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SIRT1: A Novel Way to Target Tau?

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Review of Min et al.

Tau is a microtubule-associated protein that forms pathogenic inclusions in several neurodegenerative diseases, including Alzheimer's disease (AD). Under physiological conditions, dynamic post-translational modifications of tau regulate cytoskeletal stability. Under pathological conditions, tau undergoes numerous post-translational modifications that may precede aggregation, including hyperphosphorylation, truncation, and abnormal acetylation. Neurofibrillary tangles (NFTs) are intraneuronal inclusions of tau aggregated into an amyloid structure and are one of the main histopathological characteristics of AD. Importantly, the density of NFTs in the AD brain is correlated with neuronal death and cognitive decline in the disease (Iqbal et al., 2016). Although the precise mechanisms of initial tau seeding into an amyloid structure are unknown, aggregated tau fibrils can conformationally template soluble tau and therefore "propagate" tau aggregation throughout the brain via anatomically connected pathways (Ayers et al., 2018). This spreading of pathological tau throughout the AD brain is thought to be important in disease progression (Goedert and Spillantini, 2017), and therapeutics that can halt this propagation or target NFTs might therefore be useful to treat AD and other tauopathies (Golde et al., 2010).

Much evidence indicates that acetylation of tau increases its propensity to aggregate, influences other post-translational modifications, and can reduce degradation of phosphorylated tau (Min et al., 2010; Cook et al., 2014b). In addition, tau acetylation promotes the seeding of tau *in vitro* and may contribute to tau propagation (Trzeciakiewicz et al., 2017). Studies of human AD brain found colocalization of tau acetylated on lysine residue 280 (K280) with phosphorylated tau in NFTs. Increased amounts of acetylated K280-positive NFTs were directly associated with more advanced AD stage (Irwin et al., 2012). Together, these data suggest that promoting tau deacetylation might be an effective strategy for inhibiting tau aggregation and propagation in tauopathies. However, acetylation on four residues in the microtubule binding domain of tau (Lysines 259, 290, 321, and 353) has been found to inhibit aggregation, possibly by preventing phosphorylation at these sites (Cook et al., 2014a). Therefore, any viable therapeutic approach will need to deacetylate tau preferentially at the residues (K280 and K174) that promote aggregation (Min et al., 2015).

When considering possible therapeutic strategies that target tau acetylation, the most logical direct approaches would be through inhibition of tau acetylation or by promotion of tau deacetylation (Cook et al., 2014b). One way to increase tau deacetylation is by targeting sirtuins. Sirtuins are a class of deacetylases that have widespread effects on cellular physiology through deacetylation of histones and other proteins. Sirtuin 1 (SIRT1) can deacetylate tau; and notably, its levels are reduced in AD brain tissue, with levels progressively decreasing as the disease advances (Julien et al., 2009; Jęśko et al., 2017). SIRT1 can deacetylate tau residues 160–182 and 264–287 *in vitro* (Min et al., 2010). In addition, SIRT1 deacetylates components of the autophagy pathway and inhibits mammalian target of rapamycin signaling, both of which could lead to increased breakdown of intracellular aggregates, such as tau (Ng and Tang, 2013).

In an article recently published in *The Journal of Neuroscience*, Min et al. (2018) confirmed that SIRT1 deacetylates tau at several residues *in vitro* as reported previously. In addition, the authors use the PS19 mouse model of tauopathy that overexpresses a human tau variant that contains a serine residue instead of a proline at amino acid 301 (P301S) and is associated with frontotemporal dementia with parkinsonism, a primary tauopathy (Sperfeld et al., 1999; Yoshiyama et al., 2007). The authors generated a line of these transgenic tau mice with brain-specific deletion of the SIRT1 gene to investigate the absence of SIRT1 on tau acetylation and disease progression *in vivo*.

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Brain-specific deletion of SIRT1 increased acetylation of tau at K174 *in vivo*. In addition, SIRT1 deletion modestly reduced synaptophysin levels, which is suggestive of reduced synaptic connectivity, a feature of AD (Spires-Jones and Hyman, 2014). Reduction of SIRT1 also led to increased amounts of total tau and acetylated tau at the postsynaptic compartment; increased synaptic tau has been shown to contribute to tau propagation in AD (DeVos et al., 2018). Lastly, brain SIRT1 deletion increased the mortality rate in PS19 mice, suggesting that reduction of SIRT1 in the setting of tauopathy is detrimental to survival.

The authors went on to investigate the effects of SIRT1 on the propagation of tau aggregates. To do so, they injected tau fibrils into the hippocampus on one side of the brain and virally expressed SIRT1 in the contralateral hippocampus via injection of recombinant adeno-associated virus. SIRT1 overexpression reduced the spread of tau aggregates across the midline, reducing tau staining by 50%. This result is somewhat surprising given that their previous experiment showed that SIRT1 deletion in the PS19 model did not affect the overall levels of tau aggregation. This discrepancy could be attributed to recent findings that show the PS19 mouse model can display widespread variability in tau aggregation and neurodegeneration (Woerman et al., 2017). Alternatively, this finding may indicate that tau acetylation is more relevant to tau propagation than to aggregation.

Finally, Min et al. (2018) showed that brain-specific deletion of SIRT1 had deleterious effects on learning in both nontransgenic and tau transgenic mice, indicating that SIRT1 is important for normal cognition. This is not wholly surprising, as SIRT1 affects numerous pathways other than tau deacetylation. Most importantly, as a histone deacetylase, SIRT1 regulates DNA coiling and genomewide transcriptional activity. Reported effects of SIRT1 on normal cellular physiology include upregulation of mitochondrial transcriptional programs that prevent oxidative stress via increased mitogenesis. In addition, SIRT1 can increase neurotrophic signals, such as BDNF (Jęśko et al., 2017). In this paper, SIRT1 deletion negatively impacted longevity and learning ability, suggesting that decreasing SIRT1 expression (such as that observed in AD brain) may be deleterious. Indeed, due to the extensive influences of SIRT1 on cellular physiology, it would be necessary to establish that SIRT1 overexpression will not dysregulate normal brain function if one were to propose it as a potential therapeutic.

Similar to the pleotropic effects that SIRT1 has on normal cellular processes, SIRT1 can affect tau through several pathways, including regulation of autophagy (Ng and Tang, 2013), by promoting proteasomal degradation, through posttranslational modifications and at a transcriptional level. SIRT1 inhibits mammalian target of rapamycin signaling and thereby enhances the autophagy system; stimulation of autophagy has been proposed as a potential therapeutic strategy across neurodegenerative diseases, as nearly all of the pertinent protein aggregates, including tau, can be degraded via autophagy pathways (Menzies et al., 2017). SIRT1 can promote proteasomal degradation of tau via deacetylation, which increases available sites for the ubiquitination of tau and therefore increases targeting of tau to the proteasome (Min et al., 2010). SIRT1 overexpression can also reduce tau phosphorylation (Corpas et al., 2017), and SIRT1 deletion increases tau phosphorylation (Min et al., 2010). There is a tremendous amount of evidence supporting the dephosphorylation of tau as a therapeutic strategy in AD, and SIRT1 overexpression could target tau in this manner. It should also be discussed that human tau undergoes alternative splicing to produce six distinct isoforms, containing either three (3R) or four (4R) microtubule binding domains due to exclusion or inclusion of exon 10, respectively. Increased 4R tau can increase tau phosphorylation and aggregation, and SIRT1 activity can drive exclusion of exon 10 during tau splicing (Yin et al., 2018). This is an alternative mechanism through which SIRT1 affects tau at a transcriptional level and is unique to previously proposed mechanisms that act at a protein level. In summary, these are all potential mechanisms where SIRT1 overexpression could beneficially affect tau aggregation, degradation, and propagation in AD.

In conclusion, this work by Min et al. (2018) contributes to a nascent field investigating whether SIRT1 activation or overexpression could be beneficial in tauopathies. Moving forward, as neurodegeneration is a key feature of AD, it will be valuable to determine whether tau acetylation impacts neuronal loss and whether SIRT1 overexpression is able to prevent neurotoxicity. Further experiments should also determine which of the mechanisms discussed enables SIRT1 overexpression to prevent tau propagation. While there are always concerns about off-target effects caused by overexpression of a protein with wide-ranging functions such as SIRT1, it has been previously reported that hippocampal overexpression of SIRT1 via lentiviral transduction had positive or nondeleterious effects on cognition, anxiety, locomotor activity, and memory in 10-month-old nontransgenic and 3xTg-AD mice (Corpas et al., 2017). Together, these data warrant further exploration of SIRT1 overexpression as a therapeutic strategy in AD.

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