Review

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Orchestration of cell surface proteins by Rab11

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The organization of cells into interconnected structures such as animal tissues requires a sophisticated system directing receptors and adhesion proteins to the cell surface. The Rab11 small G proteins (Rab11a, b, and Rab25) of the Ras superfamily are master regulators of the surface expression of receptors and adhesion proteins. Acting as a molecular switch, Rab11 builds distinct molecular machinery such as motor protein complexes and the exocyst to transport proteins to the cell surface. Recent evidence reveals Rab11 localization at the trans-Golgi network (TGN), post-Golgi vesicles, and the recycling endosome, placing it at the intersection between the endocytic and exocytic trafficking pathways. We review Rab11 in various cellular contexts, and discuss its regulation and mechanisms by which Rab11 couples with effector proteins.

Cytoskeletal transport tracks

Just as traffic routes and logistic centers are a necessity for daily life, the structuring and communication of cellular networks strongly depends on transport processes. Analogous to the macroscopic world, our cellular microcosm has fast track routes for long-distance transport, and slower but more flexible transport systems for the delivery of cargo to outlying areas. Microtubule tracks and associated motor proteins enable high velocity and long-distance transport, whereas transport by the dynamic actin cytoskeleton and myosin motor proteins is in the order of a magnitude slower, but enables transport beyond the less-adaptable microtubule network. The transport system delivers organelles, membranes, proteins, signaling peptides, and RNA to their respective locales. In order to build and maintain the diverse cellular networks of multicellular organisms and to enable the sophisticated communication between these networks, transport processes have to be tightly controlled and directional.

Since the mid-1980s, molecular switches of the Ras small G protein superfamily have been increasingly identified as key regulators of intracellular trafficking [1]. Ras family proteins alternate between GTP- and GDP-bound forms [2]. The nucleotide-dependent conformational forms differentiate between the interaction distinct effector and regulatory proteins. Among the Ras small G protein subfamilies, the Ras-related in brain (Rab) and ADP ribosylation factor (Arf) subfamilies regulate many of the different intracellular transport processes [3,4]. The mammalian genome encodes >60 different Rab small G proteins, thereby allowing a diverse range of transport routes to be undertaken. Although the mechanisms behind Rab family protein function remain limited, research of other Ras subfamily proteins, such as Ras proto-oncoproteins and Rho family members, has begun to provide a basic understanding of how Rab family proteins regulate transport processes. Among the best-studied Rab small G proteins are the Rab5 and Rab11 proteins [4]. Whereas Rab5 functions in endocytic processes at the plasma membrane, Rab11 regulates exocytic and recycling processes, thereby directing proteins and membranes towards the cell surface. Recent evidence has provided a new wealth of knowledge regarding the functions and regulation of mammalian Rab11 protein in cell biological processes. In this review, we introduce various mammalian Rab11 proteins and discuss their varying molecular mechanisms and protein complexes, which direct the diversity of their cell biological functions. We also discuss their functions in human diseases.

Mammalian Rab11 proteins

The mammalian genome encodes three Rab11 proteins, Rab11a, b, and c, which share high sequence identity (mouse proteins, Rab11a: Rab11b, 91% identity; Rab11a: Rab11c, 62% identity; Rab11b: Rab11c, 61% identity). Rab11c is better known as Rab25 and is termed thus henceforth in this paper. Tissue expression of mammalian Rab11 proteins is variable. Whereas Rab11a has a ubiquitous expression pattern [5], gene expression studies have shown a restricted expression of Rab11b (brain, testis, and heart) [6] and Rab25 (lung, kidney, and gastric tract) [7]. However, a detailed expression analysis of all three Rab11 genes during mammalian development and in adult tissues remains to be undertaken. The Rab11 proteins encode a CCxxx (C: cysteine) isoprenylation motif at their C termini [8] and both cysteines present in Rab11 are geranylgeranylated, allowing membrane association.

Rab11-regulated transport processes

Rab11 proteins have been implicated in a variety of cellular traffic pathways. They localize to the TGN and post-Golgi vesicles of the secretory pathway [9], as well as control traffic

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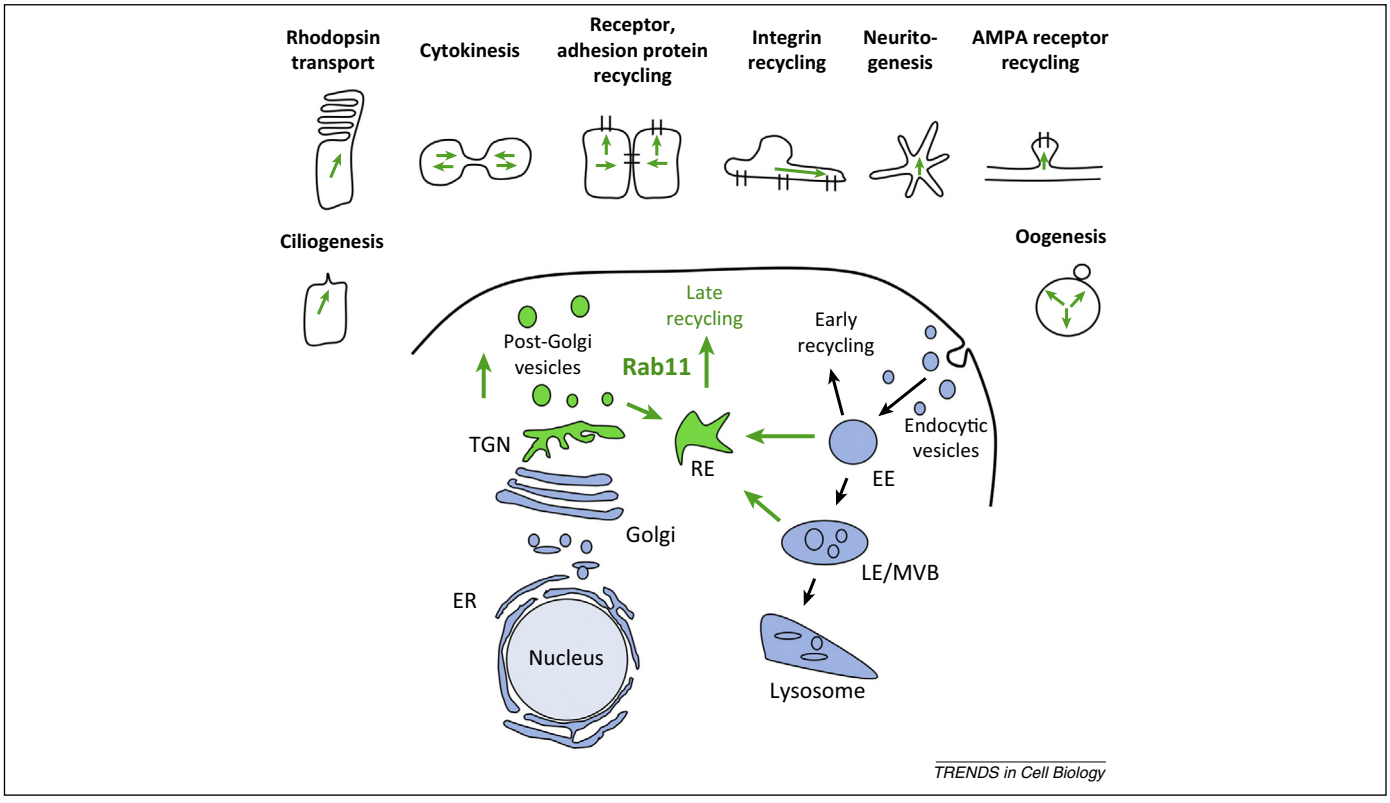

Figure 1. Rab11-regulated vesicle transport processes. Within membrane-trafficking routes, the small G protein Rab11 localizes at the TGN, post-Golgi vesicles of the secretory pathway, and the RE. During recycling of cell membrane proteins, Rab11 only functions in later transport steps from the EE and LE/MVB to the pericentriolar RE and back to the plasma membrane (late recycling), and is not involved in early recycling processes from the EE directly to the plasma membrane (early recycling). The localization of the Rab11 small G protein at intracellular membrane compartments is indicated in green. The diversity of Rab11 trafficking functions are shown. Green arrows depict the direction of the Rab11 transport in different cell types and under different cellular conditions. Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EE, early endosome; ER, endoplasmic reticulum; LE, late endosome; MVB, multivesicular body; Rab, Ras-related in brain; RE, recycling endosome; TGN, trans-Golgi network.

through the pericentriolar recycling endosome. Indeed, studies have shown that overexpression of an interfering Rab11 mutant does not influence early steps of cellular uptake and recycling of transferrin, but does inhibit recycling from the later recycling endosome [10]. Studies of Rab11 function in epithelial polarity showed that Rab11 is localized to apical recycling endosomes known as pericentriolar endosomal compartments [11,12]. To establish and maintain the apical/basolateral polarity of an epithelial cell, proteins are sorted at the TGN before their delivery to the appropriate cell surface domain [13]. This transport from the TGN to the cell surface is not always direct, and for some apical and basolateral proteins passage through a Rab8a/Rab11-positive recycling endosome has been described (Figure 1). Among these proteins is E-cadherin. Rab11-dependent trafficking and sorting of E-cadherin at the recycling endosome is important for all stages of epithelial polarity, from a nonpolarized stage through to a polarized epithelial monolayer [14]. In summary, Rab11 functions in exocytic processes at the TGN, and in recycling processes via pericentriolar recycling endosomes.

Rab11 has also been shown to regulate the transport of many receptors and adhesion proteins including the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, rhodopsin, epidermal growth factor (EGF) receptor, Toll-like receptor 4, α5β1 integrin, E-cadherin and N-cadherin (for review, see [15]) (Figure 1). In addition, Rab11 influences many diverse cellular functions including ciliogenesis, cytokinesis, neuritogenesis, and oogenesis [16–19] (Figure 1). The function of Rab11 in transport processes is closely related to the exocyst complex, a multisubunit protein complex implicated in the tethering of secretory vesicles to the plasma membrane (for review, see [20]). The Sec15 subunit of the exocyst complex directly interacts with Rab11 [21]. A detailed description of the exocyst complex is presented in Box 1.

Rab11 motor protein complexes

Important insight into the molecular mechanisms of how a single small G protein can act in various cell biological processes was gained through the discovery of Rab11 in multiple motor protein complexes. By interacting with adaptor proteins, Rab11 can form complexes with distinct motor proteins, which enable bidirectional transport along microtubule tracks, as well as actin-filament-dependent transport. The varying motor proteins guide Rab11 vesicles to varying subcellular locales of different polarity and morphology via microtubule tracks or actin/myosin forces [19,22] (Box 2).

The first Rab11 motor protein interaction was described for the actin motor protein myosin Vb (MyoVb) [23] (Figure 2). In contrast to the conventional myosin II, which is responsible for muscle contraction, MyoVb is a processive motor with an actin gliding velocity of 0.22 μm/s [24]. Actin-dependent Rab11/MyoVb transport plays an essential role in the recycling of the AMPA receptor in dendritic spines and in the transport of vesicles towards the mouse oocyte cortex [19,22] (Box 2). Specifically, Rab11 interacts directly with the MyoVb globular tail domain, while the C-terminal MyoVb sequences interact with the Rab11 effector and