MECHANISMS OF DISEASES

Excessive polyQ tracts curb autophagy

An increase in the number of Gln repeats (known as polyglutamine (polyQ) tracts) in nine different human proteins leads to their aggregation, which has been associated with several neurodegenerative diseases. Ashkenazi *et al.* now show that — when soluble — polyQ tracts regulate autophagy.

Autophagy is a process of cellular self-consumption that is stimulated by energy deprivation and other stresses, whereby cellular components are targeted to autophagosomes and eventually degraded in the lysosome. The authors studied the wild-type polyQ-containing protein ataxin 3 and found that its knockdown in mouse primary neurons or HeLa cells impaired autophagosome biogenesis. This was further associated with a decrease in the levels of the beclin 1 protein, which is an important regulator of autophagosome formation.

As ataxin 3 is a protein deubiquitylase, this raised the possibility that ataxin 3 suppresses the ubiquitylation and subsequent proteasomal degradation of beclin 1. Indeed, beclin 1 levels were restored following proteasome inhibition or when wild-type, but not deubiquitylation-deficient, ataxin 3 was re-expressed in ataxin 3-deficient cells.

Ataxin 3 was found to bind to beclin 1, and deletion of the wild-type polyQ domain in ataxin 3 considerably reduced this interaction. Interestingly, other polypeptides with polyQ tracts were also able to bind to beclin 1, with longer tracts conferring stronger binding. This suggested that polyQ tracts in other proteins compete with wild-type ataxin 3 for binding to beclin 1, and that an excess of polyQ tracts could interfere with the ataxin 3–beclin 1 interaction. Indeed, introducing additional polyQ tracts — either by ectopically expressing polyQ-containing polypeptides or by introducing disease-associated polyQ protein mutants that contain polyQ expansions — decreased beclin 1 levels and interfered with autophagosome formation. These effects were observed in the absence of polyQ aggregates.

In summary, soluble, expanded polyQ tracts increase proteasomal degradation of beclin 1 by interfering with deubiquitylation of this important regulator of autophagosome biogenesis. As autophagy is involved in the removal of toxic polyQ aggregates, this finding indicates that polyQ tract expansions may further contribute to the pathology of neurodegeneration by impairing autophagy.

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