NEURODEGENERATIVE DISORDERS

A neuroprotective role for α-synuclein

A central role for α-synuclein in neurodegenerative conditions has long been apparent: mutations or triplication of the gene cause severe Parkinson's disease, and inclusion bodies containing the protein are found in Parkinson's disease, Alzheimer's disease and other neurodegenerative 'synucleinopathies'. However, despite its involvement in pathology, the normal physiological function of α-synuclein, which is enriched in presynaptic nerve terminals, has remained an enigma. New work from the laboratory of Thomas Sudhof reveals an unexpected neuroprotective role for α-synuclein in a progressive neurodegenerative mouse model caused by deletion of cysteine-string protein-α (CSPα).

CSPα is a molecular chaperone, abundant at presynaptic nerve terminals, deletion of which results in early-onset neurodegeneration and lethality in mice by 1–4 months of age. Similarly, overexpression of human α-synuclein leads to a progressive, but late-onset, neurodegenerative phenotype. Intrigued by an apparent overlap in the localization of α-synuclein and CSPα, and a possible complementarity of their functions, Chandra and colleagues investigated the relationship between the neurodegenerative phenotypes associated with each protein, crossing transgenic α-synuclein mice with CSPα-knockout mice.

Interestingly, expression of the α-synuclein transgene abrogated the lethality and neurodegeneration caused by the CSPα knockout. Moreover, the weight loss, gliosis, and progressive loss of muscle strength and muscle coordination observed in CSPα-knockout mice were abolished by expression of human or mouse wild-type α-synuclein, or A53T mutant human α-synuclein. However, A30P mutant human α-synuclein, which has a much reduced ability to bind phospholipids, was unable to rescue the CSPα-knockout phenotype, suggesting that attachment of α-synuclein to synaptic vesicles is essential for its neuroprotective function. Impaired SNARE complex assembly observed in CSPα-knockout mice was also rescued by wild-type or A53T α-synuclein, but, again, no protection was observed with A30P α-synuclein.

Given the apparent neuroprotection provided by exogenous overexpression of α-synuclein in this model, Chandra and co-workers investigated the possibility that endogenous synucleins might partially protect against an even more severe phenotype. In support of this scenario, α/β-synuclein double knockout, which alone exhibits no phenotype, resulted in exacerbation of the CSPα-knockout phenotype, accelerating lethality and neurodegeneration. An intermediate phenotype was observed in mice lacking CSPα and α-synuclein, which indicates some redundancy between synuclein isoforms.

Differences in the cell-specific expression patterns of α-synuclein and CSPα revealed that α-synuclein is protective only of neurons in which it is expressed: photoreceptor cells lacking transgene expression degenerate in CSPα-knockout mice, and 'rescued' mice show deficits in tests requiring normal eyesight. No physical interaction could be observed between α-synuclein and either CSPα or its binding partners, nor was α-synuclein able to substitute for CSPα in stimulating heat shock cognate 70 (HSC70) ATPase activity, suggesting that α-synuclein acts through a mechanism downstream of CSPα to protect against the consequences of its absence, rather than merely substituting for loss of CSPα function. Furthermore, the neuroprotective capability of α-synuclein was specific to the deficits induced by CSPα knockout, as no rescue was seen in a separate (mutant superoxide dismutase) model of neurodegeneration.

Although the significance of these findings to patients with Parkinson's disease are not yet clear, and further dissection of the molecular mechanisms involved in synuclein-induced neuroprotection will certainly be required, knowledge of the physiological role of α-synuclein will provide a much-needed insight into its parallel pathogenic role.

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ORIGINAL RESEARCH PAPER Chandra S. *et al.* α-Synuclein cooperates with CSPα in preventing neurodegeneration. *Cell* **123**, 383–396 (2005)