (163, 174, and 180); these antibodies allowed them to establish that tau acetylation is abnormally high in the brains of AD patients, even at an early stage of the disease. Further investigation in cultured cells revealed that lysine acetyltransferase p300 acetylated, whereas the lysine deacetylase SIRT1 deacetylated, tau at the designated sites. Next, it was shown that genetic deletion of SIRT1 increases tau acetylation in cultured neurons and in the brains of adult mice and that this resulted in the accumulation of p-tau (Figure 1). Additional evidence suggested that acetylation of tau inhibited its proteasomal degradation, apparently by preventing ubiquitination of the lysines. Finally, a small molecule inhibitor of p300 prevented the accumulation of p-tau in neurons, including the excessive p-tau resulting from a mutation that causes FTD (Min et al., 2010).

Intraneuronal accumulation of p-tau aggregates, including paired-helical filaments, is strongly correlated with cognitive performance in AD, FTD, and even normal aging (Stomrud et al., 2010), and studies of human tau transgenic mice have demonstrated that accumulation of p-tau is sufficient to cause cognitive impairment (Polydoro et al., 2009). A next step toward establishing the importance of tau acetylation state in dementias will be to determine if and how manipulations of tau acetylation affect synaptic plasticity and cognitive function. A recent study of mice lacking or overexpressing SIRT1 in their neurons provided evidence that SIRT1 is essential for hippocampal synaptic plasticity and learning and memory (Michán et al., 2010). However, because tau is only one of many different substrates for lysine acetyltransferases and deacetylases, inhibiting acetyltransferases or increasing the activity of SIRT1 alone cannot

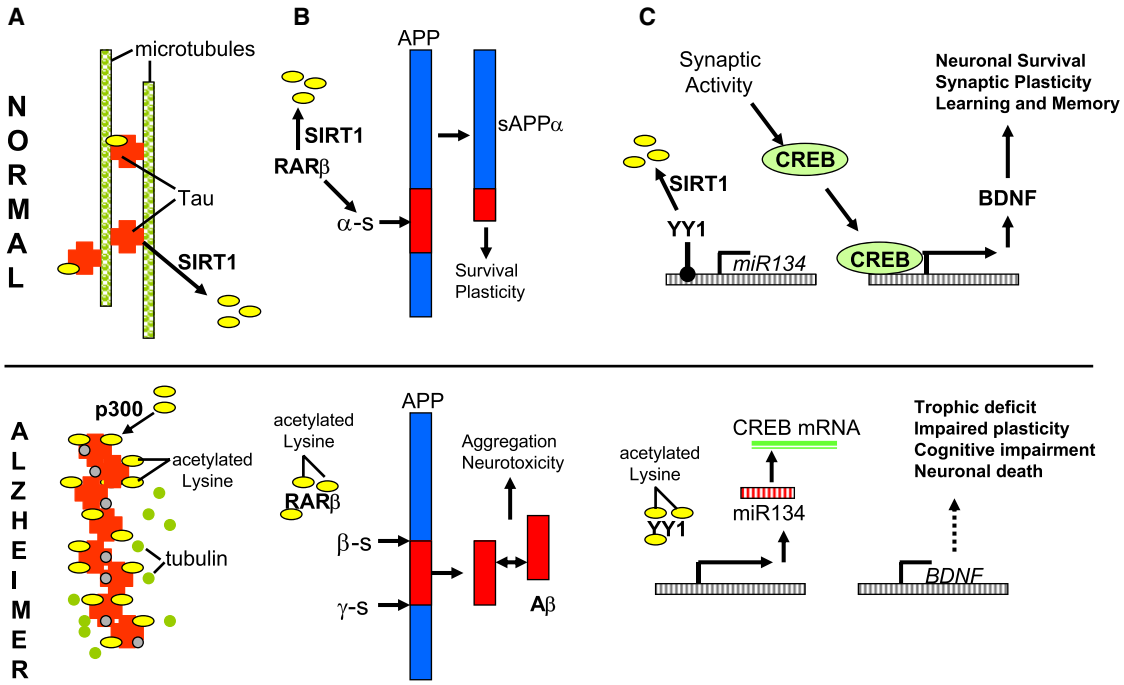

Figure 1. Hyperacetylation of Multiple Proteins Creates Havoc in Systems Regulating Neuronal Plasticity, Resulting in Pathological Accumulations of Tau and Aβ and Impaired Neurotrophic Signaling

(A) In neurons in neurologically normal individuals, tau is only lightly acetylated (yellow ovals represent acetyl groups) and interacts with microtubules in a dynamic manner to control their polymerization state, thereby enabling processes such as axonal transport and neurite outgrowth. In tauopathies, such as Alzheimers' disease (AD) and frontotemporal dementia (FTD), tau is excessively phosphorylated (gray circles) and acetylated (yellow ovals). The hyperphosphorylation of tau reduces its binding to microtubules, and hyperacetylation prevents ubiquitin-mediated proteolysis of p-tau, thereby promoting self-aggregation of tau. As a result, microtubules depolymerize and tau filaments accumulate inside neurons. Hyperacetylation of tau may result from decreased SIRT activity or increased activity of the lysine acetyltransferase p300.

(B) The β-amyloid precursor protein (APP), the source of amyloid β-peptide (Aβ, red), is cleaved in the middle of the Aβ sequence by an enzyme called α-secretase (α-s), resulting in the release of a secreted form of APP (sAPPα) from the cell surface. sAPPα modulates neuronal excitability and synaptic plasticity and promotes neuronal survival as well. The expression of α-s is induced by a transcription factor called retinoic acid receptor-β (RARβ), which is activated when it is deacetylated by the lysine deacetylase SIRT1. In AD, RARβ is hyperacetylated, resulting in reduced expression of α-s and alternative cleavage of APP by β-secretase (β-s) and γ-secretase (γ-s). In this way, excessive amounts of Aβ are produced, which then self-aggregates on the surface of neurons, resulting in their dysfunction and degeneration.

(C) In healthy individuals, activity in neuronal circuits results in the activation of the transcription factor CREB (cyclic AMP response element-binding protein), which induces the expression of brain-derived neurotrophic factor (BDNF). BDNF, in turn, activates signaling pathways, in the same neuron and synaptically connected neurons, that promote neuronal survival, synaptic plasticity and cognitive processing of information. The latter activity-dependent pathway is enabled by the transcriptional repressor YY1, which suppresses the expression of a micro RNA (miR134) that targets the CREB mRNA. The activity of YY1 is enhanced by SIRT1-mediated deacetylation. In neurodegenerative dementing disorders, YY1 may be hyperacetylated, resulting in derepression of miR134 expression, suppression of CREB translation, and reduction in BDNF expression.

establish which protein substrate(s) is critical for the observed phenotype. Substituting a different amino acid for a specific lysine residue in tau and other relevant proteins of interest is one approach that may help establish the relative contribution of tau acetylation to the pathogenesis of AD and other tauopathies.

Might protein acetylation also be involved in Aβ accumulation in the brain, the second major feature of AD? An answer to this question is provided by findings from a recent study showing that overexpression of SIRT1 in the brains of "AD mice" (mice that express AD-causing mutant forms of human APP and presenilin-1) reduces Aβ accumulation and, conversely, knocking out SIRT1 exacerbates Aβ accumulation (Donmez et al., 2010). Aβ is produced by sequential proteolytic cleavages of APP by β- and γ-secretases, with presenilin-1 being the enzymatic component of γ-secretase; another enzyme, α-secretase (ADAM10), cleaves APP in the middle of the Aβ sequence, thereby preventing Aβ production (Figure 1). It was previously demonstrated that overexpression of human SIRT1 in mice results in increased α-secretase activity levels (Qin et al., 2006). Donmez et al. (2010) found that SIRT1 induces the expression of ADAM10 by a mechanism involving deacetylation and activation of the retinoic acid receptor β (RARβ) (Figure 1). Reduction in α-secretase levels as a result of hyperacetylation of RARβ may, therefore, contribute to the pathological accumulation of Aβ and its destructive effects on neurons in AD.

The activity-dependent production of brain-derived neurotrophic factor (BDNF) is essential for synaptic plasticity and cognitive processes and also protects neurons against potentially damaging free radicals and excitotoxic and metabolic stress (Mattson et al., 2004). An intriguing role for protein acetylation

in the regulation of synaptic plasticity and memory via modulation of BDNF expression was recently described (Gao et al., 2010). Neural cell-specific SIRT1 deficiency results in impaired learning and memory in mice as a result of reduced expression of cyclic AMP response element-binding protein, a transcription factor that upregulates BDNF expression. SIRT1 deacetylates and activates the transcriptional repressor YY1, which then suppresses the expression of miR-134, a brain-specific micro RNA that selectively inhibits the production of CREB (Figure 1). The results (Gao et al., 2010) suggest a prominent, albeit circuitous role, for SIRT1 in the regulation of synaptic plasticity and memory. Although not addressed in the latter study, age- and disease-related deficits in BDNF expression and cognitive function might result from decrements in SIRT1 activity, such as those documented in brain aging and AD (Julien et al., 2009). Regulation of BDNF expression by SIRT1 also suggests potential roles for protein acetylation in the many processes in which BDNF is involved, including neurogenesis, brain injury responses and depression.

Why is it that protein acetylation in general, and SIRT1 in particular, seems to be so intimately involved in much of what goes wrong in neurodegenerative dementias? The negative impact of lysine acetylation on protein ubiquitination and degradation is one explanation of how a SIRT1 deficit and consequent hyperacetylation may cause the accumulation of tau (directly) and Aβ (indirectly via suppression of α-secretase expression). But the roles of SIRT1 in more fundamental aspects of aging provide additional clues; SIRT1 is an ortholog of SIR2, a deacetylase known to promote longevity in invertebrates. In rodents, SIRT1 mediates, at least in part, extension of lifespan and suppression of cancers and diabetes by dietary energy restriction. These effects of SIRT1 on aging involve deacetylation of several protein substrates, including PGC-1α and the tumor suppressor p53. Interestingly, dietary energy restriction has been shown to suppress Aβ and tau accumulation in mouse models of AD, which may be mediated, in part, by upregulation of α-secretase (Qin et al., 2006; Halagappa et al., 2007). Other studies have shown that energy restriction upregulates the expression of BDNF and PGC-1α, key regulators of cellular energy metabolism, oxidative stress, and inflammation in the brain (Martin et al., 2008; Arumugam et al., 2010). Thus, by deacetylating and activating proteins that regulate major cellular stress resistance pathways, and by promoting removal of potentially toxic proteins such as p-tau and Aβ, SIRT1 may protect neurons against the dark forces of aging and disease.

The recent flurry of information implicating different acetoproteins in the pathogenesis of dementias suggests the possibility of targeting specific lysine acetyltransferases and deacetylases in the development of novel therapeutic interventions. In this regard, much remains to be understood of how protein acetylation regulation goes awry and how it contributes to key events in neurodegenerative disorders. Which specific enzymes acetylate tau, APP-processing enzymes, YY1, and other proteins involved in the pathogenesis of AD? Does an increase in the level of such acetyltransferases increase in tauopathies? What of lysine deacetylases other than SIRT1—do they modify the acetylation state of proteins involved in neuronal plasticity and survival? Does the acetylation of specific lysines affect the phosphorylation state of nearby serine, threonine, or tyrosine residues in phosphoproteins involved in learning and memory? Inhibitors and activators of lysine deacetylases, and inhibitors of acetyltransferases should be vigorously pursued in translational research efforts to combat AD and FTD, diseases for which effective treatments are urgently needed.

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