Dysfunction of the Lysosome and Neurodegenerative Disorders

Jackson High*

Division of Neurology, Faculty of Medicine, Gale Hospital, Canada

*Corresponding Author**
Jackson High
Division of Neurology
Faculty of Medicine, Gale Hospital,
Canada
Email: Highj212@yahoo.com

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Introduction

A neuron's ability to function and survive depends on the end lysosomal system, which regulates synaptic and dendritic local trafficking and interacts with the soma to integrate signaling pathways and the rotation of macromolecules and organelles coming from these various and remote compartments.

The buildup, misfielding, and mis-localization of proteins are hallmarks of a number of neurodegenerative illnesses, including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS). Deficits in the endolysosomal system are being linked more and more to the pathophysiology of various diseases through genetic research, biochemical pathway analysis, and rapidly developing live cell imaging tools. The review of macro autophagy in neurons in this special edition. Axons and synapses in particular create auto phagosomes, which are then transported retrograde back to the soma for fusing, lysosomes and how lysosome function is compromised in AD, PD, and ALS.

Early endosomes develop into multi-vesicular entities by the limiting membrane budding inward into the lumen. Small external vesicles called exosomes can be produced when these intraluminal vesicles fuse with the plasma membrane. Exosome creation, how they can be filled with pathology-related proteins including synuclein and Tau, miRNA, and inflammatory chemicals, and the consequences for the spread of pathology in PD and AD brains are all covered in detail by Izco et al. These behaviors are not just limited to neurons, and glias are also described in relation to the exosome-mediated deterioration of illness in animal models.

Endosomes are essential for sorting out the material that has been endocytosed from the plasma membrane, recycling receptors and other cargo back to the plasma membrane, and transporting those materials to other organelles in the soma. When neurotrophic receptors like TrkB are bound by BDNF at synapses and dendrites, intracellular signalling pathways are triggered. Moya-Alvarado et al. discuss the involvement of Rab5 and Rab11 GTPases on recycling and signalling endosomes in mediating this process. The consequences on neuronal plasticity are explored, including both the immediate local impacts and the beginning of nuclear signaling pathways back in the soma.

The strongest evidence points to PD as the disease where endolysosomal system malfunction plays a major role in disease etiology. Brains from people with sporadic PD have been found to exhibit impaired autophagy and lysosomal activity. This has been supported by a number of familial PD-causing genes, including LRRK2, ATP13A2, VPS35, and VPS13C, which encode endolysosomal system-related proteins. Furthermore, variations in the GBA1 gene, which account for 10-15% of instances of PD, are the most significant genetic risk factor for the disease. However, several additional genes producing endolysosomal proteins have also been identified in more recent PD genome-wide association studies. It is becoming more and clearer that several of these proteins can alter the function of other PD related proteins and are also highly expressed in glia, as described by the last three publications in this special issue [1-3].
Williams et al. concentrate on the role of VPS35 in the retromer complex, which facilitates recycling to the plasma membrane or the trafficking of transmembrane protein cargo from endosomes back to the trans-Golgi network. Inhibition of autophagy, mitochondrial malfunction, and defective trafficking of neurotransmitter and cell survival receptors have all been linked to dysfunctional VPS35, all of which are likely to play a role in neurodegeneration. Retromer proteins and cargo are diminished in AD, tauopathies, and ALS in addition to their ties to PD.

Additionally, LRRK2's activity can be increased by VPS35's hyper activation. The effector protein JIP4 is known to be recruited to damaged lysosomes by LRRK2, which phosphorylates Rab10 and Rab35 before tabulating and sorting the lysosome membranes. The phosphorylation of Rab10 and Rab12 and consequent recruitment of JIP4 are caused by the recruitment of LRRK2 to various membranes of the end lysosomal system, such as recycling, early, and late endosomes. This also applied to the plasma membrane and the Golgi in their cell models and did not require the presence of Rab29, a protein suggested as being necessary to activate LRRK2 upon recruitment to membranes [4].

The bidirectional relationship between Glucocerebrosidase (GCase) and -synuclein metabolism in neurons and glia, as well as the newly discovered interaction between GCase and LRRK2, are discussed in Gegg et al's overview of the clinical and biochemical pathways in GBA1-PD. There is a lot of interest in creating medications that boost GCase activity because GBA1 mutations account for 15% of PD cases and decrease of GCase activity also happens in sporadic PD brains. Also mentioned are the various therapy approaches used.

References

1. Izco et al. . The prediction of retention in a substance abuse program based upon the assessment of congruence between personological and environmental dimensions. *Pa. State Univ.* 1990.
2. Moya-Alvarado, Guillermo, et al. "Neurodegeneration and Alzheimer's disease (AD). What can proteomics tell us about the Alzheimer's brain?." *Mol. Cell. Proteom.* 15.2 (2016): 409-425
3. Williams, Erin T., Chen, X., et al. "VPS35, the retromer complex and Parkinson's disease." *Mol. Cell. Proteom.* 7.2 (2017): 219-233. [
4. Gegg, Matthew E., and Schapira, A.V. "Lysosomal-endolysomal dysfunction and neurodegenerative diseases." *Neurobiol. Dis.* (2022).