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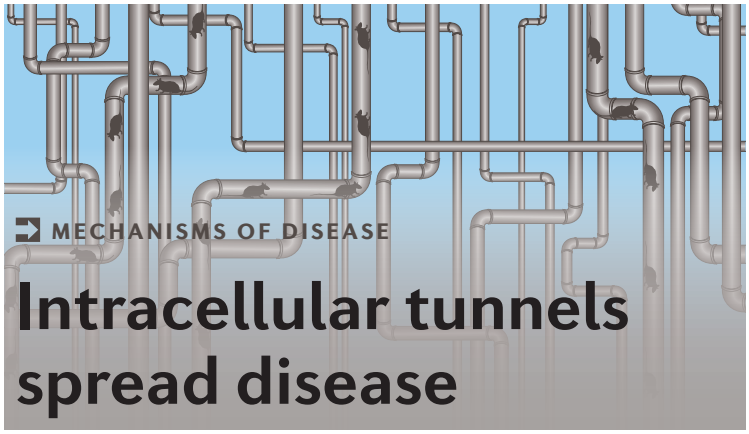

Vicky summersby/NPG

Intracellular tunnels spread disease

Synucleinopathies such as Parkinson disease are caused by the aggregation of fibrillar α-synuclein into intraneuronal inclusions, which spread through the brain in a manner that is indicative of intracellular propagation. This study details the involvement of intracellular trafficking of lysosomes through tunnelling nanotubes (TNTs) as the mechanism by which fibrillar α-synuclein spreads between neurons.

When donor mouse catecholaminergic neuron-like cells (known as CAD cells) pre-loaded with α-synuclein fibrils were co-cultured with naive acceptor CAD cells, 100% of the acceptor cells contained fibrillar α-synuclein after 24 hours, with an average of 38 α-synuclein puncta per acceptor cell compared with 70 puncta per donor cell. Thus, cell-to-cell transfer of α-synuclein is highly efficient. In line with previous studies, transferred α-synuclein fibrils were shown to recruit and aggregate soluble α-synuclein in acceptor cells.

A potential mechanism of α-synuclein fibril spreading between cells could involve exo- and endocytosis. However, overexpression of a dominant-negative mutant of dynamin 1, which is essential for endocytosis of α-synuclein (and other particles) from the medium, did not affect fibril transfer from donor to acceptor cells. Furthermore, the conditioned medium of donor cells did not efficiently transfer α-synuclein to acceptor cells, and transfer was also markedly reduced when donor and acceptor cells were separated by filters. These data indicate that intercellular transfer occurs directly through cell–cell contact, so the authors focused their attention on TNTs, which are membranous bridges that connect the cytoplasm of remote cells.

> “cell-to-cell transfer of α-synuclein is highly efficient”

CAD cells loaded with α-synuclein formed 20% more TNTs than control cells, and in co-culture experiments, α-synuclein fibrils were visualized inside TNTs directly connecting donor and acceptor cells. Overexpression of myosin 10, which increases TNT formation, promoted α-synuclein transfer, whereas impairing TNT formation by co-culturing cells in sparse conditions decreased it. Finally, within the TNTs and in acceptor cells, the majority of α-synuclein fibrils were found in lysosomal vesicles of donor origin.

In summary, these new data, which were confirmed in primary cortical neurons, show that α-synuclein fibrils spread directly between neuronal cells and that TNTs might be of particular importance in the propagation of toxic proteins underlying the pathology associated with neurodegenerative diseases.

Kirsty Minton

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