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The role of secretory and endocytic pathways in the maintenance of cell polarity

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Abstract

Epithelial cells line virtually every organ cavity in the body and are important for vectorial transport through epithelial monolayers such as nutrient uptake or waste product excretion. Central to these tasks is the establishment of epithelial cell polarity. During organ development, epithelial cells set up two biochemically distinct plasma membrane domains, the apical and the basolateral domain. Targeting of correct constituents to each of these regions is essential for maintaining epithelial cell polarity. Newly synthesized transmembrane proteins destined for the basolateral or apical membrane domain are sorted into separate transport carriers either at the *trans*-Golgi network (TGN) or in perinuclear recycling endosomes (REs). After initial delivery, transmembrane proteins such as nutrient receptors frequently undergo multiple rounds of endocytosis followed by re-sorting in REs. Recent work in epithelial cells highlights the REs as a potent sorting station with different subdomains representing individual targeting zones that facilitate the correct surface delivery of transmembrane proteins.

Keywords

Cell polarity; apical domain; basolateral domain; primary cilium; lipid raft; non-raft dependent apical sorting; BBSome; early endosomes (EEs); apical early endosomes (AEEs); basolateral early endosomes (BEEs); transcytosis; AP-1B; recycling endosomes (RE); recycling

Introduction

During polarization, epithelial cells segregate their plasma membrane into apical and basolateral domains, both enriched with a specific set of transmembrane proteins and lipids. For example, the apical membrane is enriched with glycolipids and cholesterol, whereas the basolateral membrane hosts cell adhesion proteins and nutrient receptors such as LDL receptor (LDLR) and Tfn receptor (TfnR). Apical and basolateral membranes are separated by tight junctions that serve as diffusion barriers. Furthermore, fully polarized simple epithelial cells such as Madin-Darby canine kidney (MDCK) cells grow out a primary cilium from the apical membrane. The primary cilium represents a third distinct membrane domain with its own subset of constituents.

Throughout the lifetime of individual epithelial cells, it is important to faithfully sort transmembrane proteins and lipids to their correct target location to maintain polarity. Moreover, cells need to distinguish between proteins destined for plasma membrane domains or intracellular organelles such as endosomes and lysosomes.

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Transmembrane proteins destined for endosomes or lysosomes, or the different plasma membrane locations typically move together from the endoplasmic reticulum to the Golgi apparatus. However, upon arrival at the TGN, proteins are sorted away from each other by means of specific sorting signals encoded in either their luminal or transmembrane domains (majority of apical proteins), or cytoplasmic tails (majority of lysosomal and basolateral proteins), which are recognized by specialized sorting machineries. In general, cytoplasmic tail signals that direct a protein to the basolateral membrane are *cis*-dominant over apical sorting information. Moreover, not all proteins destined for the apical or basolateral domain are sorted at the TGN. Instead, some proteins move from the TGN into REs for subsequent sorting.

Unlike REs in fibroblasts that do not have the specific task of sorting plasma membrane proteins to different membrane domains, REs in epithelial cells are much more elaborate with domains involved in apical targeting (also named apical REs = ARE) or basolateral targeting (also named common REs = CRE) (reviewed in [1]). In fact, the sorting functions of both domains are so distinct, that some groups believe they are entirely distinct REs (reviewed in [2]). Furthermore, it is highly likely that a third domain exists for trafficking into the primary cilium. In analogy to the model of Rab domains in early endosomes (EEs) established by Marino Zerial and coworkers [3], the different REs domains may be established by Rab proteins involved in targeting processes. In addition to multi-faceted REs, epithelial cells also have two different kinds of EEs: apical EEs (AEEs) that underlie the apical membrane and basolateral EEs (BEEs) that underlie the basolateral membrane (reviewed in [1]). Proteins internalized from either membrane first arrive in AEEs or BEEs, from which they may immediately return to their membrane of origin or shuttle into REs for re-sorting. In the following sections, surface delivery of transmembrane proteins will be discussed with a focus on the endosomal compartments involved in these processes (summarized in figure 1).

Sorting to the apical membrane

Cargos destined for the apical membrane have diverse sorting signals. The most common are perhaps N- or O-linked glycans attached to their luminal domains. These signals can be found in for example endolyn and the neurotrophin receptor p75. Other proteins such as influenza hemagglutinin (HA) contain apical sorting information in their transmembrane domains. In addition, glycosylphosphatidylinositol (GPI) anchors may also serve as apical targeting determinants. Despite their diverse nature, a common theme is that apical targeting may be facilitated by sorting lectins of the galectin family that bind glycan residues at the luminal side of vesicles thereby clustering the cargos for incorporation into transport carriers. Curiously, galectins are synthesized in the cytosol and it is currently not clear how they end up in the lumen of nascent vesicles. In addition, apical cargos may also be clustered because of the physical properties of their sorting signals. Clustering of apical cargos occurs either into lipid raft or non-raft domains (reviewed in [4,5]).

Lipid rafts are defined as clusters of sphingolipids (glycosphingolipids and sphingomyelin) and cholesterol that are resistant to Triton X-100 extraction at 4°C (reviewed in [6]). Raft-dependent cargos such as influenza HA and GPI-anchored proteins are thought to associate with lipid rafts at the TGN. This association is mediated by physical affinity to the raft lipids or may be facilitated by galectin-4 that has an affinity to glycosphingolipids. In addition, the phosphatidylinositol 4-phosphate adaptor protein FAPP2 enhances apical delivery of raft-associated proteins (reviewed in [5]). Interestingly, instead of being directly delivered to the apical membrane, raft-associated cargos seem to travel to AEEs first where they mix with cargos internalized from the apical membrane before surface appearance [7].

Apical targeting of raft-independent cargos such as endolyn or the neurotrophin receptor p75 depends on galectin-3. Furthermore, apical delivery of endolyn can be inhibited by ablating the apical sorting power of REs [7]. Proteins needed for apical targeting from REs are for example Rab11 and its effector myosin Vb [7]. Other apically targeted proteins such as the apical variant of the vesicular stomatitis virus glycoprotein (A-VSVG) were shown to move through recycling endosomal subdomains containing TfnR (reviewed in [1]). Interestingly, TfnR-positive REs are thought to function as basolateral sorting stations. Most likely, A-VSVG moves together with proteins destined for the basolateral membrane from the TGN into REs, before segregating away into the apical pathway.

In conclusion, raft-dependent cargos seem to move through AEE, whereas raft-independent cargos may move through Rab11-positive recycling endosomal domains, before arriving at the apical membrane.

Sorting to endosomes and the basolateral membrane

Sorting signals that direct proteins into the basolateral pathway are frequently encoded in the cytoplasmic tails of transmembrane proteins and consist of short dileucine (LL) or tyrosine-based (YxxØ or FxNPxY) peptide motifs. These signals are similar to endocytic motifs and lysosomal targeting determinants and are recognized by cytosolic adaptor complexes. There are monomeric clathrin adaptors like the TGN- localized GGA (Golgi-localized, γ -ear-containing, ADP-ribosylation-factor-binding) proteins and heterotetrameric adaptor protein (AP) complexes that may link cargo binding to the recruitment of clathrin. There are five main classes of heterotetrameric AP complexes, all of which have two large ~100 kDa subunits (γ , α , δ , ϵ , ζ and $\beta 1 - \beta 5$), a medium ~ 50 kDa σ subunit, and a small ~ 20 kDa μ subunit. AP-2 facilitates clathrin-mediated endocytosis, AP-3 and AP-4 facilitate sorting of lysosomal cargos at the TGN or endosomes, and the recently discovered AP-5 complex localizes to late endosomes [8,9]. In addition, epithelial cells express two highly homologous AP-1 complexes, AP-1A and the tissue-specific AP-1B. AP-1A and AP-1B share both large subunits and the small subunit, but differ in the incorporation of their respective medium subunit $\mu 1A$ or $\mu 1B$. Whereas AP-1A localizes at the TGN and endosomes and sorts proteins in the endosomal system, AP-1B exclusively localizes in TfnR-positive REs and is required for basolateral sorting from this location (reviewed in [1]). It is thought that $\mu 1B$ empowers AP-1B with the necessary properties needed for basolateral sorting from REs. However, it is currently not entirely clear how this is possible given that $\mu 1A$ and $\mu 1B$ are ~80% identical at the amino acid level.

Sorting at the TGN

Interestingly, all AP complexes recognize similar sorting signals, yet they direct proteins into different targeting pathways towards endosomes and lysosomes, or towards the basolateral membrane. Perhaps subtle differences in the preferences for amino acid combinations in YxxØ motifs, where x describes any amino acid and Ø describes a hydrophobic residue, impact the efficiencies with which cargo is selected into nascent coated vesicles [10]. This would result in some proteins being preferentially incorporated into AP-1A, AP-3 or AP-4 vesicles at the TGN for sorting into the endosomal system. Moreover, some cargos with LL or YxxØ sorting signals are packaged at the TGN for basolateral surface delivery, and there has been some evidence that AP-4 may be involved in such a step (reviewed in [1]). An open question in the field is whether AP-1A and AP-3 may also participate in basolateral sorting. Furthermore, are there different coated vesicles leaving the TGN for endosomes and basolateral membrane? Perhaps, cargos packaged into coated vesicles at the TGN move together into BEEs, from which basolateral proteins reach their target membrane together with receptors that were internalized from that region.

Indeed, low amounts of lysosomal transmembrane proteins such as Igp120/lamp1 are known to cycle through the basolateral membrane [11].

Sorting in REs

Some proteins with YxxØ motifs such as VSVG are not efficiently incorporated into transport vesicles at the TGN and travel instead into TfnR-positive REs. This step is regulated by Rab13 (reviewed in [1]). In REs, cargo may directly interact with AP-1B for basolateral sorting, or may interact with the co-adaptor autosomal recessive hypercholesterolemia protein ARH. For example, LDLR encodes an FxNPxY sorting motif that is recognized by ARH in REs. ARH in turn interacts with AP-1B and thus facilitates AP-1B-dependent sorting of LDLR [12]. Notably, AP-1B is the only AP complex that localizes exclusively in REs. Membrane recruitment of AP-1B is facilitated by Arf6 and depends on phosphatidylinositol 3,4,5-trisphosphate (PI[3,4,5]P₃) [13,14]. Remarkably, PI(3,4,5)P₃ is enriched in TfnR-positive REs, and depends on AP-1B expression. It is likely that PI(3,4,5)P₃ is generated by a phosphatidylinositol 4-phosphate 5-kinase, PIPKIγ-90, in conjunction with a PI3-kinase. PIPKIγ-90 directly interacts with AP-1B, and its localization in REs is dependent on AP-1B [13]. In REs, AP-1B triggers the recruitment of at least some subunits of the mammalian exocyst complex, Exo70 and Sec8, for incorporation into AP-1B vesicles. The exocyst is a vesicle tethering complex thought to tie AP-1B vesicles to the basolateral membrane in a RalA-dependent manner. Additional regulators of the AP-1B pathway are Cdc42, Rab8, and Rab10 (reviewed in [1]).

An interesting spin-off of AP-1B-dependent sorting through REs is the surface delivery of E-cadherin, which depends on PIPKIγ-90 and AP-1B. In addition, E-cadherin trafficking is dependent on Rab11 (reviewed in [1]). Thus, E-cadherin may move through REs that contain markers of both basolateral and apical sorting domains.

In sum, basolateral cargos may be sorted at the TGN and subsequently may move through BEEs. Alternatively, basolateral cargos may move from the TGN into REs for sorting along the AP-1B pathway. Special features that μ1B bestows on AP-1B are an affinity to PI(3,4,5)P₃ and the ability to trigger membrane recruitment of the exocyst complex, both features are needed for proper basolateral delivery from REs. The importance of AP-1B for epithelial cells is highlighted by the fact that proteins implicated in cancer development such as epidermal growth factor receptor (EGFR) and its ligand amphiregulin depend on AP-1B for basolateral sorting [15,16], and researchers found that μ1B/AP-1B was down regulated in colon cancer models and Crohn's disease patients [17,18]. This is especially interesting knowing that not all polarized epithelial cells express AP-1B, and AP-1B is for example not expressed in hepatocytes and cells derived from the renal proximal tubule (LLC-PK1 cells) [19].

Transcytosis

Some proteins are first delivered to the apical or basolateral membrane and after endocytosis are re-sorted to the opposite membrane domain in a process called apical-to-basolateral or basolateral-to-apical transcytosis. Common to both processes is that the internalized proteins need to reach REs for re-sorting. Perhaps one of the best-studied transcytotic proteins is the polymeric immunoglobulin receptor (pIgR) that mediates apical delivery of IgA. pIgR is first sorted to the basolateral membrane and can be found in BEEs and REs on its pathway (reviewed in [1]). Although pIgR's biosynthetic path is not entirely clear, it has recently been suggested that at least its maintenance at the basolateral membrane depends on AP-1B [18]. After IgA binding, pIgR transcytoses from the basolateral membrane through TfnR-positive and Rab11-positive REs to the apical membrane [20]. Apical transcytosis depends on Rab11 and Rab25 [21]. Likewise, basolateral-to-apical transcytosis of the neuron glia cell

adhesion molecule (NgCAM) follows a path through Rab11-positive REs [22]. NgCAM has a YxxØ sorting motif in its cytoplasmic tail that is needed for basolateral recycling via AP-1B. This motif is phosphorylated during transcytosis, which inhibits AP-1B binding [23].

An interesting transcytotic receptor is FcRn that transports IgG across epithelial monolayers in both apical-to-basolateral and basolateral-to-apical directions. Transcytosis in both directions depends on Rab25 and myosin Vb. Curiously, Rab11 is necessary only for basolateral recycling [24]. Thus besides E-cadherin, FcRn is the second known protein to require Rab11 for basolateral sorting.

Collectively, an emerging theme is that Rab25 regulates transcytosis in general. How exactly Rab25 works alongside Rab11 and other effectors of REs will be seen in the future.

Sorting into primary cilia

In recent years, sorting into primary cilia gained much needed momentum. Central to this take off was the description of the so-called BBSome, an octameric complex of conserved Bardet-Biedl syndrome proteins that promotes ciliogenesis. The BBSome was described as a coat that forms on membranes, and in vitro work suggested that the BBSome has highest affinity to phosphatidylinositol 3,4-bisphosphate (PI[3,4]P₂)-positive membranes (reviewed in [25]). However, it is currently not clear, where in the cell these membrane domains exist. Interestingly, the inositol polyphosphate-5-phosphatase E (INPP5E) was linked to ciliopathies such as Joubert syndrome. INPP5E hydrolyzes the 5-phosphate of PI(3,4,5)P₃ or phosphatidylinositol 4,5-bisphosphate (PI[4,5]P₂) [26]. This is interesting, because as discussed in the section on basolateral sorting, TfnR-positive REs are enriched in PI(3,4,5)P₃. Perhaps membranes originating from REs play a role in targeting to cilia, and INPP5E is involved in creating a PI(3,4)P₂-positive membrane domain from a PI(3,4,5)P₃ pool.

In forming primary cilia, the BBSome cooperates with Rab8 (reviewed in [25]). In this process, Rab8 is activated via its exchange factor Rabin8, which in turn is activated by Rab11 [27]. Thus, ciliogenesis involves Rab proteins that also work in the basolateral pathway (Rab8) or the apical pathway (Rab11). Although it is not clear at which intracellular compartment this activation cascade takes place, it is tempting to speculate that this may involve trafficking from a putative recycling endosomal subdomain where Rab8 and Rab11 may overlap. Intriguingly, other players already known for their role in basolateral sorting are also involved in ciliogenesis such as the exocyst subunit Sec10 (reviewed in [28]) as well as Cdc42 [29] and perhaps Rab10. Although there are no data yet confirming a role for Rab10 in ciliogenesis, Rab10 antibodies were recently shown to stain the entire length of primary cilia [30].

Movement within the cilia is mediated by intraflagellar transport (IFT) particles. Interestingly, IFT88 levels are decreased upon knock down of Sec10. This indicates that the exocyst complex may regulate IFT88 transport into primary cilia, perhaps involving REs (reviewed in [28]). Ciliary delivery of other IFT proteins such as IFT20 was shown to depend on Golgi markers GMAP210/TRIP11 (reviewed in [25]). This suggests that transport of IFT20 to the cilia perhaps follows a direct pathway from the Golgi.

Taken together, the outgrowth of primary cilia involves protein complexes specific for cilia (BBSome, IFT proteins), and components this pathway shares with apical (Rab11) or basolateral (Rab8, Cdc42, and Sec10) pathways. Furthermore, components may reach cilia directly from the Golgi or perhaps from REs. However, despite these clear advances, many issues concerning the molecular mechanisms of ciliogenesis remain unresolved.

Conclusion

Apical or basolateral proteins were once thought to be packaged into different transport carriers at the TGN during biosynthetic delivery followed by direct transport – without traversing endosomes – to their target membrane. REs were then thought to ‘just’ sort internalized cargos, and they came in two flavors: Rab11-positive REs for apical targeting and TfnR-positive REs for basolateral targeting. Both viewpoints have been challenged in recent years. First, through ablation of endosomal compartments, researchers find ever more evidence that instead of being sorted directly from the TGN to the plasma membrane, cargos move through endosomes to reach their final destination. However, more work is needed to fully understand the role of endosomes in biosynthetic targeting. Second, we can no longer look at REs as a compartment with just two simple specifications. Instead, recent advances indicate that REs possess a high plasticity to accommodate the specific sorting needs of a diverse range of transmembrane proteins. Still, it is currently not entirely clear how different subdomains of REs are formed perhaps with the help of Rab proteins. Notably, in biosynthetic surface delivery REs emerge as a post-TGN compartment with perhaps equal sorting capacity as the TGN, and it is in REs where internalized proteins are correctly delivered back to the plasma membrane. This is a rapidly evolving field and it is increasingly becoming clear that the correct sorting of proteins implicated in for example cancer development is important for disease prevention.

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Summary

- Epithelial cells distinguish at least three different plasma membrane locations: apical domain, basolateral domain, and primary cilia.
- Plasma membrane proteins encode targeting signals in their luminal domains or cytoplasmic tails that are recognized by specific sorting machineries.
- Biosynthetic delivery of transmembrane proteins to the plasma membrane frequently involves the passage through endosomes.
- Basolateral and lysosomal proteins encode similar sorting signals in their cytoplasmic tails that are recognized by cytosolic AP complexes; and lysosomal proteins cycle exclusively through the basolateral membrane.
- REs present a plastic sorting station with multiple subdomains that aid in correct protein sorting of endocytic and biosynthetic cargos.
- AP-1B is instrumental for basolateral sorting from REs where it facilitates the generation of its own recycling endosomal subdomain.
- Primary cilia emerge from the apical membrane when epithelial cells are fully polarized. Ciliogenesis requires some proteins that are also involved in apical or basolateral targeting highlighting the plasticity of sorting pathways.

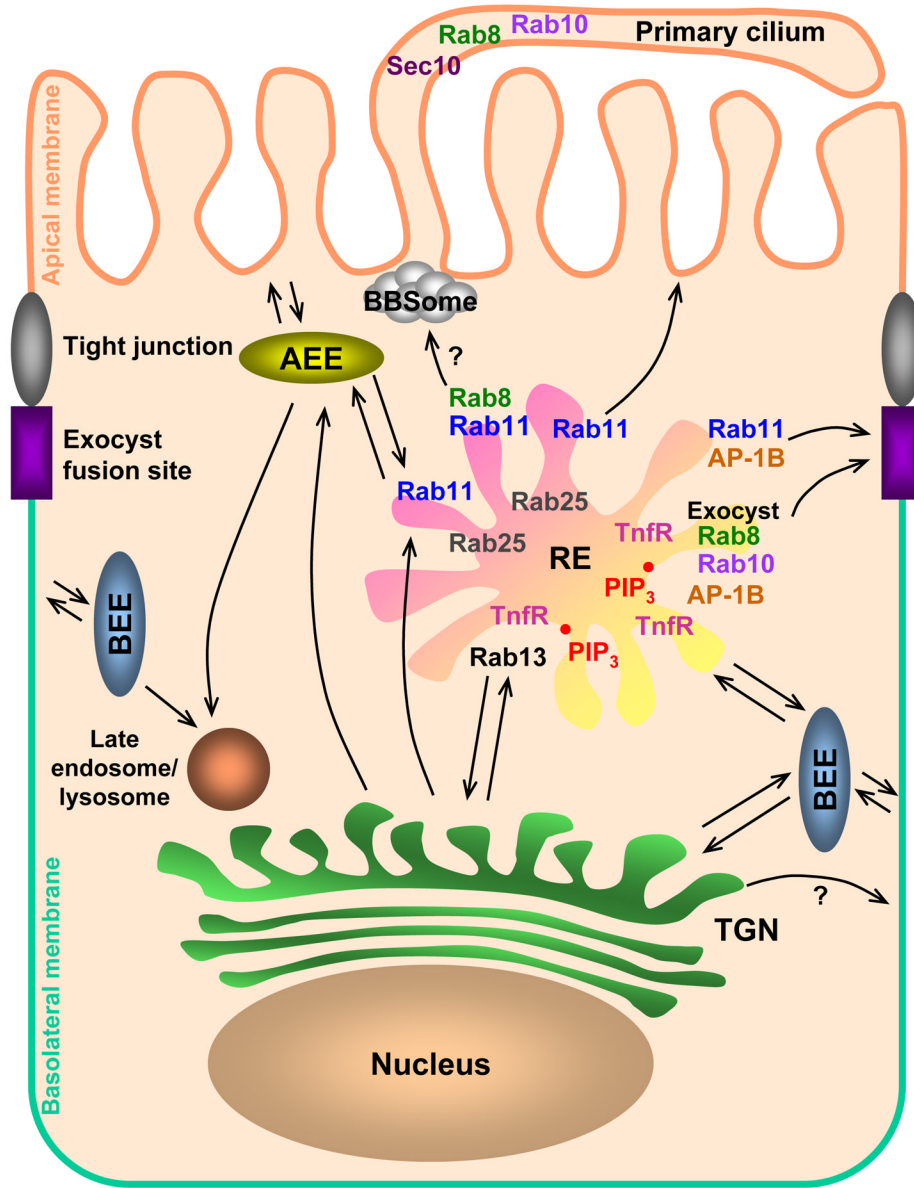


Figure 1. Model of different sorting pathways in a polarized epithelial cell
 The sorting of biosynthetic cargos to different plasma membrane domains occurs either at the *trans*-Golgi network (TGN) or in the recycling endosome (RE) in a polarized epithelial cell. Arrows indicate the direction of movement of representative cargos at various compartments. AEE, apical early endosomes; BEE, basolateral early endosomes; BBSome, octameric complex of Bardet-Biedl syndrome proteins; PIP₃, PI(3,4,5)P₃; TfnR, transferrin receptor. Question marks denote pathways that are not proven yet.