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Editorial

Lysosomal-endolysosomal dysfunction and neurodegenerative diseases

The endolysosomal system is vital for the function and survival of neurons, mediating local trafficking in synapses and dendrites, while also communicating with the soma to integrate signalling pathways and the turnover of organelles and macromolecules originating in these distinct and distant compartments.

Several neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are characterised by the accumulation, misfolding and mislocalisation of proteins. Genetic studies, the dissection of biochemical pathways and rapidly evolving techniques for live cell imaging are increasingly implicating deficits in the endolysosomal system in the pathogenesis of these diseases.

In this special issue Cai and Ganesan review macroautophagy in neurons. In particular the formation of autophagosomes in distal axons and synapses and their retrograde transport back to the soma for fusion with lysosomes and how this is impaired in AD, PD and ALS.

Multivesicular bodies are formed from early endosomes by inward budding of the limiting membrane into the lumen. These intralumenal vesicles can fuse with the plasma membrane and be released as small extracellular vesicles known as exosomes. Izco *et al* detail the formation of exosomes and how they can be loaded with disease related proteins such as α-synuclein and Tau, miRNA and inflammatory molecules and the implications this has for the spread of pathology in PD and AD brains. These phenomena are not only confined to neurons, and the role of glia in exosome-mediated exacerbation of disease in animal models is also discussed.

Endosomes play a key role in the sorting of endocytosed material from the plasma membrane, recycling receptors and other cargo back to the plasma membrane or trafficking them onwards to other organelles in the soma. Moya-Alvarado *et al* review the role of Rab5 and Rab11 GTPases on recycling and signalling endosomes in mediating the intracellular signalling pathways initiated upon binding of neurotrophic receptors such as TrkB by BDNF at synapses and dendrites. The effects on neuronal plasticity, both immediately at a local level, but also the initiation of nuclear signalling pathways back in the soma, are discussed.

Evidence for dysfunction of the endolysosomal system playing a central role in disease pathogenesis is strongest in PD. Impairment in autophagy and lysosomal function have been reported in sporadic PD brains. This has been strengthened by several genes that cause familial PD, such as *LRRK2*, *ATP13A2*, *VPS35*, and *VPS13C* encoding proteins involved in the endolysosomal system. Furthermore, variants in the *GBA1* gene are the most important genetic risk factor for PD accounting for 10–15% of cases, while more recent PD genome-wide association studies have further implicated many more genes encoding endolysosomal proteins. As detailed by the last three papers in this special issue it is becoming increasingly evident that several of these proteins can affect the function of other PD associated proteins and are also highly expressed in glia.

Williams et al. focus on the function of VPS35 in the retromer complex, which helps facilitate the trafficking of transmembrane protein cargo from endosomes back to the trans-Golgi network or recycling to the plasma membrane. Dysfunctional VPS35 has been implicated in inhibition of autophagy, mitochondrial dysfunction and impaired trafficking of neurotransmitter and cell survival receptors: all likely to contribute to neurodegeneration. In addition to links with PD, retromer proteins and cargo are also decreased in AD, tauopathies and ALS. VPS35 can also hyperactivate LRRK2, increasing kinase activity.

LRRK2 is known to be recruited to damaged lysosomes phosphorylating Rab10 and Rab35, which then recruit the effector protein JIP4, resulting in tubulation and sorting of lysosome membranes. Kluss *et al* present new data showing that recruitment of LRRK2 to other membranes of the endolysosomal system, including recycling, early and late endosomes, leads to the phosphorylation of Rab10 and Rab12 and subsequent recruitment of JIP4. In their cell models this also applied to the plasma membrane and the Golgi, and did not require the presence of Rab29, nominated as a protein required to activate LRRK2 upon recruitment to membranes.

Gegg *et al* review the clinical and biochemical pathways in *GBA1*-PD, including the bi-directional relationship between glucocerebrosidase (GCase) and α-synuclein metabolism in neurons and glia, and the emerging interaction between GCase and LRRK2. Since *GBA1* variants account for 15% of PD cases and loss of GCase activity also occurs in sporadic PD brains, there is considerable interest in developing drugs to increase GCase activity. The different therapeutic strategies being pursued are also discussed.

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