Nature Reviews Molecular Cell Biology | Published online 21 Mar 2017; doi:10.1038/nrm.2017.24

PROTEIN METABOLISM

Counteracting toxic protein aggregation

Sirtuin (SIRT) proteins are deacylases with important roles in ageing. For example, SIRT2 has been shown to modulate, through a poorly understood mechanism, the aggregation and toxicity of α-synuclein (α-syn), which is associated with neurodegenerative disorders such as Parkinson disease. Outeiro and colleagues now reveal that SIRT2 deacetylates α-syn at two amino-terminal Lys residues, thereby favouring α-syn aggregation.

The authors first showed that SIRT2 directly interacts with α-syn when the two proteins were co-expressed in cultured human cells, and, in a more physiologically relevant context, by co-immunoprecipating α-syn with SIRT2 from mouse brain extracts. Moreover, α-syn was deacetylated by SIRT2 at Lys6 and Lys10. Consistent with this finding, acetylation of α-syn does not decrease when immunoprecipitation assays are performed with an inactive SIRT2 mutant, and α-syn is hyperacetylated in the brains of *Sirt2* knockout mice.

> “SIRT2-mediated deacetylation of α-syn promotes toxic protein aggregation”

To assess whether SIRT2-dependent deacetylation influences the aggregation of α-syn, SIRT2 levels were reduced by RNAi in a cellular model of Parkinson disease in which α-syn has a high propensity for aggregation. Remarkably, this resulted in fewer α-syn inclusions, increased solubility and reduced size of α-syn-containing protein aggregates. Furthermore, mutating Lys6 and Lys10 to create α-syn mutants that either mimic constitutive acetylation or are acetylation-resistant, showed that acetylation at these residues prevents aggregation.

The authors further investigated the cellular and physiological impact of SIRT2-mediated deacetylation of α-syn. They found that SIRT2 knockdown decreased the cytotoxicity of the protein inclusions, as indicated by a reduction in the amount of lactate dehydrogenase released from cells. Also, interestingly, although the basal level of autophagy was unaffected by SIRT2knockdown, in the presence of α-syn aggregates, SIRT2 knockdown potentiated autophagy to efficiently clear the aggregates. Last, expression of acetylation-resistant or acetylation-mimic α-syn mutants in cultured neurons and *in vivo* (in the rat substantia nigra) showed that lower levels of α-syn acetylation induce neuronal loss.

Together, these results indicate that SIRT2-mediated deacetylation of α-syn promotes toxic protein aggregation, and suggest that the inhibition of SIRT2 activity could be a potential therapeutic avenue for the treatment of neurodegenerative diseases.

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ORIGINAL ARTICLE de Oliveira, R. M. *et al.* The mechanisms of sirtuin 2-mediated exacerbation of alpha-synuclein toxicity in models of Parkinson disease. *PLOS Biol.* **15**, e2000374 (2017)
FURTHER READING Bonkowski, M. S. & Sinclair, D. A. Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds. *Nat. Rev. Mol. Cell Biol.* **17**, 679–690 (2016)

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