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CELL BIOLOGY OF THE NEURON

Lightening the load

Removing dysfunctional mitochondria and neurotoxic protein aggregates is crucial for neuronal homeostasis, and failure to do so may contribute to neurodegeneration. Driscoll and colleagues now report a new mechanism for the clearing of aggregated proteins and mitochondria from adult neurons in *Caenorhabditis elegans*.

The authors studied the six gentle-touch-responsive neurons in adult *C. elegans*. Expression of the fluorescent, aggregable marker mCherry in these neurons resulted in large (~4 μm), membrane-bound vesicles containing aggregated mCherry extruding from the soma of these cells. The authors termed these vesicles exophers and saw that they were also produced by other *C. elegans* neurons, to varying degrees. Initially, exophers remain attached to the neuronal soma by a thin tube but eventually fully detached.

As aggregated mCherry seemed to be more concentrated inside the exophers than in the soma after exopher production, the authors asked whether aggregable or neurotoxic proteins might be preferentially sequestered into these extrusions. Indeed, neurons expressing a neurotoxic, aggregable variant of huntingtin (Q128) produced more exophers than did neurons expressing a non-neurotoxic, non-aggregable form of huntingtin. In mCherry-expressing worms, RNAi-mediated knockdown of mCherry expression approximately halved the number of neuronal exophers produced. Furthermore, exophers formed from neurons expressing both mCherry and non-aggregating green fluorescent protein (GFP) showed higher mCherry red fluorescence than green fluorescence. These data suggest that exophers preferentially export aggregable and/or neurotoxic proteins.

The authors next asked whether exophers might represent a new mechanism for restoring proteostasis after proteostatic challenge. Consistent with this hypothesis, exopher production was increased by a deficiency in chaperone expression or following pharmacological inhibition of autophagy. Moreover, Q128-expressing worms that extruded exophers from the touch-responsive ALMR neuron on adult day 2 showed better touch sensitivity 2 days later compared with their siblings that did not form ALMR neuron-derived exophers, indicating that exophergenesis may be beneficial for the function of proteotoxically stressed neurons.

The authors reasoned that, given their large size, exophers might also be well suited to export organelles. Indeed, fluorescent labelling revealed that these vesicles can contain lysosomes and mitochondria, and genetic or pharmacological manipulations that decreased mitochondrial quality (for example, deletion of the *C. elegans* homologues of the genes encoding PINK1 and parkin) increased exophergenesis. Thus, exophers could be a means of removing dysfunctional mitochondria from the neuron.

What happens to extruded exophers? The authors noted that the fluorescence of these vesicles declined over the course of 1–12 hours after detachment from the neuron, suggesting that they either degrade their contents internally or are digested by other cells. Global genetic disruption of an engulfment pathway increased the detection of multiple exophers, and mCherry expressed specifically in touch neurons was observed later in scavenging cells, known as coelomocytes, distant from the neurons, suggesting that exophers or their contents may be engulfed by other cells.

This study identifies a novel potential mechanism for maintaining neuronal homeostasis in response to proteostatic challenge or mitochondrial dysfunction. The authors propose that an analogous process in mammals might play a part in neurodegenerative diseases.

Natasha Bray

> “exophergenesis may be beneficial for the function of proteotoxically stressed neurons”

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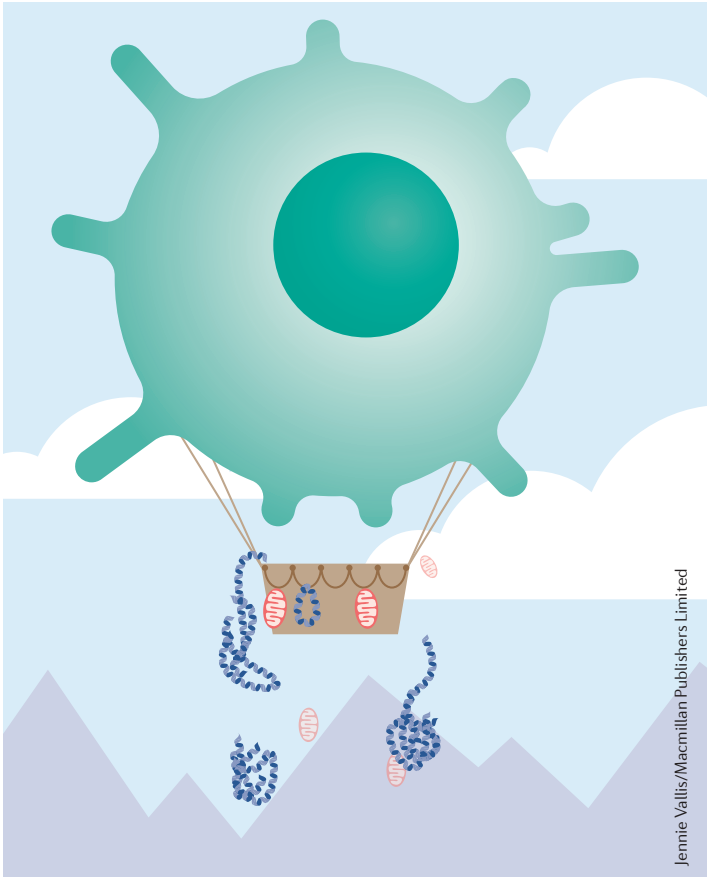

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