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CELL SCIENCE AT A GLANCE

Cellular functions of Rab GTPases at a glance

Yan Zhen[1,2] and Harald Stenmark[1,2,*]

ABSTRACT

Rab GTPases control intracellular membrane traffic by recruiting specific effector proteins to restricted membranes in a GTP-dependent manner. In this Cell Science at a Glance and the accompanying poster, we highlight the regulation of Rab GTPases by proteins that control their membrane association and activation state, and provide an overview of the cellular processes that are regulated by Rab GTPases and their effectors, including protein sorting, vesicle motility and vesicle tethering. We also discuss the physiological importance of Rab GTPases and provide examples of diseases caused by their dysfunctions.

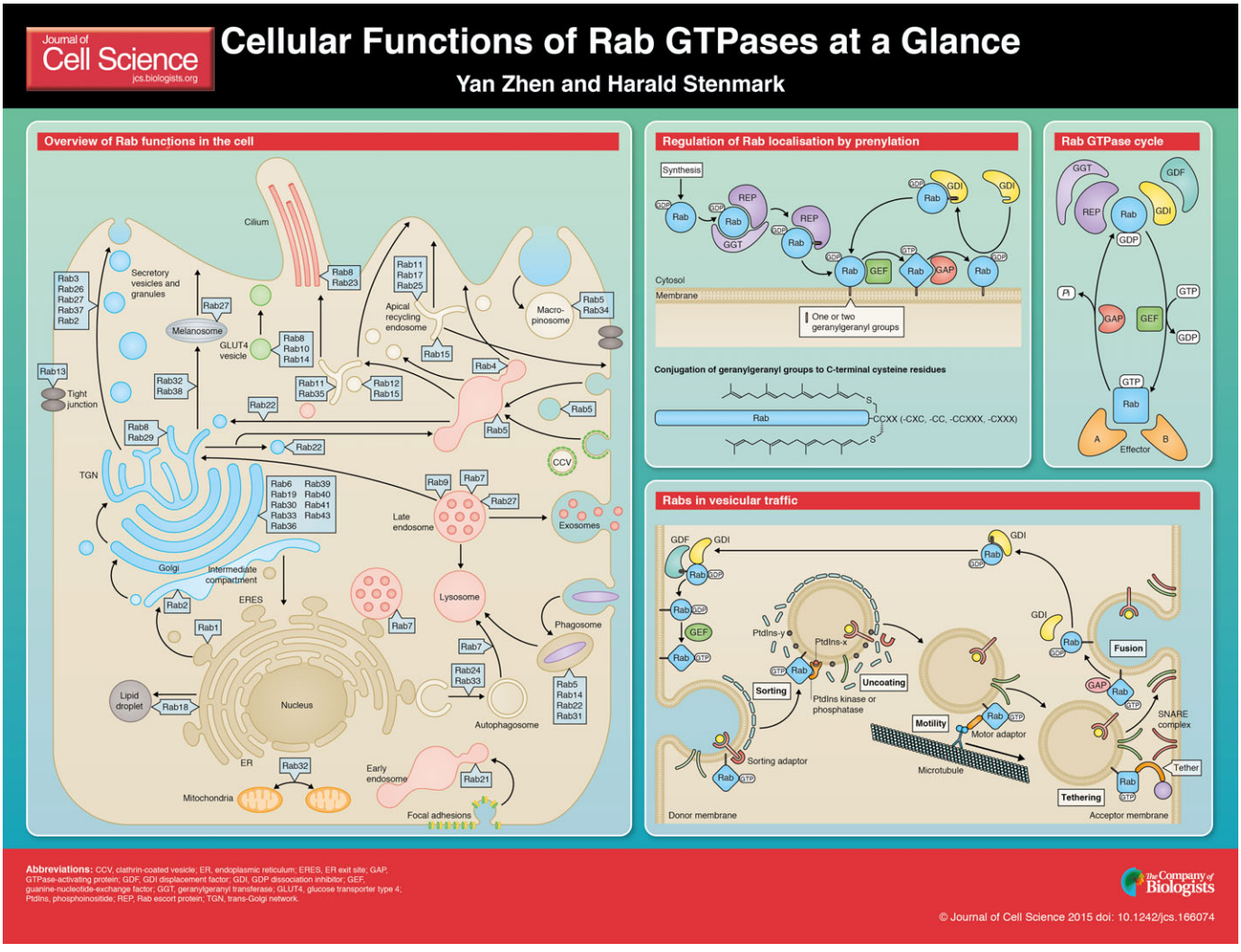
KEY WORDS: GTPase, Rab, Traffic

[1]Centre for Cancer Biomedicine, Faculty of Medicine, University of Oslo, Montebello, Oslo N-0379, Norway. [2]Department for Molecular Cell Biology, Institute for Cancer Research, Oslo University Hospital, Montebello, Oslo N-0379, Norway.

*Author for correspondence (stenmark@ulrik.uio.no)

Introduction

Rab GTPases constitute the largest family of small GTPases (almost 70 members in humans) and are known as master regulators of intracellular membrane traffic (Stenmark, 2009; Wandinger-Ness and Zerial, 2014). Distinct Rab GTPases localize to different membrane compartments in order to control the specificity and directionality of membrane trafficking pathways, mostly related to vesicular transport. In doing so, they contribute to confer membrane identity (Pfeffer, 2013) and to ensuring that membrane-bound cargoes are transported to their correct destinations within the cell. For many human Rab GTPases several isoforms (structurally related



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proteins encoded by different genes) exist that perform partially redundant functions, either by working in slightly different ways or by being expressed differentially in different cell types. A useful web-based tool has recently been developed to identify Rab GTPases and classify them into subfamilies based on sequence (Diekmann et al., 2011). In this Cell Science at a Glance and the accompanying poster, we will provide a brief overview of the cellular functions of Rab GTPases with a focus on their regulators and effectors, and the pathways they control.

Rab GTPases as molecular switches in membrane traffic

Like other small GTPases, Rab GTPases principally function as molecular switches that are 'on' when GTP is bound and 'off' when GDP is bound. Conformational differences between the GDP- and GTP-bound forms mainly involve two regions, termed switch I and switch II, which specifically interact with effector proteins when GTP is bound (Eathiraj et al., 2005). In the GDP-bound state, the switch regions appear to be unfolded, whereas they adopt well-defined conformations when GTP is bound, and this allows effector binding (Lee et al., 2009). Examples of structurally well-characterized Rab-effector interactions include those of Rab3a with rabphilin-3A (Ostermeier and Brunger, 1999), Rab5a with rabaptin-5 (Zhu et al., 2004), Rab4 and Rab22 with rabenosyn-5 (Eathiraj et al., 2005), Rab27a with Slp2-a (also known as Sytl2-a) (Chavas et al., 2008), Rab6a with Rab6IP1 (also known as DENND5A) (Recacha et al., 2009), and Rab11a with PI4KIIIβ (Burke et al., 2014).

Rab GEFs and GAPs

As is the case for other small GTPases, the nucleotide cycle of Rab GTPases is tightly controlled by guanine-nucleotide-exchange factors (GEFs) and GTPase-activating proteins (GAPs) that are specific for single Rab GTPases or Rab subfamilies (see poster) (Barr and Lambright, 2010). GEFs mediate the activation of Rab GTPases by promoting the exchange of bound GDP with GTP, which is in large excess over GDP in cytosol. Different types of GEFs function in slightly different ways and have different catalytic domains, such as DENN and Vps9 domains. Whereas DENN domains appear to promote GDP release by forcing contacts between a lysine residue in the phosphate-binding 'P loop' and glutamine and aspartate residues in the switch II region, Vps9 domains (which are found in GEFs for the Rab5 subfamily) contribute an acidic residue that interacts with the P-loop lysine (Langemeyer et al., 2014). Rab GAPs turn Rab GTPases off by stimulating their ability to hydrolyze GTP into GDP. Most (but not all) Rab GAPs are distinguished by the presence of a TBC1 domain. Because many Rab GTPases, including Rab5, hydrolyze GTP at a relatively high intrinsic rate, Rab GAPs might be less crucial than GEFs in general (Barr and Lambright, 2010).

Rab effectors

Rab effectors, defined as proteins that interact specifically with the GTP-bound from of a Rab GTPase, come in many flavours and include molecular tethers, fusion regulators, motors, sorting adaptors, kinases, phosphatases, components of membrane contact sites and Rab regulators (Gillingham et al., 2014). The recruitment of such effectors in a spatiotemporally controlled manner contributes strongly to the fidelity and specificity of intracellular membrane traffic. There are also a few examples of proteins that are regulated by GDP-bound Rabs or that interact with Rabs in a nucleotide-independent fashion, including the interactions between Rab21 and β1-integrin, Rab11 and protrudin, Rab7 and VPS34, and Rab27a and Coronin3 (Kimura et al., 2008; Pellinen et al., 2006; Shirane and Nakayama, 2006; Stein et al., 2003); however, the term 'effector' should be reserved for those proteins that interact exclusively with the GTP-bound form of a Rab GTPase. In some cases, different Rab GTPases bind to overlapping or non-overlapping sites on the same effector, such as the interaction of Rab4, Rab5 and Rab22 with rabenosyn-5, Rab4, Rab5 and Rab33 with rabaptin-5, Rab5 and Rab22 with EEA1, and Rab2, Rab6 and Rab39 with bicaudal-D (Eathiraj et al., 2005; Gillingham et al., 2014; Valsdottir et al., 2001; Vitale et al., 1998). There are also examples of Rab effectors that have Rab GAP or GEF activity, such as RUTBC1 and RUTBC2, which are effectors for Rab9 and GAPs for Rab32, Rab33 and Rab36 (Nottingham et al., 2011, 2012), the rabaptin-5–Rabex5 complex, which is an effector and GEF for Rab5 (Horiuchi et al., 1997), and the HOPS complex, an effector of Rab5 and a GEF for Rab7 (Nottingham et al., 2011, 2012; Rink et al., 2005). The resulting feed-forward loops in GEF activation are likely to promote the rapid membrane accumulation of Rab GTPases whereas feedback loops involving GAPs likewise promote their rapid removal. Together, these systems enable the promotion of time-limited membrane domains with unique compositions (Barr, 2013; Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Isoprenylation and reversible membrane localization of Rab GTPases

Rab GTPases exist in both soluble and membrane-bound pools. Strong membrane association is ensured by posttranslational modification of C-terminal cysteine residues with one or (in most cases) two lipophilic geranylgeranyl groups (20-carbon isoprenoid groups; see poster). Geranylgeranylation is mediated by Rab geranylgeranyl transferase (GGTase II, also known as RABGGTB) in cooperation with Rab escort protein (REP, for which there are several isoforms) (Leung et al., 2006). The latter protein chaperones the newly geranylgeranylated Rab GTPase to its correct cellular membrane. A related protein, Rab GDP dissociation inhibitor (GDI, for which there are several isoforms), mediates dissociation of geranylgeranylated Rab GTPases from membranes and chaperones the hydrophobic conjugates in the cytosol. Rab GDI specifically recognizes Rabs in their GDP-bound form and thereby serves to solubilize Rabs from membranes once GTP hydrolysis has been completed (Goody et al., 2005). GDI also serves to present Rab GTPases to specific membranes (Soldati et al., 1994; Ullrich et al., 1994). This has been proposed to occur through a membrane-associated GDI displacement factor (GDF) that recognizes the Rab–GDI complex (Sivars et al., 2003). However, there is also evidence that a membrane-bound GEF is sufficient to lead to the accumulation of a Rab GTPase on a specific membrane (Schoebel et al., 2009), and in budding yeast, GEFs but not GDFs are required for membrane-targeting of Rab GTPases (Cabrera and Ungermann, 2013). This indicates that compartment-specific GEFs play a central role in defining the precise localization of Rab GTPases.

Rab GTPases in vesicle traffic and beyond

The fact that Rab effectors are highly diverse illustrates that Rab GTPases control multiple biochemical events (see poster). Most functions of Rab GTPases and their effectors are related to vesicular traffic between a donor and an acceptor compartment, and it is interesting to note that distinct Rab effectors are involved in the sorting of cargo into budding vesicles, vesicle uncoating or vesicle motility along actin filaments or microtubules, as well as vesicle tethering to acceptor membranes (Stenmark, 2009). Through these activities, Rab GTPases control compartment maturation, as well as

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Table 1. Rab GTPases and their regulators/effectors whose genes are mutated in genetic diseases

Protein type	Protein name	Disease	Manifestation	Reference(s)
Rab GTPase	Rab7a	Charcot–Marie–Tooth type 2B	Peripheral neuropathy	Verhoeven et al., 2003
	Rab18	Warburg micro syndrome, Martsolf syndrome	Mental retardation, cataracts, hypogonadism	Bem et al., 2011; Handley et al., 2013
	Rab23	Carpenter syndrome	Obesity, cranofacial malformations, syndactyly	Jenkins et al., 2007
	Rab27a	Griscelli syndrome type 2	Partial albinism, immunodeficiency	Menasche et al., 2001
	Rab39b	X-linked mental retardation, early onset Parkinson's disease	Mental retardation, neurodegeneration	Wilson et al., 2014
	Rab28	Cone-rod dystrophy	Impaired vision	Roosing et al., 2013
GAP for Rab3	Rab3GAP1 and Rab3GAP2	Warburg micro syndrome, Martsolf syndrome	Mental retardation, cataracts, hypogonadism	Handley et al., 2013
GEF for Rab32 and Rab38	HPS1, HPS4	Hermansky-Pudlak syndrome	Partial albinism, bleedings, lysosomal accumulation of ceroid lipofuscin	Gerondopoulos et al., 2012
REP	REP1	Choroideremia	Progressive blindness	Andres et al., 1993
GGT	Rab GGTa	Hermansky-Pudlak syndrome (in mice)	Partial albinism, bleedings, lysosomal accumulation of ceroid lipofuscin	Detter et al., 2000
GDI	GDI1	X-linked mental retardation	Mental retardation	D'Adamo et al., 1998
Effector for Rab27a	Melanophilin	Griscelli syndrome type 3	Partial albinism	Menasche et al., 2003
Effector (indirectly) for Rab27a	Myosin 5a	Griscelli syndrome type 1	Partial albinism, neurological abnormalities	Menasche et al., 2003
Effector for Rab27a	Munc13-4	Familial hemophagocytic lymphohistiocytosis type 3	Hyperinflammation, immunodeficiency	Feldmann et al., 2003
Effector for Rab6	COH1/VPS13b	Cohen syndrome	Microcephaly, mental retardation, hypotonia, myopia, retinal dystrophy, obesity	Seifert et al., 2015
Effector for Rab8a and Rab11a	Myosin Vb	Microvillus inclusion disease	Chronic diarrhea	Knowles et al., 2014

vesicle shuttling between different membrane compartments. The first Rab GTPases identified through yeast genetics, Sec4 (Rab8) and Ypt1 (Rab1), were shown to have crucial roles in vesicle transport in the exocytic pathway (Hutagalung and Novick, 2011), but studies in multiple organisms have identified a number of Rab GTPases that also control endocytic membrane traffic (Wandinger-Ness and Zerial, 2014). Furthermore, mostly through their roles in vesicular transport, Rab GTPases also control specialized structures, such as primary cilia, lipid droplets, autophagosomes, focal adhesions, tight junctions and interorganeller membrane contact sites (see poster) (Deretic, 2013; Martin et al., 2005; Martin and Parton, 2008; Marzesco et al., 2002; Munafo and Colombo, 2002; Pellinen et al., 2006; Raiborg et al., 2015). Because membrane traffic impacts on numerous cellular functions, Rab GTPases are not only regulators of membrane traffic as such, but, indirectly they also control cell signaling, polarity, migration and division (De Franceschi et al., 2015; Militello and Colombo, 2013; Numrich and Ungermann, 2014; van IJzendoorn et al., 2003). This illustrates the wide functional repertoire and great importance of this GTPase family.

Table 2. Rab GTPases and cancer

Rab	Cancer	Reference(s)
Rab1a	Tongue cancer, colorectal cancer	Shimada et al., 2005; Thomas et al., 2014
Rab3a	Brain tumours	Kim et al., 2014
Rab5a	Breast cancer	Frittoli et al., 2014; Yang et al., 2011
Rab7a	Lung cancer, melanoma	Alonso-Curbelo et al., 2014; Nakano et al., 2012
Rab14	Non-small-cell lung cancer	Wang et al., 2011
Rab23	Bladder cancer	Ho et al., 2012
Rab25	Ovarian cancer, breast cancer, colon cancer, head and neck cancer	Cheng et al., 2006; Cheng et al., 2004; Goldenring, 2013
Rab31	Breast cancer	Kotzsch et al., 2008
Rab38	Glioma	Wang and Jiang, 2013
Rab40b	Breast cancer, gastric cancer	Jacob et al., 2013; Li et al., 2015

In general, these Rab GTPases are overexpressed in cancers. The exception is Rab25, whose expression is decreased in triple-negative breast cancer, colon cancer and head and neck cancer (Goldenring, 2013).

Rab GTPases and diseases

Given the importance of Rab GTPases in membrane traffic, and the importance of membrane traffic for human health (Olkkonen and Ikonen, 2000), it is perhaps surprising that only a limited number of genetic diseases are associated with Rab dysfunctions. The existence of multiple Rab isoforms and trafficking pathways presumably makes humans less vulnerable to mutations in individual Rab-encoding genes. Nevertheless, several mutations in Rab GTPases or their effectors or regulators are associated with genetic diseases (Seixas et al., 2013). Examples of genetic diseases associated with mutations in Rab GTPases include albinism, immunodeficiences, neuropathies, mental retardation and ciliopathies (see Table 1). Rab27a provides a good illustration of how mutations in a Rab GTPase or its effectors can cause genetic disease. This GTPase controls exocytosis of lysosome-related organelles, such as melanosomes (in melanocytes) or lytic granules (in natural killer and T cells), and mutations in the *RAB27A* gene cause a combined albinism and immunodeficiency syndrome known at Griscelli syndrome type 2 (Menasche et al., 2001). Interestingly, mutations in the gene encoding the Rab27a effector

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Munc13-4 (also known as UNC13D) in natural killer and T cells cause an immunodeficiency disease, familial hemophagocytic lymphohistiocytosis type 3 (Feldmann et al., 2003), and mutations in *RAB27A* that selectively affect binding to this effector cause a form of Griscelli syndrome without an albinism phenotype (Cetica et al., 2015). In melanocytes, the Rab27a effector melanophilin (also known as Slac2-a) functions as a motor adaptor that connects Rab27a-positive melanosomes to the actin motor myosin-5a to promote melanosome exocytosis, and mutations in the genes encoding melanophilin or Myosin-5a cause Griscelli syndrome variants with an albinism phenotype but not immunodeficiency (Menasche et al., 2003).

In addition to genetic mutations, dysregulation of Rab GTPases is also observed in cancers (Table 2). Typically, increased expression levels of certain Rab GTPases, such as Rab1a, Rab3a, Rab5a or Rab7a, are associated with progression of specific cancer types, although there are also examples suggesting that loss of Rab expression can drive cancers, as shown for Rab25 in colon cancer (Goldenring, 2013). An example of how increased Rab expression might drive cancer progression is provided by Rab5a, which is overexpressed in aggressive breast cancers. Together with Rab4 and the Rab5 and Rab4 effector rabenosyn-5, Rab5a drives an endocytic–exocytic cycle that is crucial for the formation of invadopodia, cancer cell protrusions that promote tissue invasions and metastasis (Frittoli et al., 2014).

Rab GTPases and parasite–host interactions

Rab GTPases play a crucial role in phagocytosis and phagosome maturation, and as such they are important components of innate immunity (Flannagan et al., 2012). Many intracellular pathogens target Rab GTPases in order to interfere with the ability of the host cell to phagocytose and degrade pathogens. Frequent targets for bacterial effectors are Rab GTPases that reside on endosomes and phagosomes, such as Rab4, Rab5, Rab9, Rab11 and Rab22, but a number of Rab GTPases found in the endoplasmic reticulum (ER) and Golgi are also targeted by pathogenesis factors, including Rab1, Rab2, Rab6 and Rab8 (Sherwood and Roy, 2013). These bacterial pathogenesis factors can either act as Rab GEFs or GAPs that activate or inactivate specific Rab GTPases, or they can interfere with Rab functions through enzymatic modifications, such as lipidation, AMPylation or proteolytic cleavage, or by antagonizing Rab effectors. A typical outcome of such interference with Rab functions is that the pathogen achieves a remodeling of the endomembranes of the host, which enables it to evade destruction in the phagolysosome and establish a replicative niche within the host.

Rab GTPases as research tools

The specific localization of different Rab GTPases to defined membrane compartments, and their ability to regulate specific trafficking pathways, have made them attractive as research tools to study intracellular membrane transport. It must be noted that overexpression of various Rab GTPases frequently produces profound cellular phenotypes, such as changes in organelle and cell morphology, or cytoskeletal rearrangements (Bucci et al., 1992; Peranen et al., 1996); therefore, the use of transfected Rab GTPases as membrane markers is only advisable when expression levels are kept low. Likewise, dominant-negative and constitutively active Rab mutants have been frequently used to dissect membrane trafficking, but the interpretations of experiments that employ Rab mutants are complicated by the fact that similar mutations affect different Rab GTPases differentially. For instance, whereas an 'activating' mutation of the conserved glutamine residue in switch II in Rab5 inhibits its intrinsic but not GAP-stimulated GTP hydrolysis, a similar mutation in Rab1 and Rab35 inhibits GAP-stimulated but not intrinsic GTP hydrolysis. The same mutation also prevents GEF-mediated activation of Rab35 but not of Rab1 (Langemeyer et al., 2014). Thus, although Rab mutants are very useful research tools, conclusions that are based on soley their use should be made with caution.

Conclusions

Together with SNARE proteins that mediate specificity of vesicle docking and fusion (Sudhof and Rothman, 2009), Rab GTPases are central regulators of intracellular membrane traffic. The diversity of Rab GTPases and their effectors is consistent with the view that intracellular trafficking pathways are complex, and such complexity indeed started to evolve early in eukaryotic history (Diekmann et al., 2011; Klopper et al., 2012). In contrast to canonical SNARE proteins, which are irreversibly anchored to membranes by transmembrane segments, Rab GTPases shuttle between the cytosol and membranes, and this makes them well suited to define the directionality of vesicle transport processes (Stenmark, 2009). Our appreciation of the importance of Rab GTPases in cell biology and biomedicine is continuously increasing as we learn more about these proteins, their regulators and effectors.

Competing interests

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