

Editorial Summary

GTPases in Intracellular Trafficking: An Overview

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Abstract

Small GTPases that belong to the ras sub-families of Rab, Arf, and Rho, and the large GTPase dynamin, regulate intracellular trafficking. This issue of *Seminars of Cell and Developmental Biology* highlights topics regarding mechanisms by which these GTPases regulate the different steps of vesicular transport: vesicle formation, scission, targeting and fusion. In addition, the emerging roles of GTPases in coordination of individual transport steps as well as coordination of intracellular trafficking with other cellular processes are reviewed. Finally, common structures and mechanisms underlying the function of the ras-like GTPases and the importance of their function to human health and disease are discussed.

Text

In the exocytic and endocytic pathways, proteins are transported between different intracellular compartments via membrane-bound tubule-vesicular structures. The machinery that mediates this vesicular transport is highly conserved both between the different transport steps and between organisms. Small GTPases have emerged as key regulators of vesicular transport. Small GTPases are proteins that switch between the GDP- and GTP-bound forms with the help of guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). In addition, GTPases cycle between the cytoplasm and membranes, sometimes with the aid of the GDP-dissociation inhibitor (GDI) and the GDI-dissociation factor (GDF) (Seabra and Wasmeier, 2004). When on membranes and in the GTP-bound form, GTPases interact with their specific effectors, which mediate vesicular transport ([Figure 1](#)).

Until 1988, large and small GTPases, e.g., the large hetero-trimeric G-proteins and the small ras oncogene, were thought to function only in transduction of signals across the plasma membrane (Barbacid, 1987; Gilman, 1987). The first GTPase implicated in trafficking inside cells was Ypt1, which was shown to localize to the yeast Golgi and to have a mammalian homolog, Rab1, with conserved localization (Segev *et al.*, 1988). Ypt/Rab is the largest ras sub-family, with eleven yeast Ypts and ~70 human Rabs (Stenmark and Olkkonen, 2001). Subsequently, Arf, which was originally identified as a co-factor in ADP-ribosylation of hetero-trimeric G-proteins (Kahn and Gilman, 1986), was also shown to act in transport inside cells and to localize to the Golgi (Stearns *et al.*, 1990). The Arf sub-family consists of seven members in yeast and 29 in humans (Gillingham and Munro, 2007). The Rho GTPase sub-family includes five

yeast and twenty-two mammalian members and is known to regulate the actin and microtubular cytoskeletons and to affect multiple biological processes like cell polarity and motility (Jaffe and Hall, 2005). Only recently, were Rho GTPases also implicated in the regulation of intra-cellular trafficking. Lastly, the large GTPase Dynamin was linked to endocytosis in the 1990s (Robinson, 1994), but the mechanism by which it functions has been under a debate since then.

During the past two decades the field of trafficking GTPases was engaged in elucidation of the molecular mechanisms by which these proteins regulate individual transport steps, and identifying their upstream regulators and downstream effectors. It is now clear that individual GTPase sub-families function is somewhat overlapping, but can be divided roughly to the different vesicular transport sub-steps ([Figure 2](#)): Arf GTPases regulate coat assembly during vesicle formation (Kreis *et al.*, 1995), and the first review highlights the role of Arf GAPs in vesicle coat assembly and disassembly (East and Kahn, 2011). The second review presents progress in our understanding of the mechanisms by which dynamin mediates vesicle fission (Ramachandran, 2011). Ypt/Rab effectors have been implicated in all aspects of vesicular life (Segev, 2001b, a). However, their most established role is in vesicle targeting. The third review describes how interactions of Ypt/Rabs with tethering factors, SNAREs and vesicle coats regulate vesicle targeting (Angers and Merz, 2011). Finally, the role of Rho GTPases in tethering and fusion of vesicles of polarized and regulated exocytosis is summarized in the fourth review (Ory and Gasman, 2011).

Currently, the field is busy investigating the role of GTPases in a higher level of regulation. The fifth review summarizes what we know about coordination of individual

transport steps by GTPases (Segev, 2011). An example of GTPase-dependent coordination of intra-cellular trafficking with other cellular processes is presented in the sixth review. Here, the impact of Arf-mediated endocytosis on three processes, cell motility, cytokinesis and cholesterol homeostasis, is described (Schweitzer *et al.*, 2011). Structures, interactions and mechanisms of small GTPases are compared in the seventh review (Itzen and Goody, 2011). The last review summarizes what we currently know about the involvement of Rab GTPases in human disorders (Mitra *et al.*, 2011).

Figures

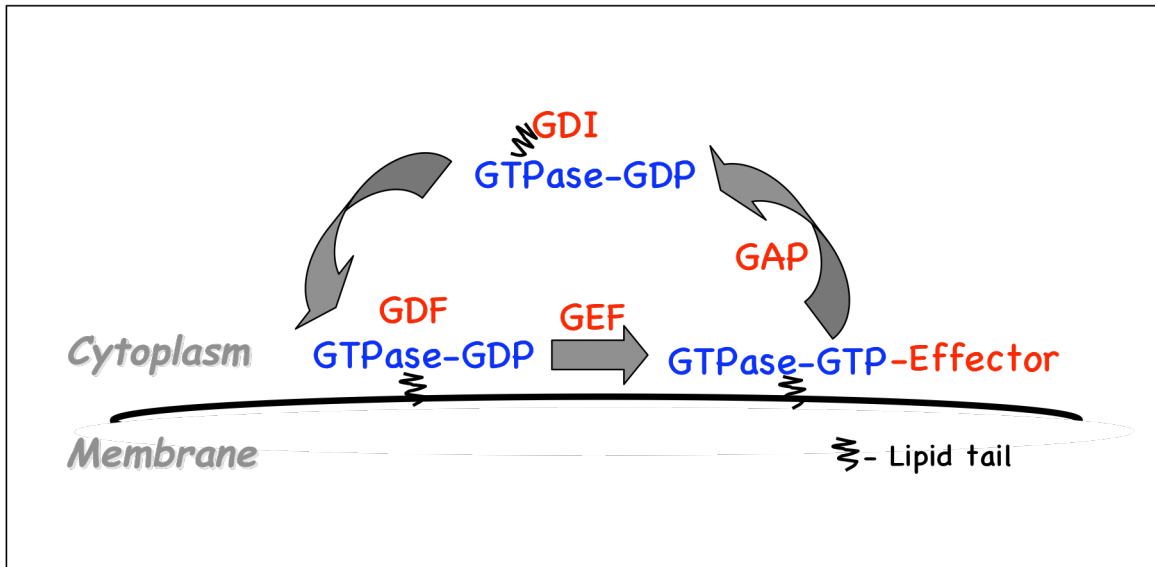


Figure 1: A diagram illustrating how the switching of GTPases between the GDP- and GTP-bound forms (in blue) is coupled with their cycling between the cytoplasm and membranes with the help of their accessory factors: GEF, GAP, GDI and GDF (red). GTPases attach to the membrane via a lipid tail, which is masked by GDI when in the cytoplasm. When on the membrane in their GTP-bound form, GTPases interact with their effectors, which mediate the different steps of vesicular transport.

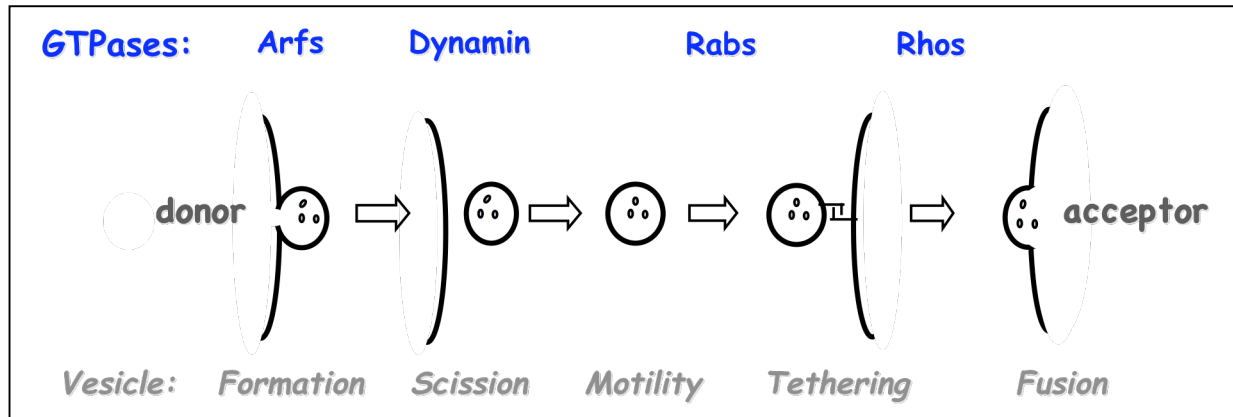


Figure 2: A diagram showing the GTPase families that regulate vesicle transport sub-steps as highlighted in this issue: vesicle formation is regulated by Arfs, vesicle scission by dynamin, vesicle motility by Rabs (not discussed here), vesicle tethering by Rabs and Rhos, and vesicle fusion by Rhos.

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