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Review

Emerging new roles of the pre-Golgi intermediate compartment in biosynthetic-secretory trafficking

Jaakko Saraste *, Hege A. Dale, Sarah Bazzocco, Michaël Marie

Department of Biomedicine and Molecular Imaging Center, University of Bergen, Jonas Lies Vei 91, N-5009 Bergen, Norway

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ABSTRACT

The intermediate compartment (IC) between the endoplasmic reticulum (ER) and the Golgi apparatus appears to constitute an autonomous organelle composed of spatially and functionally distinct, but interconnected, vacuolar and tubular subdomains. In mammalian cells the IC network is stably anchored at the cell center, communicating directly with the endocytic pathway via a pericentrosomal membrane system (PCMS). This finding suggests that the secretory pathway divides at the level of the IC, which functions as a sorting station both in Golgi-dependent and -independent trafficking. The tubular subdomain of the IC is capable of expansion in accordance with its proposed biosynthetic functions such as cholesterol synthesis.

1. Introduction

The secretory pathway was originally described as a transport system that delivers newly synthesized soluble proteins from the endoplasmic reticulum (ER) via the Golgi apparatus and post-Golgi carriers to the cortical region of the cell, where they are released to the extracellular space by exocytosis [1]. Subsequent studies have established that cells also manifest various exocytic processes that typically do not involve regulated or constitutive protein secretion, but instead the directed transfer of individual membrane components or patches to specific regions of the plasma membrane (PM), leading to its local reorganization or expansion [2]. Such polarized exocytic events, which frequently involve Golgi repositioning, play an important role during neurite outgrowth and the formation of filopodia and lamellipodia by migrating fibroblasts [2–4]. They also operate in phagocytosis and cytokinesis, and evidently also contribute to the development of invadopodia, specialized membrane protrusions found in tumour cells [5–7].

How the above exocytic processes relate to the classical post-Golgi secretory pathways has remained unclear [2]. Namely, some of these events do not seem to require an intact Golgi apparatus and bypass the *trans*-Golgi network (TGN), from which different exocytic carriers are thought to originate [2,8–12]. Instead, the endosomal system, in particular the endocytic recycling compartment (ERC; also referred to as the recycling endosome, RE), is emerging as the principal site for the formation of transport intermediates that support e.g. cell motility, neurite outgrowth and cytokinesis [13]. The ERC is a long-lived, tubulovesicular compartment that typically associates with the microtubule-organizing center (MTOC)/centrosome. Its important function is to recycle internalized lipids and proteins, such as the transferrin receptor, back to the PM [14]. Thus, an additional key role of this organelle turns out to be the delivery of membrane components to PM domains that are subject to dynamic reorganization [15]. Surprisingly, the ERC and ERC-derived carriers harbour transport machineries that were initially assigned to the TGN and post-Golgi secretory vesicles. These include Rab11, Rab8 and the exocyst, a multi-subunit tethering complex, which interacts with these GTPases and operates in many of the above processes by recruiting exocytic carriers to areas of active membrane remodeling or growth [16–18].

Numerous newly synthesized proteins also pass through the ERC en route to the PM [13,19–21], raising the question on how this compartment interfaces with the biosynthetic-secretory pathway. In this review, we discuss briefly the development of ideas on the organization of the early secretory pathway, focusing on different views on the operation of the intermediate compartment (IC) at the ER–Golgi boundary. Strikingly, our recent results show that

Abbreviations: COP, coat protein; ERC, endocytic recycling compartment; IC, intermediate compartment; MT, microtubule; pcIC, pericentrosomal IC; PCMS, pericentrosomal membrane system

* Corresponding author. Fax: +47 55 586360.
E-mail address: jaakko.saraste@biomed.uib.no (J. Saraste).

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the IC is composed of spatially and functionally distinct vacuolar and tubular domains that constitute a dynamic, but at the same time permanent, interconnected membrane system [10,22]. Of particular interest is the finding that the tubular domain of the IC, defined by the GTPase Rab1A, is stably anchored in the pericentrosomal region, revealing that the centrally located IC elements communicate directly with the endosomal system via the Rab11-containing ERC [22]. We propose that this previously unrecognized IC-endosome connection plays an important role in the transport pathways that support different polarized exocytic events by allowing newly made molecules to bypass the Golgi apparatus on their way to the PM.

2. Membrane traffic at the ER–Golgi boundary

Studies of professional secretory cells highlighted the role of small vesicular or tubular intermediates in transport between morphologically distinct transitional ER sites and the nearby *cis*-Golgi elements, establishing a paradigm for membrane traffic [1]. Ever since, a number of developments have added to the complexity of the transport events that take place at the ER–Golgi boundary [23–26]. The first was the identification of the pleiomorphic IC as a way station (“intermediate organelle”) in ER-to-Golgi transport [27]. Besides forward transport and post-translational modification of proteins [28–30], this pre-Golgi compartment was soon implicated in retrograde transport of lumenal ER components [31,32], and we know now that membrane recycling in this cellular region occurs both in coat (coat protein I, COPI)-dependent and -independent fashion [33,34]. Subsequently, the first marker proteins of the IC – also referred to as ERGIC (ER–Golgi IC) or VTCs (vesicular-tubular clusters) – rat p58 (Fig. 1) and its human counterpart ERGIC-53 – were identified [35,36]. Detailed studies of ERGIC-53 revealed that it functions as a mannose-binding cargo receptor in ER–Golgi trafficking [26], whereas studies of rat p58 [37,38] and visualization of ER-to-Golgi transfer of virus proteins in living cells [39,40] revealed an unexpected topography of this process by showing that it involves MT-dependent, long-distance movement of transport intermediates between widespread transitional ER sites (also called ER exit sites; ERES) and the Golgi region (reviewed in Ref. [41]). In parallel with the above developments, different types of ER-derived carriers have been identified, of which COPII-coated, small transport vesicles have been characterized in detail [42–44].

2.1. Different views of the IC

The above mentioned studies formed the basis for the currently prevailing model of the IC, stating that it consists of large-sized transport carriers that form via homotypic fusion of primary ER-derived vesicles [45], or protrude directly from ERES [44], and then move along MTs to the cell center where they transfer ER-derived cargo to the Golgi by fusing with or transforming into *cis*-Golgi cisternae [24,26,46]. Recently, however, based on studies on the dynamics of fluorescent variants of ERGIC-53 in living cells an alternative model has been presented. According to Hauri and coworkers, the IC represents a collection of tubulovesicular membrane clusters, which reside close to the ERES and communicate with the ER and Golgi via distinct transport carriers [26,47]. The basic difference between these models is that the former emphasizes the dynamic and transient character of this compartment, whereas the latter proposes that the membrane clusters defined by ERGIC-53 represent immobile, stable structures. However, the attachment of a fluorescent protein to the NH_2-terminus of ERGIC-53 could, e.g. affect the binding of cargo proteins to the carbohydrate recognition domain, which together with over-expression leads to the preferential accumulation of the fusion protein at the peripheral sites [47]. Namely, the p58-containing, large IC elements also accumulate in the pericentrosomal region [22], indicating that they are mobile, and both endogenous ERGIC-53 [36] and p58 [35,37] reach the *cis*-most Golgi cisterna (see Fig. 1).

Another major discrepancy has dealt with the ultrastructural organization of the large-sized IC elements, i.e. whether they correspond solely to clusters of small vesicles and tubules, or also include a vacuolar component [23–26]. Evidently, the tubulovesicular appearance of the IC predominates in ultrathin cryosections, which display high membrane contrast (see e.g. Ref. [25]), whereas localization of cargo proteins or p58 (see Fig. 1) by immunoperoxidase EM – due to lumenal accumulation of

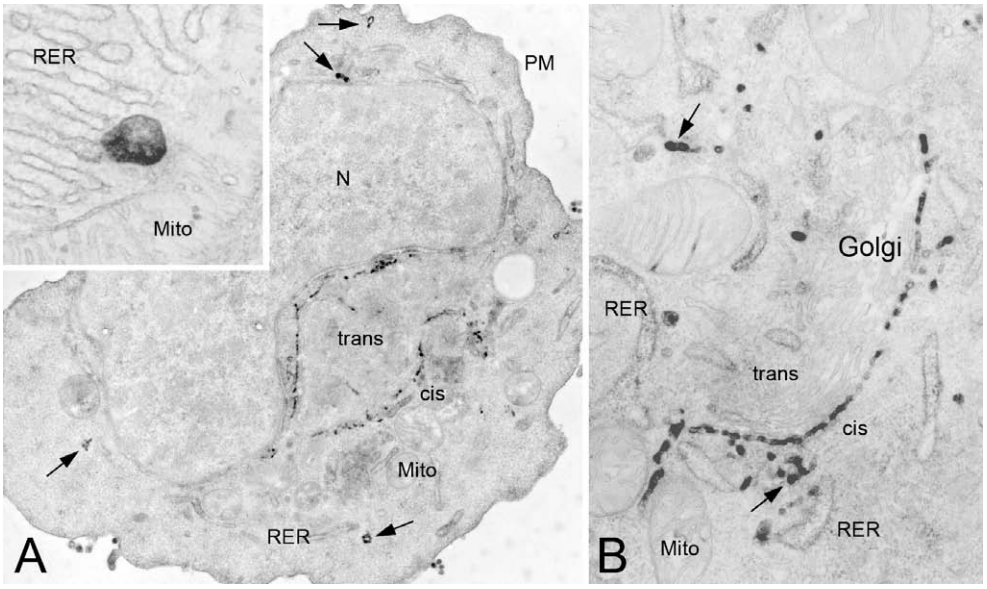

Fig. 1. Structural and spatial aspects of the IC. Immunoelectron microscopic localization of p58 in mouse myeloma (A and B) and rat pancreatic exocrine cells (A, inset). The protein is detected in the rough ER (RER), pleiomorphic vacuolar and tubulovesicular IC elements at the periphery of the cells, as well as in the *cis*-most Golgi cisterna. The inset shows a p58-positive, vacuolar IC element (diameter of about 200 nm) within the RER network of the pancreatic acinar cell, lying next to a mitochondrion (Mito). For more details, see Refs. [35,37,38].