Nature Reviews Neuroscience | AOP, published online 3 April 2014; doi:10.1038/nrn3728

NEURODEGENERATION

Ageing neurons need REST

Individuals who develop Alzheimer's disease typically exhibit neuronal loss in the hippocampus and cortex. In the healthy ageing brain, both of these neuronal populations are preserved, but little is known about the mechanisms that protect neurons against stress and toxic insults. Yankner and colleagues now show that the transcriptional repressor REST (RE1-silencing transcription factor) has a crucial role in neuroprotection during ageing.

The authors carried out a bioinformatic analysis of previous transcriptional profiling studies of the ageing brain, which suggested that REST activation may underlie changes in gene expression during ageing. To explore this possibility, they examined post-mortem samples of the prefrontal cortex (PFC) from young adult and aged individuals. They found that ageing is associated with a significant induction of REST in neuronal nuclei together with increased REST binding to target genes. By contrast, nuclear REST expression was substantially reduced in individuals with mild cognitive impairment (MCI) and almost absent in those with Alzheimer's disease. Furthermore, REST levels closely correlated with cognitive function scores derived from longitudinal neuropsychometric testing.

These findings suggest that deregulation of genes targeted by REST might occur in Alzheimer's disease. To determine which genes are involved, the authors carried out chromatin immunoprecipitation and deep sequencing on a neural cell line and confirmed the results in neuronal nuclei isolated from the human PFC. This showed that REST regulates many genes associated with cell death pathways and Alzheimer's disease pathogenesis. Analysis of human brain samples demonstrated reduced REST binding and increased expression of many of these genes in individuals with Alzheimer's disease.

> "nuclear REST expression was substantially reduced in individuals with mild cognitive impairment (MCI) and almost absent in those with Alzheimer's disease"

The repression of cell death-associated genes suggests that REST might be neuroprotective. Indeed, the authors found that neuronal cultures derived from conditional knockout mice lacking REST were more vulnerable than control cultures to degeneration and cell death induced by oxidative stress or incubation with toxic oligomers of amyloid-β (Aβ). Furthermore, mice lacking REST exhibited progressive neurodegeneration, including neuronal loss in the hippocampus and cortex.

What are the mechanisms by which REST is boosted in the healthy ageing brain? The authors demonstrated the induction of REST in primary cultures of cortical neurons exposed to various stressors associated with ageing. REST was also induced in a neural cell line exposed to the medium in which the 'stressed' neurons had been cultured or to extracts of aged human brain, suggesting that a cell-non-autonomous pathway is involved. Further experiments showed that enhancing signalling through the WNT–β-catenin pathway induced REST and that β-catenin levels were increased in the aged PFC and colocalized in the nucleus with REST, suggesting that this pathway contributes to the induction of REST in the ageing brain.

These findings suggest that loss of neuroprotective nuclear REST contributes to neuronal cell death in Alzheimer's disease, prompting the authors to consider the mechanisms underlying this loss. Dysregulation of autophagy, a process that can sequester proteins in the cytoplasm, occurs in several neurodegenerative diseases, and the authors showed that REST is present in autophagosomes together with misfolded proteins such as Aβ, tau and α-synuclein in several neurodegenerative disorders. Moreover, activating autophagy in cultured neural cells reduced nuclear REST levels and resulted in REST appearing in autophagosomes.

This study shows that REST induction in the ageing brain is a crucial neuroprotective factor and suggests that boosting this response might provide a strategy to combat age-related neurodegenerative disease, especially Alzheimer's disease.

Katherine Whalley

ORIGINAL RESEARCH PAPER Lu, T. *et al.* REST and stress resistance in ageing and Alzheimer's disease. *Nature* http://dx.doi.org/10.1038/nature13163 (2014)