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Review

Alterations of Golgi organization in Alzheimer's disease: A cause or a consequence?

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ABSTRACT

The Golgi apparatus is a central organelle of the secretory pathway involved in the post-translational modification and sorting of lipids and proteins. In mammalian cells, the Golgi apparatus is composed of stacks of cisternae organized in polarized manner, which are interconnected by membrane tubules to constitute the Golgi ribbon, located in the proximity of the centrosome. Besides the processing and transport of cargo, the Golgi complex is actively involved in the regulation of mitotic entry, cytoskeleton organization and dynamics, calcium homeostasis, and apoptosis, representing a signalling platform for the control of several cellular functions, including signalling initiated by receptors located at the plasma membrane. Alterations of the conventional Golgi organization are associated to many disorders, such as cancer or different neurodegenerative diseases. In this review, we examine the functional implications of modifications of Golgi structure in neurodegenerative disorders, with a focus on the role of Golgi fragmentation in the development of Alzheimer's disease. The comprehension of the mechanism that induces Golgi fragmentation and of its downstream effects on neuronal function have the potential to contribute to the development of more effective therapies to treat or prevent some of these disorders.
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1. Introduction

The Golgi complex (GC) is the major station of the secretory pathway, that processes and sorts proteins and lipids to the plasma membrane (PM) or the *endo*-lysosomal system (De Matteis and Luini, 2008). In mammals, the GC is formed by stacks of flattened cisternae that are laterally linked by tubules to equivalent cisternae of other stacks to form a continuous membrane structure known as ribbon, close to the centrosome. The stacks are polarized, consisting of a *cis*-side and a *trans*-side associated with a tubular reticular network (*cis*-Golgi Network (CGN) and *trans*-Golgi Network (TGN), respectively) (Wei and Seemann, 2010). The GC can undergo dynamic rearrangements during several physiological and pathological events (Wilson et al., 2011). For example, during mitosis and apoptosis, mammalian cells disassemble their GC into

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vesicles and tubular clusters. In addition, GC fragmentation is usually observed in cells subjected to stressful conditions (Machamer, 2015).

Cells across all organisms have evolved adaptive mechanisms to survive adverse environmental conditions such as limited availability of nutrients, non-physiologic pH or temperature, osmotic shock, exposure to oxidative radicals, or the accumulation of toxic protein species (Machamer, 2015). How cells deal with these stressors determines the fate, which might be survival, death, or malignant transformation. Therefore, it is not surprising that cellular stress responses culminating in Golgi fragmentation were suggested to be involved in a plethora of diseases among them neurodegenerative disorders (Gonatas et al., 2006; Joshi et al., 2015). Here we briefly summarize the main regulatory mechanisms of Golgi organization and its modifications under physiological and stressful conditions. Moreover, we discuss the role of alterations of Golgi structure in neurodegenerative disorders, and in particular in the development of Alzheimer's disease.

1.1. Maintenance and regulation of the Golgi ribbon

The Golgi apparatus has a central role in the processing and transport of proteins and lipids and in directing their delivery to their final destinations (De Matteis and Luini, 2008). Despite its basic function is conserved throughout evolution, its structural organization varies between species. For instance, in the yeast *Saccharomyces cerevisiae*, the Golgi membranes are organized as isolated and dispersed cisternae (Morin-Ganet et al., 2000). In contrast, in *Drosophila melanogaster* and plants, the cisternae form stacks (Yano et al., 2005; Driouich et al., 1993). In mammals, the stacks are connected by membrane tubules to form a ribbon-like structure that is generally located in a perinuclear location (Sütterlin and Colanzi, 2010). The complex three-dimensional modular organization of the GC relies on the cooperation of a large number of factors. First, the cisternae are held together in the form of stacks by the Golgi Reassembly And Stacking Proteins (GRASPs; GRASP55 and GRASP65) (Sengupta et al., 2009). GRASP65 and GRASP55 contain an N-terminal myristic acid for membrane association and are localized at the *cis* and the *medial/trans*-side of the Golgi, respectively. They both display a GRASP domain composed of two PDZ domains and a C-terminal serine/proline-rich regulatory (SPR) domain (Sengupta et al., 2009; Vinke et al., 2011). The more N-terminal PDZ domain can homodimerize in trans with the second PDZ domain of another molecule of GRASP to form *trans*-oriented membrane tethers (Zhang and Wang, 2015). In addition, the second PDZ of GRASP65 binds to the C-terminal of GM130, while GRASP55 binds to Golgin-45. These two protein complexes are localized between the cisternae, where stacking takes place (Zhang and Wang, 2015).

Further essential contribution to Golgi organization is ascribed to the golgins, which are Golgi-localized proteins characterized by an extensive coiled coil domain associated to the cytoplasmic face of the GC through their C-terminal domains (Barr and Short, 2003; Witkos and Lowe, 2015). This trait enable golgins to extend into the cytoplasm for tethering other membranes and cytoskeletal components (Gillingham and Munro, 2016). This family includes at least 11 members, such as GM130, Giantin, Golgin-160 among others, which are important for vesicular transport, structure and positioning of the GC inside the cells (Witkos and Lowe, 2015).

In addition, the maintenance of the ribbon in the pericentrosomal region depends on an intact microtubule (MT) and actin cytoskeleton and MT-dependent molecular motors, as they control the correct location of Golgi assembly after the exit of mitosis, trafficking and cell polarity (Sütterlin and Colanzi, 2010). Moreover, the ribbon organization requires the continuous input of membranes from the Endoplasmic Reticulum (ER) in the form of ER-to-Golgi carriers that are incorporated into the *cis*-stacks (Marra et al., 2007). Besides, overstimulation of post-Golgi carriers formation at the TGN leads to fragmentation and dispersal of the Golgi stacks (Weller et al., 2010). Thus, the overall GC structure depends on the balance of anterograde and retrograde membrane transport.

It is important to note that this may be a still limited picture of the complex regulatory mechanism of the Golgi organization, as systems biology approaches have identified hundreds of potential new Golgi regulatory elements (Chia et al., 2010). Nevertheless, the existing evidence indicates that the steady-state structure of the GC is based on a dynamic equilibrium between two levels of organization – the individual Golgi stacks and the interconnected Golgi ribbon (Colanzi et al., 2007; Cervigni et al., 2015). This is the result of the opposing activities of the ribbon forming components like the Golgi tethering proteins GRASP65 and GRASP55, and fission-inducing BARS (Corda et al., 2012). BARS controls mitotic disassembly of the Golgi stacks by cleaving the tubular interconnections among stacks (Colanzi et al., 2007). How BARS is specifically activated in G2-phase to promote the severing of the Golgi ribbon is not known.

Conversely, much more is known about the role of GRASP proteins in the interlinking of the stacks to form the Golgi ribbon (Valente and Colanzi, 2015). Thus, we will describe in more detail the role of GRASP55 and GRASP65, as they have been extensively investigated and are of specific interest to this review (see later). Of note, ribbon cleavage may result in isolated stacks (or small groups of stacks) that remain clustered in their usual position (Colanzi et al., 2007). Thus, this structurally minimal modification of Golgi organization may not be detected without specifically designed approaches (Ayala and Colanzi, 2016). For this reason, Fluorescence Recovery after Photobleaching (FRAP) investigations of GFP-tagged Golgi residents have been used to show that while these reporters can freely move between bleached and non-bleached zones via the tubular connections of an intact Golgi ribbon, their movement is hindered after depletion of either GRASP65 (Puthenveedu et al., 2006; Jarvela and Linstedt, 2014a) or GRASP55 (Jarvela and Linstedt, 2014a; Feinstein and Linstedt, 2008), which can be explained by reduced connectivity among the stacks. However, the lack of connectivity after GRASP55 depletion has not been confirmed in one study (Duran et al., 2008), suggesting that lack of a single GRASP is not always sufficient to induce full ribbon breakup or this may be limited to specific cisternal subnetworks (Veenendaal et al., 2014), thanks to the intervention of compensatory mechanisms. In addition, many studies have shown that GRASP depletion can induce defects in glycosylation (Puthenveedu et al., 2006; Veenendaal et al., 2014; Jarvela and Linstedt, 2014b; Xiang and Wang, 2010; Xiang et al., 2013).

The function of GRASPs in ribbon maintenance is further supported by their role in the cleavage of the ribbon during the G2 phase of cell cycle. As introduced before, GRASP proteins form homo-oligomers in trans, and these interactions are prevented by specific phosphorylations. CDK1 targets GRASP65 at four serine/threonine residues (i.e., S216/S217, T220, S277, S376) within the C-terminal serine/proline-rich domain to inhibit GRASP65 tethering and to induce unstacking of the cisternae (Tang et al., 2010). Moreover, PLK1 phosphorylates GRASP65 at S189, which disrupts its tethering function in ribbon formation (Sengupta and Linstedt, 2010). More recently, it has been shown that the kinase JNK2 is a potent and crucial regulator of Golgi unlinking during G2 through phosphorylation of S277 of GRASP65. Replacement of endogenous GRASP65 with the expression of the phosphodepleted mutant GRASP65-S277A in G2-blocked cells results in compaction of the dispersed Golgi stacks and restoration of a connected ribbon (Cervigni et al., 2015). JNK inhibition leads to reformation of a compact Golgi also in tumour cell lines that have a constitutively fragmented Golgi (Cervigni et al., 2015), suggesting that the

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