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Review

Lipid transfer proteins and the tuning of compartmental identity in the Golgi apparatus

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ABSTRACT

The Golgi complex constitutes a central way station of the eukaryotic endomembrane system, an intricate network of organelles engaged in control of membrane trafficking and the processing of various cellular components. Previous ideas of compartmental stability within this network are gradually being reshaped by concepts describing a biochemical continuum of hybrid organelles whose constitution is regulated by compartmental maturation. Membrane lipid composition and lipid signaling processes make fundamental contributions to compartmentalization strategies that are themselves critical for organizing cellular architecture and biochemical activities. Phosphatidylinositol transfer proteins (PITPs) are increasingly recognized as key regulators of membrane trafficking through the secretory pathway. They do so by coordinating lipid metabolism with lipid signaling, translating this information to core protein components of the membrane trafficking machinery. In this capacity, PITPs can be viewed as regulators of an essential lipid-protein interface of cisternal maturation. It is also now becoming appreciated, for the first time, that such an interface plays important roles in larger systems processes that link secretory pathway function with cell proliferation.

Contents

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1. The Golgi complex: an integral part of the eukaryotic endomembrane system

The Golgi complex performs a central role in eukaryotic cell biology serving as an intermediary bidirectional trafficking hub for proteins and lipids navigating the endomembrane system. Despite years of study, many aspects of its biology remain enigmatic including the organelle's remarkable ability to maintain compartmental identity in the face of constant bidirectional flux. The concept that the Golgi apparatus along with the endoplasmic reticulum (ER), lysosome/vacuole, endosomes, transport vesicles and the nuclear and plasma membranes form part of an integrated whole known as the endomembrane system has existed for some time (Mollenhauer and Morre, 1974). Until recently however, this theory has received little attention except in the context of membrane synthesis and lipid flow between organelles (Voelker, 1991). Once thought of as a series of stable compartments, we are now increasingly forced to accept that membrane trafficking through the secretory/endosomal pathways occurs, to a large extent, via organelle maturation, and a biochemical continuum of hybrid organelles (Glick, 2002; Glick and Malhotra, 1998; Glick and Nakano, 2009; Lippincott-Schwartz et al., 2000; Lippincott-Schwartz and Zaal, 2000; Lowe and Barr, 2007).

1.1. Golgi structure and function

Structurally consisting of polarized, flattened, disk shaped membranes known as cisternae, the Golgi apparatus exists in 3 major forms: a) singular unlinked units: present during certain developmental stages of *Drosophila melanogaster* and in some fungi, most notably the yeast *Saccharomyces cerevisiae*; b) in laterally-linked (ribbon-like) stacks of multiple cisternae such as those found in mammalian cells (usually 40–100 stacks per cell (Duran et al., 2008)) and c) stacks of unlinked cisternae: such as those found in plants and insects (Ayscough et al., 1993; Griffiths and Simons, 1986; Kondylis and Rabouille, 2009; Latijnhouwers et al., 2005; Marra et al., 2007; Preuss et al., 1992). Despite such structural diversity however, Golgi function and regulation are closely conserved throughout the eukaryotic domain (Wilson and Ragnini-Wilson, 2010). By providing an essential link between the endocytic and secretory pathways the Golgi mediates: 1) the processing and anterograde trafficking of cargo from the ER to distal secretory compartments; 2) the retrograde trafficking of cargo from the plasma membrane and endosomes; and 3) the retrograde retrieval and recycling of ER and Golgi components (Bankaitis et al., 2012; Bonifacino and Rojas, 2006; Farquhar and Palade, 1981; Mousley et al., 2012a; Rothman, 2010).

Golgi cisternae are believed to form from the homotypic fusion of ER-derived COPII vesicles, produced at transitional ER (tER) sites or ER exit sites (Barlowe and Miller, 2013; Bevis et al., 2002; Shindiapina and Barlowe, 2010). Golgi cisternae vary in composition (Farquhar, 1985; Papanikou and Glick, 2009, 2014) and the Golgi has previously been described as a tandem pair of organelles (Rothman, 1981), referring to significant differences between the *trans*-Golgi network (TGN) and other Golgi compartments. More recent studies have revealed additional compartmentalization exists, including observable differences between individual cisternae preceding the TGN (Dunphy and Rothman, 1985; Staehelin and Kang, 2008) and the existence of the ER-Golgi intermediate compartment (ERGIC) (Appenzeller-Herzog and Hauri, 2006; Hauri et al., 2000; Schweizer et al., 1990; Schweizer et al., 1991). It has been suggested that the organelle actually consists of four or more compartments (Brigance et al., 2000; Farquhar, 1985), and given that mammalian stacks typically contain 4–8 cisternae and other organisms stacks can contain 30 or more per stack (Becker and Melkonian, 1996; Donohoe et al., 2013; Manton, 1966) the potential for much greater degree of compartmentalization exists. The most distal compartment is referred to as the *trans*-Golgi Network (TGN), a specialized structure from which secretory vesicles are produced. Differing opinions exist as to whether this structure should actually be considered a distinct organelle, (Gu et al., 2001; Novikoff, 1976; Papanikou and Glick, 2014; Rothman, 1981). This has led to suggestion that Golgi cisternae may be better defined by functionality, in terms of: cisternal assembly; carbohydrate synthesis and carrier formation units (Day et al., 2013; Mellman and Simons, 1992; Papanikou and Glick, 2014).

Anterograde trafficking is initiated when newly synthesized proteins, exported from the ER in COPII vesicles, enter stacked cisternae at the *cis*-face through a complex process of guiding, tethering and vesicle fusion (Appenzeller-Herzog and Hauri, 2006; Barlowe and Miller, 2013; Hauri et al., 2000; Saraste and Kuismanen, 1984). Subsequent passage through the Golgi in the *cis-trans* direction exposes the cargo to resident enzymes that endow maturation of secretory precursors via carbohydrate addition and/or proteolytic cleavage. Secretory cargoes exit the organelle at the *trans*-face and are sorted at the TGN into trafficking shuttles such as clathrin-coated vesicles, for specific delivery to final destinations (Bard and Malhotra, 2006; De Matteis and Luini, 2008; Dunphy and Rothman, 1985; Farquhar, 1985; Glick and Nakano, 2009; Griffiths and Simons, 1986; Guo et al., 2014). Much debate has centered on how anterograde (*cis-trans*) cargo progression occurs through the organelle, the role of retrograde trafficking within the system and how the conserved function of highly physically different Golgi can be reconciled.

Current theories describing how secretory cargo traverses the Golgi apparatus center around two main hypotheses: 1) the vesicular trafficking model, or 2) the cisternal progression-maturation model. The vesicular trafficking model proposes that secretory cargo traverses the organelle sequentially through stable (unchanging) *cis*-, medial- and *trans*- cisternae, in anterograde COPI vesicles (Dunphy and Rothman, 1985; Farquhar, 1985; Farquhar and Palade, 1981; Patterson et al., 2008; Rothman, 1981; Rothman and Wieland, 1996). The distinct populations of resident proteins, in each cisternae, act on the cargo in assembly line fashion (Glick and Luini, 2011; Kleene and Berger, 1993; Nilsson et al., 2009; Rabouille et al., 1995). However, the observation that large cargo such as algal scales, lipoproteins and procollagen are absent from vesicles and traverse the Golgi apparatus without leaving the cisternal lumen, raises questions as to the models validity (Bonfanti et al., 1998; Mironov et al., 1997a; Mironov et al., 2001; Mironov et al., 2000; Polishchuk et al., 2000). Further complications for this model include the observations that: COPI vesicles appear less abundant during active trafficking events (Glick and Luini, 2011; Orci et al., 2000a; Pelham and Rothman, 2000); that many Golgi cargoes are found to be absent or at depleted levels in COPI vesicles (Dahan et al., 1994; Gilchrist et al., 2006; Martinez-Menarguez et al., 2001) and that a vesicle–mediated anterograde pathway through the yeast Golgi complex has never been identified (Barlowe and Miller, 2013). These shortcomings led to the proposal of the cisternal progression-maturation model based on concepts proposed decades earlier as the "progression model", in which it was noted that the formation of new *cis*-cisternae balances the loss of vesicles from the *trans*-face (Brown et al., 1970; Franke et al., 1971; Grasse, 1957; Morre and Ovtracht, 1977). In this model physical maturation of the cisternae drives cargo processing, with the cisternae existing transiently in various states of development, selectively retaining cargo while acquiring and losing distinct populations of resident Golgi proteins over time. Cargo processing in stacked Golgi, such as those found in mammals, would occur simultaneously with an outward, *cis*- to medial- to *trans*- flow of the maturing cisternae and concurrent