Editorial: Golgi Pathology in Neurodegenerative Diseases

Catherine Rabouille1,2* and Georg Haase3*

1 Hubrecht Institute of the KNAW (Royal Academy of Sciences) and UMC Utrecht, Utrecht, Netherlands, 2 Department of Cell Biology, UMC Utrecht, Utrecht, Netherlands, 3 Institut de Neurosciences de la Timone, Centre National de la Recherche Scientifique and Aix-Marseille Université UMR 7289, Marseille, France

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The Editorial on the Research Topic

Golgi Pathology in Neurodegenerative Diseases

The Golgi apparatus is a central organelle that lies at the heart of the secretory pathway sustaining the delivery of proteins from their site of synthesis in the endoplasmic reticulum to their final destination, the extracellular medium, the plasma membrane, and the endo-lysosomal system. It ensures post-translational protein modifications such as glycosylation and proteolytic cleavage and processing and acts as a sorting device including to neuronal axons and dendrites (Horton and Ehlers, 2003; Ye et al., 2007).

The mammalian Golgi apparatus was first described by Camillo Golgi in 1898 as “apparato reticolare interno,” “a fine and elegant network within the cell body … completely internal in the nerve cells” (Golgi, 1898a,b). This large reticulum comprises stacks of flattened membrane bound compartments called cisternae which are laterally linked to form the so-called Golgi ribbon.

Structural and functional alterations of the Golgi apparatus, which are here collectively termed Golgi pathology, are now recognized as a constant pathological hallmark of various neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Parkinson, Alzheimer, Huntington, and prion diseases (Fan et al., 2008). In ALS, structural Golgi alterations have been revealed by the pioneering work of Gonatas and colleagues (Mourelatos et al., 1990; Gonatas et al., 1992; Fujita et al., 2002). They manifest as fragmentation—transformation of the Golgi ribbon into disconnected stacks, cisternae, tubules and vesicles, and as atrophy—loss of Golgi membrane material.

These morphological changes are often accompanied by functional Golgi alterations, such as those affecting the anterograde and retrograde transport in the early secretory pathway, both in cellular models of Parkinson (Cooper et al., 2006; Cho et al., 2014), Huntington (Caviston et al., 2007; Pardo et al., 2010), and Alzheimer (Annaert et al., 1999; Joshi et al., 2014) diseases as well as in ALS (Stieber et al., 2004; Soo et al., 2015). At least in ALS, Golgi pathology manifests as an early pre-clinical feature in degenerating neurons both in affected patients and in animal models (Mourelatos et al., 1996), suggesting that it may be relevant to the disease process instead of just representing an epiphenomenon. Yet, neither the molecular mechanisms underlying the changes in the functional organization of the Golgi apparatus nor their precise relevance to neurodegeneration have yet been completely elucidated.

These important questions got a new boost by the discovery of mutations in genes encoding Golgi-related proteins as direct causes of neurodegeneration. For instance, mutations in Optineurin (Maruyama et al., 2010), VPS54/wobbler (Schmitt-John et al., 2005), and TBCE/pmn (Martin et al., 2002) have been identified in ALS and related motor neuron diseases. Furthermore, mutations in the Parkinson disease-associated proteins α-Synuclein (Cooper et al., 2006;
Electron microscopy has been used to unravel Golgi fragmentation (Mourelatos et al., 1996) and in particular the Golgi fragmentation into tubules and vesicles observed in degenerating motor neurons (Bellouze et al., 2014), and its resolution may be further improved in tissues prepared by high pressure freezing (Walther et al., 2013). 3D reconstructions of the Golgi and its microtubules (Marsh et al., 2001; Efimov et al., 2007) may illustrate pathological changes in their intricate connections. 

Golgi fragmentation can also be monitored by live imaging (Altan-Bonnet et al., 2006), and super resolution microscopy (Betzig et al., 2006; Lippincott-Schwartz and Manley, 2009) may help refining the process. Last, system biology approaches may shed light on new pathways connecting Golgi fragmentation to neurodegeneration by identifying novel gene networks (Alvarez-Miranda et al.). However, this field faces further challenges. It will be crucial to determine whether Golgi pathology is contributory, causative or homeostatic in neurodegeneration. In particular, it is important to understand whether Golgi alterations are linked to axonal degeneration and synapse loss or dysfunction.

It will also be crucial to analyze whether Golgi pathology in each neurodegenerative disease is restricted to the neuron types that are specifically affected, i.e., motor neurons in ALS, dopaminergic neurons in PD, striatal neurons in Huntington. If so, what may be the corresponding mechanisms of vulnerability and resistance?

Furthermore, we will need to determine whether Golgi alterations in degenerating neurons impact on the function of their non-neuronal cellular neighbors, including astrocytes, microglia and Schwann cells. Can this provide a potential explanation for the non-cell autonomous disease spread observed in numerous neurodegenerative diseases? Finally and most importantly, can our burgeoning knowledge on the molecular mechanisms of Golgi pathology in neurodegenerative diseases be translated into earlier disease diagnosis and new therapies for these severe and hitherto untreatable disorders?

**AUTHOR CONTRIBUTIONS**

CR and GH prepared and wrote the manuscript.
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