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Intermediate Compartment: A Sorting Station between the Endoplasmic Reticulum and the Golgi Apparatus

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Glossary

Anterograde transport Transport from endoplasmic reticulum (ER) toward the cell surface.
ER exit sites ER subdomains specialized in the export of newly synthesized molecules.
Golgi stacks Stacks of flat membrane-bound cisternae. The mammalian Golgi stacks contain 4–8 cisternae.
Lumen The space inside a membrane-bound structure.
Microtubules Cytoskeletal filaments that provide tracks for motor-dependent long-distance transport of organelles and transport carriers.
Pleomorphic Variable in size and shape.
Retrograde transport Transport from post-ER compartments toward the ER.
Saccule Membrane-bound structure with a large lumen.
Vesicle Membrane-bound structure with a small lumen.

Introduction

Newly synthesized proteins and lipids leave the endoplasmic reticulum (ER) at specialized transitional regions called ER exit sites (ERES) (Jamieson and Palade, 1967; Sesso et al., 1994; Bannykh et al., 1996; Hammond and Glick, 2000; Tang et al., 2005) and enter the intermediate compartment (IC) that has been shown to operate as an obligatory a post-ER sorting station in the early biosynthetic-secretory trafficking of mammalian cells. From the IC they are typically transported to the cisternal stacks of the Golgi apparatus, prior to their delivery to the different organelles of the endomembrane system or secretion to the extracellular space. Bidirectional ER–Golgi trafficking involves the sequential operation of membrane-bounded coat protein II (COPII) and COPI coats (Aridor and Balch, 1996; Scales et al., 1997; Stephens et al., 2000). ER-derived COPI vesicles mediate forward (anterograde) transport, while IC- and Golgi-derived COPI vesicles are thought to act in the opposite (retrograde) direction (Lee et al., 2004; Rabouille and Klumperman, 2005). Retrograde transport also involves COPI-independent routes (Kano et al., 2009).

Despite the conservation of the transport machineries (such as the COP coats), the organization of the ER–Golgi interface varies in different eukaryotic cells. For example, in plants, certain yeasts, and the fruit fly Drosophila melanogaster, the individual Golgi stacks lie next to the widespread ERES, establishing units for short range ER–Golgi communication. By contrast, in animal cells the Golgi stacks are linked together into a continuous ribbon around the microtubule-organizing center (MTOC)/centrosome, whereas the ER extends throughout the cytoplasm. Hence, a large proportion of the ERES reside at the cell periphery and ER–Golgi trafficking depends on the long distance movements of the IC elements along MT tracks (Saraste and Svensson, 1991; Presley et al., 1997; Scales et al., 1997; Brandizzi and Barlowe, 2013; Day et al., 2013). Thus, it has been proposed that the IC represents a late evolutionary invention, which developed to meet the special sorting, transport and recycling requirements of the large-sized animal cells, but lacks lower eukaryotes. However, results showing that the IC constitutes an extensive membrane system that can be compared with the endosomal network in complexity, are questioning this view.

Historical Perspective

15 °C Compartment

Electron microscopic (EM) studies using a temperature-sensitive mutant of Semliki Forest virus (SFV ts-1) to synchronize the transport of viral membrane glycoproteins from ER to the plasma membrane (PM) showed that when the cells are shifted from 39 °C to 15 °C the proteins exit the ER, but accumulate in vacuoles/saccules (up to 0.5 μm in diameter), tubules, and vesicles in the cis-Golgi region and more peripheral locations (Saraste and Kuismanen, 1984). By light microscopy (LM) the proteins were localized at 15 °C to scattered globular structures in the cytoplasm, a pattern distinct from that of ER or Golgi (Kuismanen and Saraste, 1989). The transport block was readily reversible, and the proteins entered the Golgi stacks and reached the PM following the transfer of cells from 15 °C to 28 °C, showing that these structures are normal transport intermediates.

Studies employing a similar mutant of vesicular stomatitis virus (VSV tsO45) showed that the ‘15 °C compartment’ also acts as a way station during the transport of the VSV G glycoprotein (Balch et al., 1986; Bonatti et al., 1989; Schweizer et al., 1990; Duden et al., 1991; Lotti et al., 1992). Like the SFV proteins, the G-protein was found to maintain its ER-type high-mannose glycans at 15 °C, indicating lack of processing by Golgi enzymes. Furthermore, cell fractionation experiments showed that newly synthesized secretory proteins are arrested in a post-ER location when pancreatic exocrine cells are kept at 16 °C (Saraste et al., 1986). Live cell imaging of green fluorescent protein (GFP) equipped with an ER targeting signal (ssGFP) and EM studies of procollagen and growth hormone constructs verified that the transport of membrane and secretory proteins is similarly affected at 15–16 °C (Blum et al., 2000; Volchuk et al., 2000; Trucco et al., 2004). In addition, the transport of virus glycoproteins and cholesterol appears to...
be blocked at the same site at this temperature (Urbani and Simoni, 1990; Heinonen et al. 2000).

**Coronavirus Budding Compartment**

EM of mouse hepatitis virus (MHV)-infected cells showed that the budding of progeny virus initially takes place at tubulovesicular membranes located in the transitional region between the ER and the Golgi apparatus (Tooze et al., 1984). The first step of O-glycosylation, the attachment of N-acetyl-galactosamine (GalNAc) to the viral membrane (M) glycoprotein, was suggested to occur in this compartment, causing its reactivity with the lectin Helix pomatia, which specifically binds GalNAc (Tooze et al., 1988; Krijnse-Locker et al., 1994). Subsequent studies showed that the intracellular maturation of various coronaviruses occurs at the same budding site, which corresponds to the IC (Klumperman et al., 1994).

**Salvage Compartment**

The discovery of the lys-asp-glu-leu tetra-peptide (KDEL)-motif in abundant, luminal ER proteins lead to the proposal that the 15 °C budding compartment is the post-ER site from which these proteins are retrieved to the ER (Munro and Pelham, 1987; Warren, 1987; Pelham, 1989). The first mammalian KDEL-receptor, a multispanning membrane protein, was identified and shown to predominantly localize to the IC and cis-Golgi (Lewis and Pelham, 1990; Tang et al., 1993; Griffiths et al., 1994; Orci et al., 1997). Also, KDEL proteins, such as the immunoglobulin binding protein (Bip/GRP78), glucose-regulated protein of 94 kDa (GRP94), protein disulfide isomerase (PDI) and calreticulin (CR), are present in the IC (Griffiths et al., 1994; Connolly et al., 1994; Zuber et al., 2001; Ying et al., 2002; Brezza et al., 2004). Following binding to their receptor, the proteins are retrieved to the ER in COPII vesicles (Orci et al., 1997; Martinez-Menárguez et al., 1999; Majoul et al., 2001). Attachment of the KDEL-motif to lysosomal enzymes and the use of the 15 °C block suggested that the enzyme that initiates the formation of their lysosomal targeting signal (mannose-6-phosphate) resides in the IC (Pelham, 1988; Lazzarino and Gabel, 1988; Dittmer and von Figura, 1999). The cytoplasmic tails of certain type I integral membrane proteins were shown to contain dilyisine (KKXX)-motifs, which by directly interacting with COPI coats result in their retrieval from the IC/cis-Golgi to the ER (Nilsson et al., 1989; Jackson et al., 1990, 1993; Cosson and Letourneau, 1997).

**p58/ERGIC-53/LMAN1**

The first endogenous IC markers rat p58 and human ER-Golgi intermediate compartment (ERGIC)-53 (89% homology) were identified by the generation of antibodies against the 16 °C post-ER fraction isolated from pancreatic acinar cells (Saraste et al., 1987) and a Golgi fraction derived from epithelial Caco-2 cells (Schweizer et al., 1988), respectively. The cytoplasmic C-terminal tails of these non-glycosylated, hexameric, type-1 integral membrane proteins (Schindler et al., 1993; Lahtinen et al., 1992, 1996; Neve et al., 2005) contain a KKFF-motif, which interacts with COPII and COPI coats and gives rise to their continuous cycling between ER, IC, and cis-Golgi (Kappeler et al., 1997; Tisdale et al., 1997). At 15 °C the recycling of p58/ERGIC-53 to the ER is inhibited and the proteins pile up in the same pre-Golgi structures that contain the SFV or VSV membrane proteins (Schweizer et al., 1990; Saraste and Svensson, 1991; Putnam et al., 1992), verifying that the p58/ERGIC-53 compartment (Figures 1 and 4) is equivalent to the site where cargo is arrested at low temperature.

ERGIC-53 and the related VIP36 were shown to share homology with leguminous plant lectins (Fiedler and Simons, 1994) and to be identical with a mannose-binding protein MR60 of human myelomocytic (HL60) cells (Arar et al., 1995). The N-terminal domain of p58/ERGIC-53 binds mannos in a calcium-dependent manner (Iljin et al., 1996; Vellioso et al., 2003; Zheng et al., 2013); hence the name lectin mannos-binding protein 1 (LMAN1). It is the best characterized mammalian cargo receptor, facilitating the COPI vesicle-mediated export of a subset of soluble glycoproteins from the ER (Nichols et al., 1998; Appenzeller et al., 1999; Hauri et al., 2000).

**Compositional Aspects**

Most well-characterized IC proteins are components of the transport machinery. Many of them cycle at the ER–Golgi boundary and are also found in cis-Golgi, supporting the view of the IC as a transient structure (see below). In fact, EM studies showing the specific metal (osmium) staining of the IC and cis-Golgi provided the first indication of their compositional similarity (Friend and Murray, 1965; Rambourg et al., 1974). However, the fungal compound brefeldin A (BFA) helps to discriminate between IC and Golgi components. It releases COPI coats, disassembles the Golgi stacks and redistributes Golgi components to the ER, whereas cycling proteins (such as p58/ERGIC-53/LMAN1 and the KDEL-receptor) are arrested in the drug-resistant IC elements (Lippincott-Schwartz et al., 1990; Saraste and Svensson, 1991; Tang et al., 1995b; Fülekrug et al., 1997; Ward et al., 2001; Marie et al., 2009). The BFA resistance of the IC has been utilized for its proteomics analysis (Brezza et al., 2004), and indicates its stability.

**The p24 Protein Family**

Like p58/ERGIC-53, the p24 family proteins contain motifs for COPII and COPI binding, resulting in their cycling between the ER, IC, and cis-Golgi (Rojo et al., 1997; Domínguez et al., 1998; Blum et al., 1999; Gommel et al., 1999; Strating and Martens, 2009). As abundant type-1 transmembrane proteins they participate in the biogenesis of COPI vesicles (Stamnes et al., 1995; Majoul et al., 2001; Beck et al., 2009), but have also been implicated in tubulation (Simons et al., 2006) and the formation of membrane domains (Lavoie et al., 1999; Emery et al., 2003). Studies in yeast first suggested their function as receptors for the exit of
glycosylphosphatidylinositol (GPI)-anchored proteins from the ER (Schimmöller et al., 1995).

**COPI Coats**

The COPI coats are mainly recruited to the cytoplasmic surface of IC and cis-Golgi membranes, but also associate with the lateral rims of the Golgi stacks (Duden et al., 1991; Oprins et al., 1993; Griffiths et al., 1995; Orci et al., 1997; Klumperman et al., 1998). COPI vesicle budding depends on the activation of small GTPases of the ADP-ribosylation factor (Arf) family (Popoff et al., 2011). The guanine nucleotide exchange factor (GEF) of these Arfs, GBF1, is the master regulator of COPI recruitment and the target of BFA (Niu et al., 2005). It localizes to the IC and cis-Golgi and plays a key role in ER-to-Golgi trafficking (Kawamoto et al., 2002; Garcia-Mata et al., 2003; Zhao et al., 2006; Szul et al., 2007). GBF1 knock down or specific inhibition by Golgicide A releases COPI coats and arrests the VSV G-protein in the IC, indicating its involvement in anterograde IC-to-Golgi transport (Manolea et al., 2008; Sáenz et al., 2009). However, the prevailing view is that the main function of COPI vesicles is to recycle membrane and selected proteins to the ER. In pancreatic exocrine cells approximately 70% of the coats associate with the VTCs, suggesting that the IC represents the main point for recycling (Martínez-Menárguez et al., 1999).

**Rab1 and Rab2**

The roles of two GTPases of the large Rab family, Rab1 and Rab2, in ER–Golgi trafficking are relatively well understood (Plutner et al., 1991; Tisdale et al., 1992). Both interact with multiple effectors suggesting that they coordinate successive transport steps (Barneckow et al., 2009). The association of Rab1 with the cytoplasmic surface of IC and cis-Golgi membranes, and its absence from the ER, has been demonstrated by EM (Griffiths et al., 1994; Saraste et al., 1995; Satoh et al., 2003; Marie et al., 2012; Figure 2). The two Rab1 isoforms, Rab1A and RAB1B (93% homology), are recruited to IC membranes at ERES, show similar localizations by LM (Mochizuki et al., 2013; Figure 3(a)), but seem to play distinct roles in tubular and vesicular (long and short range) trafficking within the IC. Accordingly, live cell imaging and cell fractionation have shown that Rab1A mainly associates with IC tubules (Sannerud et al., 2006; Marie et al., 2009), while Rab1B interacts with GBF1 and evidently modulates COPI recruitment to globular IC domains (Alvarez et al., 2003; Monetta et al., 2007; see below). Also, Rab1A is specifically

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**Figure 1** (a) Immunofluorescence LM localization of p58/ERGIC-53 in baby hamster kidney, (b) mouse myeloma, (c) rat neuroendocrine PC12, and (d) human HeLa cells. The protein marks the IC elements accumulating in the perinuclear Golgi region (asterisks), scattered throughout the cytoplasm, and located close to the PM (arrows). The reticular staining indicates the ER pool of p58/ERGIC-53, which varies in the different cell types. Nu, nucleus. Bar: 10 μm.
interacts with the transmembrane tethers golgin-84 and giantin, which appear to act in COPI vesicle trafficking at the lateral rims of the Golgi stacks (Diao et al., 2003; Malsam et al., 2005; Barnekow et al., 2009; Munro, 2011).

The membrane fusion machinery (SNARE proteins) operating in ER–Golgi trafficking in the yeast Saccharomyces cerevisiae has been well characterized (Cai et al., 2007; Barlowe and Miller, 2013), whereas the fusion events that take place in mammalian cells remain enigmatic. The determination of the exact fusion steps is complicated by the continuous cycling of the SNAREs in COPI vesicles (Hay et al., 1998; Martinez-Menárguez et al., 2001). In analogy to yeast, Rab1 (Ypt1) has been suggested to recruit p115 (Uso1p) to COPII vesicles at ERES (Allan et al., 2000), followed by the formation of a SNARE complex (Sec22B, membrin, Bet1 and syntaxin 5), which mediates either homotypic fusion of COPII vesicles or their heterotypic fusion with the stationary IC (Zhang et al., 1997; Xu et al., 2000; see below). Another SNARE complex (syntaxin 5, GS28, Bet1 and Ykt6) is involved in a later cis-Golgi transport step (Zhang and Hong, 2001).

**Structure, Distribution, and Dynamics**

By EM the IC elements can be readily distinguished from the ER and Golgi, but share structural similarity with endosomes. They reside close to peripheral and central ERES as clusters of vesicles and tubules (VTs; Figure 4(f)) that frequently contain COPI coats (Balch et al., 1994; Bannykh et al., 1996; Martinez-Menárguez et al., 1999). However, they display considerable size heterogeneity (Ying et al., 2000) and also include large sacules that are found within the membrane clusters, free in the cytoplasm, or at the cis-face of the Golgi stacks (Saraste and Svensson, 1991; Lahtinen et al., 1992, Connolly et al., 1994; Stinchcombe et al., 1995; Ladinsky et al., 1999; Fan et al., 2003; Figures 4(a)–4(e)). These pleiomorphic sacules can accommodate large-sized cargo, such as procollagen or luminal protein aggregates (Volchuk et al., 2000; Trucco et al., 2004; Zuber et al., 2004), and based on correlative microscopy (LM/EM) correspond to many of the mobile carriers that are visible in living cells (Mironov et al., 2003). Like endosomes, they extend narrow tubules and also bind COPI coats, indicating that they represent sites for vesicle budding (Saraste and Kuismanen, 1984; Volchuk et al., 2000; Horstman et al., 2002; Figures 4(c) and 4(d)). The hypertrophy of the sacicular domains most likely gives rise to the pre-Golgi vacuoles seen in cells kept at 15 °C (Saraste and Kuismanen, 1992; Trucco et al., 2004).

LM shows the division of the IC into globular and tubular domains (Presley et al., 1998). The former contain anterograde cargo, cargo receptors and COPI coats, most likely corresponding to individual VTs or free sacules, while the latter are highlighted by Rab1A (Sannerud et al., 2006). The tubules extend from the globular domains (Figure 5). Some of them contain recycling proteins, but lack anterograde cargo, indicating that they function in retrograde transport (Palskangas et al., 1998; Simpson et al., 2006). However, under synchronized conditions cargo is also detected in the tubular domain, due to overload or the existence of different types of

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**Figure 2** Immunogold EM localization of Rab1 in the Golgi region of a normal rat kidney (NRK) cell. The 15 nm gold particles predominantly label pleiomorphic IC elements at the cis-face of the Golgi stacks. A sacucle (asterisk) and a vesicular tubular cluster (VTC; dashed area) are indicated. The micrograph was kindly provided by Dr. Karin Pernet-Gallay (University Joseph Fourier, Grenoble, France). Bar: 3 μm.

Tethers and Soluble NSF Attachment Protein Receptors

Most of the known Rab1 and Rab2 effectors are cytoplasmically oriented, long coiled-coil proteins, which function in the tethering of vesicle and organelle membranes preceding their soluble NSF attachment protein (SNARE)-mediated fusion (Barnekow et al., 2009; Sztul and Lupashin, 2009). Besides the IC/cis-Golgi tethers GM130 and GMAP-210 (Rios et al., 2004), Rab2 has been shown to interact with medial- and trans-Golgi tethers, suggesting a more widespread function (Short et al., 2001; Sinka et al., 2008). The Rab1 effector p115 is functional already at the peripheral ERES (Alvarez et al., 1999), while GM130 (bound to its membrane anchor GRASP65) cycles between central IC and cis-Golgi (Marra et al., 2001) and regulates membrane tethering at a later transport step (Alvarez et al., 2001; Marra et al., 2007). Rab1 also phosphorylated at mitosis (Bailly et al., 1991), correlating with the cessation of tubular IC dynamics, whereas COPI-mediated vesicular transport continues (Marie et al., 2012). Rab1A can functionally replace Ypt1, which coordinates two-way ER–Golgi trafficking in the yeast Saccharomyces cerevisiae (Hau-bruck et al. 1989; Segev, 2001; Kamena et al., 2008).

Rab2 has been localized to IC and cis-Golgi membranes (Chavrier et al., 1990; Lotti et al., 1992) and proposed to regulate the formation of retrograde COPI vesicles that contain p58/ERGIC-53 (Tisdale, 1999). It has also been implicated in the recruitment of the motor protein dynein to IC membranes and the association of IC elements with MTs (Tisdale et al., 2009; see below).
IC tubules (Figure 6). For example, incubation of cells at 15–16 °C inhibits the formation of IC tubules, but causes the expansion of the globular domain, while the shift of cells to 37 °C generates tubular networks containing both anterograde and retrograde markers (Blum et al., 2000; Ben-Takaya et al., 2005; Simpson et al., 2006). Proliferation of the tubules is induced when COPI function is compromised (Szul et al., 2007; Marie et al., 2009; Ben-Takaya et al., 2010; Tomáš et al., 2010; Hamlin et al., 2014), but also occurs under physiological conditions. In differentiating neuroendocrine PC12 cells the Rab1A-positive tubular IC domain expands and the tubules move from the cell body to the forming neurites accumulating in their growth cones (Sannerud et al., 2006; Figure 5). An analogous pathway connects the IC with the leading edge of fibroblasts (Figure 6).

Live imaging of various fluorescent IC markers indicates that the tubules are highly dynamic, while the globular domains are typically more stationary. Due to their differential localization within these domains, the constructs highlight different aspects of IC dynamics (see below). Long distance ER-to-Golgi transport involves the movement of IC elements from the cell periphery to the central cis-Golgi region, resulting in the division of the IC into spatially distinct early (ERES-adjacent) and late (cis-Golgi-adjacent) domains (Saraste and Svensson, 1991; Presley et al., 1997; Scales et al., 1997; Marra et al., 2001). Two types of anterogradely moving IC elements can be resolved by LM, narrow tubules and large pleomorphic structures. Some of the latter appear to represent saccular elements that transform into elongated structures (‘thick tubules’) (Presley et al., 2002; Marie et al., 2009). In addition, narrow tubules establish dynamic connections between the globular IC domains (Ben-Takaya et al., 2005; Sannerud et al., 2006).

**Association with the Cytoskeleton**

The long distance movements of the IC elements depend on MTs (Murshid and Presley, 2004; Palmer et al., 2005; Figures 3

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**Figure 3** (a) Immunofluorescence LM localization of the two Rab1 isoforms at different phases of the cell cycle. NRK cells stably expressing GFP-Rab1A were stained with monoclonal antibodies against Rab1B (kindly provided by Prof. Angelika Barnekow, University of Münster, Germany). At interphase the proteins colocalize in the Golgi ribbon, the separated pcIC (arrow) and peripheral IC elements (insets). During mitosis (at metaphase), following Golgi disassembly, the isoforms maintain their pericentrosomal co-localization at the spindle poles (arrows). (b) Association of IC elements with MTs. NRK cells were stained for the IC markers Rab1 or p58 and β-tubulin (to visualize MTs). Only the image overlays are shown. The insets show co-alignment of IC elements with MTs (arrowheads). See also Marie et al., 2012. Bars: 10 μm.
and 6). The plus- and minus-end directed motor proteins kinesin and dynein associate with the IC elements (Lippincott-Schwartz et al., 1995; Roghi and Allan, 1999; Stauber et al., 2006), explaining their bidirectional movements even along the same MT tracks (Sannerud et al., 2006). When the MTs in mammalian cells are depolymerized by nocodazole the IC elements become immobile and accumulate close to ERES (Saraste and Svensson, 1991; Hammond and Glick, 2000; Ben-Tekaya et al., 2005; Sannerud et al., 2006). Although the central Golgi ribbon breaks down, the formation of Golgi ministacks in the vicinity of ERES re-establishes ER–Golgi communication as a short range process (as in plants), explaining the ongoing Golgi modification and secretion of proteins (Saraste and Svensson, 1991; Cole et al., 1996; Storrie et al., 1998).

The Rho family GTPase cdc42, which regulates actin dynamics, interacts with COPI coats and affects dynein function, suggesting functional coupling between the actin filament system and MT-dependent motility of IC/cis-Golgi carriers (Luna et al., 2002; Chen et al., 2005). Similarly, WHAMM, which promotes actin nucleation and interacts with MTs, has been localized to the IC and implicated in the formation and transport of pre-Golgi tubules (Campellone et al., 2008).

**Different IC Models**

**Transport Complexes**

Based on imaging of fluorescent cargo, such as the VSV G-protein and procollagen, in living cells (Presley et al., 1997; Scales et al., 1997; Stephens and Pepperkok, 2002), it has been proposed that the IC represents a collection of large, pleiomorphic transport complexes (TCs) (Bannykh and Balch, 1997; Stephens and Pepperkok, 2001), which form via homotypic fusion of COPI vesicles, or protrude directly from the ER (Mironov et al., 2003; Xu and Hay, 2004; Yu et al., 2006). Thereafter, they move in a MT- and dynein-dependent (Burkhardt et al., 1997) 'stop-and-go' fashion to the Golgi region, where they either fuse with or transform into cis-Golgi cisternae (Figure 7(a)). In other words, the IC elements are transient structures which are first formed de novo at ERES and then consumed at cis-Golgi. These mobile structures (speed of
about 1 μm/sec) corresponding to saccules or more complex, pleomorphic elements (Mironov et al., 2003) appear to consist of subdomains enriched in antero- or retrograde cargo, or COPI (Shima et al., 1999; Stephens et al., 2000). They have also been shown to contain other machinery proteins, such as p23/24, p58, VIP36, membrin and Rab1A (Blum et al., 1999;
Three views of the IC. All models take into account the existence of two types of ERES in mammalian cells, peripheral and Golgi-adjacent. For simplicity, lateral communication between ERES-adjacent IC elements is not illustrated. (a) The IC elements form de novo at ERES (via homotypic fusion of COPII vesicles), giving rise to pleiomorphic transport complexes (TC) that move along MTs to the cis-Golgi region where they either transform into cis-Golgi cisternae (as shown here) or fuse with the stationary Golgi stacks. (b) The IC consists of stationary membrane clusters located close to ERES. In this case ER-to-Golgi trafficking involves two distinct transport steps, since the IC recieves cargo from the ER via heterotypic fusion of COPII vesicles and forms special anterograde carriers (AC) that move along MTs to cis-Golgi. (c) The IC represents a stable interconnected network that is anchored both next to ERES and the centrosome. Bidirectional transport between these sites and between the central IC elements and the Golgi stacks involves vesicular, tubular or saccular carriers. ERES-IC communication via COPII vesicles occurs as in model b. COPII, COPI and clathrin coats are shown in gray, orange, and blue, respectively, and the centrosome in red.

Chao et al., 1999; Dahm et al., 2001; Sannerud et al., 2006; Monetta et al., 2007; Tomás et al., 2010).

Stationary Compartment

Another model of the IC (Figure 7(b)) is largely based on the imaging of GFP-ERGIC-53 dynamics in living cells (Bentekay et al., 2005). It proposes that the IC consists of stationary, long-lived membrane clusters, located close to the ERES, which communicate with the ER and Golgi via distinct transport carriers (Appenzeller-Herzog and Hauri, 2006). Thus, in a two-step transport process cargo is first transferred from ER to the IC via heterotypic fusion of COPII vesicles. The IC then generates novel (possibly COPI-coated) anterograde carriers (ACs) that move along MTs to the cis-Golgi. The recycling of GFP-ERGIC-53 to the ER evidently occurs mainly from the ERES-associated IC, since it was not detected in the ACs containing soluble, Golgi-directed cargo. The identification of a motif in the neuronal GABA transporter, that seems to be required for its exit from the IC, supports the stable nature of the IC (Farhan et al., 2008).

Interconnected Membrane System

Visualization of IC dynamics using GFP-Rab1A showed that the pleiomorphic transport carriers arriving along MTs from the cell periphery do not move directly to cis-Golgi, but are targeted to the MTOC/centrosome that is normally positioned next to the Golgi ribbon. In cells displaying centrosome motility, for example, cells that are migrating or entering mitosis, the centrosome-targeted membranes can be resolved as a separate compartment, called the pericentrosomal IC (pcIC), which is distinct from the cis-Golgi-adjacent IC domain (Marie et al., 2009, 2012; Mochizuki et al., 2013; Figure 3(a)). Live imaging further showed that the separated pcIC and the Golgi communicate via tubular and globular carriers. The pcIC contains its own pool of COPI coats, and mediates the BFA-induced, COPI-independent backflow of Golgi enzymes to the ER, suggesting that forward pcIC-to-Golgi transport depends on COPI coats, and thus is blocked by BFA (Marie et al., 2009). Both the peripheral IC elements and the pcIC persist upon Golgi disassembly by BFA and maintain their communication with via dynamic tubules (Marie et al., 2009). Accordingly, the IC has been proposed to constitute a dynamic, but stable membrane network due to its anchoring next to the ERES and the centrosome (Saraste et al., 2009; Figure 7(c)). This model is supported by studies of mitotic cells, showing that the IC persists despite Golgi breakdown and the rearrangement of the MTs, and maintains its spatial organization due to its ongoing association with the spindle MTs and the centrosomes at the spindle poles (Marie et al., 2012; Figure 3(a)).

Functional Aspects

Sorting and Transport

In the endocytic pathway, soluble proteins and particles bound to lysosomes accumulate in the lumen of vacuolar endosomes, while many membrane proteins are sorted into narrow tubules for recycling to the PM. The observed major
concentration of soluble secretory proteins within the IC (Oprins et al., 2001) could be explained by similar geometry-based sorting, namely, their exclusion from vesicles and tubules, which recycle lipids and membrane-bound proteins back to the ER (Martinez-Menarguez et al., 1999). Membrane recycling is a major function of both the IC and endosomes in mammalian cells. Due to the similarity of the tubular domain of the IC with the endocytic recycling compartment (ERC), its ‘mirror compartment’ next to the centrosome, it has been designated as the biosynthetic recycling compartment (BRC; Saraste and Goud, 2007; Marie et al., 2009).

Lumenal conditions: Receptor-mediated retrieval of KDEL proteins from the IC requires that it is discontinuous with the ER and maintains special lumenal conditions (Pelham, 1989). The finding of low pH-dependent binding of KDEL-ligands to their receptor in vitro suggested the existence of a pH gradient between the ER and cis-Golgi (Wilson et al., 1993). The pH-sensitive interactions of the low density lipoprotein (LDL)-receptor-related protein (LRP) and procollagen with the chaperones RAP and Hsp47, respectively (Bu et al., 1995; Satoh et al., 1996), and partial co-localization of DAMP (a marker for acidic compartments) and p58/ERGIC-53 in central IC elements (Palokangs et al., 1998), are in accordance with this idea. The pH of the ER and cis-Golgi has been estimated to be about 7.2 and 6.5–6.7, respectively (Paroutis et al., 2004; Vavassori et al., 2013).

Although the effect pH on the binding of mannose-containing cargo to p58/ERGIC-53/LMAN1 remains unclear, it appears that cargo release is caused by a drop in free calcium concentration between the ER and IC lumen (Appenzeller-Herzog et al., 2004; Bentley et al., 2010; Zheng et al., 2013). On the other hand, the depletion of lumenal calcium stores affects the morphology of the IC and the recycling of cargo receptors at the ER–Golgi boundary, and the IC has been reported to contain the calcium-ATPase SERCA, as well as the calcium-binding proteins BiP, GRP94, CR, and CALNUC (Ying et al., 2002; Breuza et al., 2004; Howe et al., 2009; Bentley et al., 2010), suggesting its role in intracellular calcium storage.

Role of COPI coats: There are at least three subtypes of COPI coats (Beck et al., 2009), and four Arf GTPases that regulate their membrane binding (Popoff et al., 2011). Three Arfs appear to act at the ER–Golgi boundary and two of these associate with membranes in a BFA-resistant manner (Volpicelli-Daley et al., 2005; Chun et al., 2008; Duijsings et al., 2009; Ben-Tekaya et al., 2010; Hamlin et al., 2014), suggesting that different types of COPI vesicles mediate two-way trafficking at the level of the IC. The role of COPI in anterograde transport has been considered for some time (Hosobuchi et al., 1992; Pepperkok et al., 1993; Peter et al., 1993; Orci et al., 1997; Malsam et al., 2005). In addition, although both p58/ERGIC-53 and KDEL-receptor employ COPI vesicles in their recycling, their transport itineraries differ (Tang et al., 1995a; Marie et al., 2009, 2012). In addition to acting in vesicle budding the COPI coats may form membrane domains (Presley et al., 2002).

Golgi bypass: Besides mediating bidirectional ER–Golgi trafficking, the IC has been suggested to be involved in Golgi-independent pathway(s) (Marie et al., 2008; Saraste et al., 2009). The route between the IC and the leading edge or growth cone of motile fibroblasts or neurons, respectively (Figures 5 and 6), could participate in cholesterol and integrin trafficking (Urbani and Simoni, 1990; Sannerud et al., 2006; Wang et al., 2010) or correspond to the BFA-resistant ER-IC-PM route that supports phagocytosis (Becker et al., 2005; Saraste and Goud, 2007; see below). Direct pericentrosomal communication between the IC and the endosomal system seems to be used by the cystic fibrosis transmembrane conductance regulator (CFTR) during its Golgi-independent transport to the cell surface (Yoo et al., 2002; Marie et al., 2009; Gee et al., 2011). Further, the presence of the IC in neuronal dendrites may provide a Golgi-independent satellite pathway for local dendritic trafficking (Krijnse-Locker et al., 1995; Sannerud et al., 2006; Ehlers, 2013).

Posttranslational Modification

Questioning the studies on coronavirus maturation, which suggested that O-glycosylation is initiated in the IC (see above), subsequent EM studies showed that the GalNAc-transferases are predominantly found in the Golgi. However, the activation of cells (by epidermal growth factor) causes their incorporation into COPI vesicles and relocation to the IC and ER, which consequently become positive for the lectin Helix pomatia (Gill et al., 2010). The cycling of cis-Golgi proteins to the IC could be a constitutive event (Lin et al., 1999; Marra et al., 2001; Jarvela and Linstedt, 2012). Moreover, the construction of the sugar chains on proteoglycans has been suggested to begin in the IC (Jönsson et al., 2003).

Protein Maturation

The KDEL-containing molecular chaperones present in the IC (BiP, PDI, and GRP94; see above) could be cycling while still bound to their unfolded client proteins, opening for a post-ER level of protein folding and quality control. The presence of quality control machinery in the IC and the finding that the ER-associated degradation of certain proteins requires their ER export is in accordance with this idea (Zuber et al., 2001; Anelli and Sitia, 2008). The PDI family member ERp44 and p58/ERGIC-53 cooperate in the IC/cis-Golgi in sequential assembly of IgM polymers (Anelli and Sitia, 2008). Unassembled IgM or T-cell antigen receptor subunits bound to ERp44 or BiP, respectively, can be retrieved to the ER by the KDEL-receptor in a pH-dependent manner (Yamamoto et al., 2001; Vavassori et al., 2013), similarly as the overexpressed, misfolded VSV G-protein (Hammond and Helenius, 1994) and mutant V2 vasopressin receptors (Hermosilla et al., 2004). Additional proof for a post-ER checkpoint is provided by studies showing the accumulation of the deletion mutant AF508 of CFTR (Gilbert et al., 1998), misfolded MHC class I proteins (Hsu et al., 1991; Raposo et al., 1995), and proinsulin (Zuber et al., 2004) in expanded IC elements.

Signaling

The level of p58/ERGIC-53 mRNA is up-regulated by the unfolded protein response (UPR), which also requires yeast Ypt1 function, supporting a link between this signaling pathway and ER–Golgi trafficking (Nyfeler et al., 2003; Tsvetanova et al., 2012). Protein kinases Src, aPKC, and Scy11 have been
implicated in COPI function at the level of the IC (Tisdale and Artalejo, 2006; Hamlin et al., 2014) and PKC and its downstream effectors appear to control IC morphology (Ben-Tekaya et al., 2010; Sugawara et al., 2012). The activation of neuronal Trk receptor tyrosine kinases in the IC initiates signaling via the MEK pathway leading to Golgi fragmentation (Schecterson et al., 2010).

Autophagy

Membranes enriched in IC markers (p58/ERGIC-53/LMAN1, KDEL-receptor, and Sec22B) play a role in the biogenesis of autophagosomes by representing the primary membrane source for the lipidation of LC3, which triggers this process (Ge et al., 2013). Moreover, Ypt1/Rab1 is a key regulator of autophagy in yeast and mammals (Lynch-Day et al. 2010; Winslow et al., 2010; Zoppino et al., 2010; Huang et al., 2011; Lipatova et al., 2012). A phosphatidylinositol 3-phosphatase (MTMR6) acting in vesicle transport and autophagy is regulated by Rab1B and localizes predominantly to the pdc (Mochizuki et al., 2013), further supporting the role of the IC in autophagy.

Phagocytosis and Antigen Presentation

Supporting the existence of an unconventional pathway that connects the ER with the PM-derived phagosome (Gagnon et al., 2002), the IC-enriched SNARE Sec22B/ERS-24 (Zhang et al., 1999) was shown to influence phagocytosis independently of its role in ER–Golgi trafficking (Becker et al., 2005; Hatusawa et al., 2009). In dendritic cells the delivery of certain proteins – such as the peptide transporter (TAP), CR, and tapasin – from ER to the phagosome is required for antigen cross-presentation. This pathway depends on the interaction between Sec22B and the PM SNARE syntaxin 4 and involves efficient recruitment of the integral IC components sec22B and p58/ERGIC-53 to the phagosomes (Gebrian et al., 2011), in accordance with the idea that the IC provides an important membrane source for their formation. The presence of CR, tapasin, and functional TAP in the IC/cte-Golgi support this possibility (Kleijmeer et al., 1992; Howe et al., 2009; Ghanem et al., 2010).

Links to Disease

The IC plays a role in the Golgi-independent trafficking of CFTR (see above). Mutations in p58/ERGIC-53/LMAN1, or its partner MCFC2 (multiple coagulation factor deficiency protein 2) result in an autosomal recessive bleeding disorder called combined deficiency of coagulation factors V and VIII. They disrupt the lectin mannose-binding protein 1 (LMAN1)-MCFC2 receptor complex, thereby inhibiting the secretion of these factors and reducing their serum levels (Nichols et al., 1998; Zheng and Zhang, 2013). Parkinson’s disease-related cytotoxic protein, α-synuclein, has been suggested to interfere with ER–Golgi trafficking and to arrest autophagy by inhibiting Rab1 function (Cooper et al., 2006; Winslow et al., 2010). Many phagocytosed bacterial pathogens, such as Legionella, hijack the ER-to-IC-to-phagosome pathway during their intracellular replication (Isberg et al., 2009; Arasaki et al., 2012; see above). In addition to coronaviruses, the IC has been implicated in the replication of buny-, entero-, flav-, picorna, and vacciniaviruses (Jäntti et al., 1997; Risco et al., 2002; Miller and Krijnse-Locker, 2008; Hsu et al., 2010). Surprisingly, p58/ERGIC-53 interacts in a lectin-independent manner with fusion proteins of a number of membrane viruses and participates in different stages of their life cycle (Klaus et al., 2013).

See also: Interorganellar Communication: Interplay and Processes: Endoplasmic Reticulum Stress in Disease; ER–Golgi Transport; Regulation of the Secretory Pathway; Unconventional Protein Secretion: Fibroblast Growth Factor 2 and Interleukin-1β as Examples. Intracellular Infectiology: Cell Processes: Phagocytosis. Organelles: Structure and Function: At the Center of Autophagy: Autophagosomes; Golgi and TGN; The Endoplasmic Reticulum

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