Rab GTPases at a glance

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The authors regret that in Table 1 under '**(13) Rab1, Rab3, Rab8, Rab10, Rab12, Rab13, Rab15, Rab35, Rab40**', Rab35 was incorrectly referred to as an uncharacterized member of the Rab family.

The correct details are given below.

Rab	Localization	Function	Reference
Rab35	Plasma membrane, endosomes, intercellular bridge	Rapid endocytic recycling and cytokinesis	Kouranti et al., 2006

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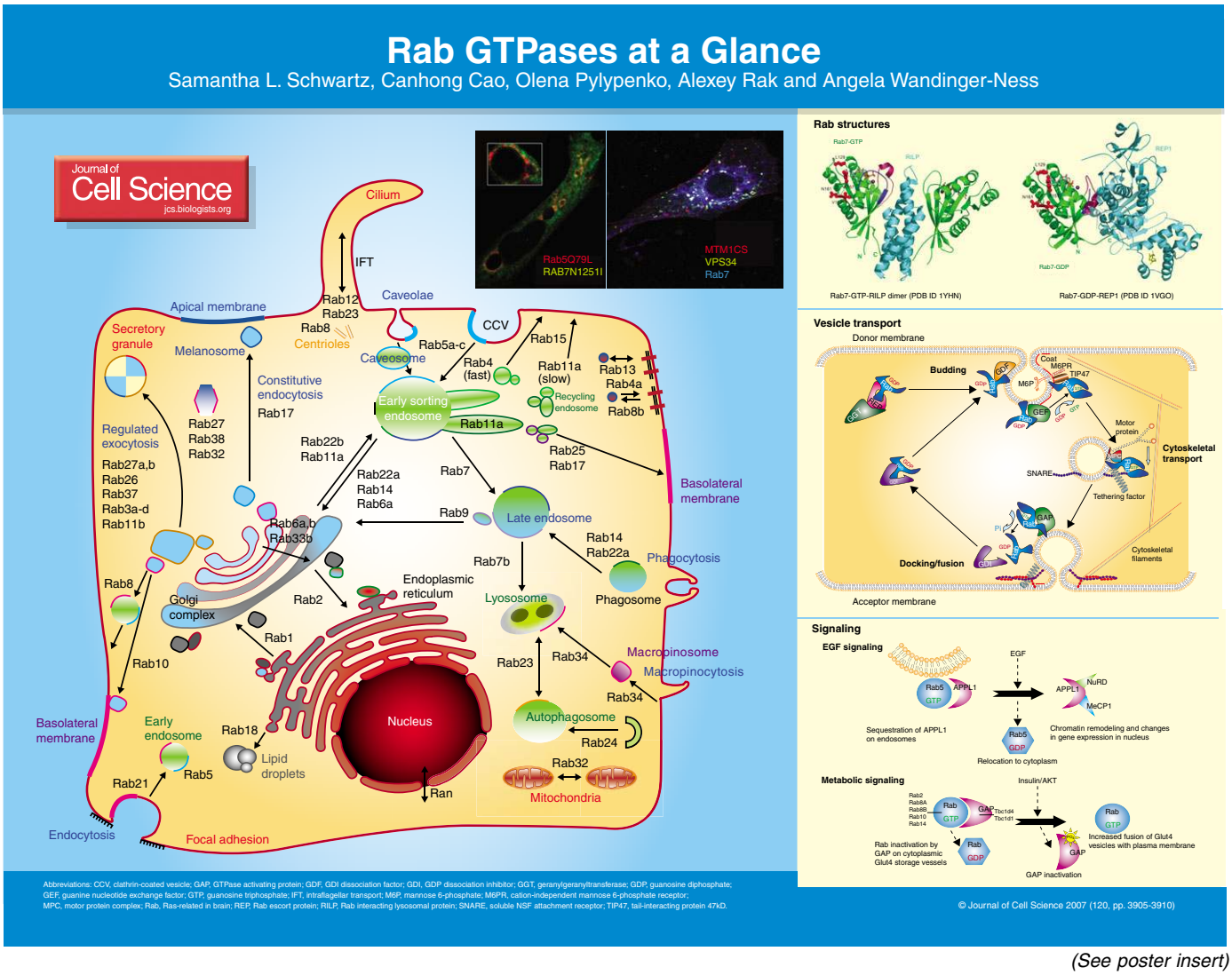
It has been two decades since the yeast Ypt1 and Sec4 proteins and the mammalian Rab (Ras-related proteins in brain) GTPases were first identified as evolutionarily conserved, essential regulators of membrane trafficking (Salminen and Novick, 1987; Schmitt et al., 1986; Touchot et al., 1987). The proteins are members of the wider Ras superfamily of GTPases (Wennerberg et al., 2005). Over 70 human Rab and Rab-like members of the Ras superfamily have been identified (Colicelli, 2004; Stenmark and Olkkonen, 2001), and the functions of 36 Rab GTPases have been delineated. Rab GTPases are molecular switches, cycling between active and inactive states and serving as scaffolds to integrate both membrane trafficking and intracellular signaling in a temporally and spatially sensitive manner (Bucci and Chiariello, 2006; Zerial and McBride, 2001). Despite the small sizes of Rab proteins (20-25 kDa), structural analyses reveal they have multiple interaction surfaces through which they associate with regulatory molecules and downstream effectors to exert their functions (Chen et al., 2003; Pereira-Leal and Seabra, 2000; Pfeffer, 2005).

Rab GTPases regulate membrane trafficking, cell growth and differentiation

Characterization of around half of the known Rab GTPases has revealed the extraordinary complexity of membrane trafficking circuits and shows that Rab GTPases are also essential for signaling and the control of cell proliferation and differentiation. Rab proteins are present on all compartments of the endomembrane system (endoplasmic reticulum, Golgi, endosomes, lysosomes), the nucleus, the plasma membrane (including cell junctions and focal adhesions), mitochondria and centrioles. In addition, they help regulate



(See poster insert)

a vast array of basic cellular functions – from macromolecular homeostasis to growth control.

Rab proteins are best known for their essential roles in exocytic and endocytic membrane trafficking, which encompass the constitutive and regulated secretory routes, endocytosis via caveolae or clathrin-coated vesicles (CCVs), micropinocytosis and phagocytosis. They control anterograde and retrograde trafficking between compartments to coordinate cargo delivery and membrane recycling and also subcompartmentalize organelles by organizing specific membrane domains that function in trafficking of cargo to different destinations (colored lines on the poster denote such domains; the micrograph illustrates alternating Rab7 and Rab5 domains on dilated early endosomes) (Barbero et al., 2002; Vitale et al., 1998; Vonderheit and Helenius, 2005). In this way, Rab GTPases regulate plasma membrane delivery, organelle biogenesis and degradative pathways (lysosomal and autophagic). They also contribute to cell-type-specific functions, such as regulated secretion (secretory granules/lysosomes in endocrine and exocrine cells), synaptic transmission [synaptic vesicles (SVs) in neurons] and phagocytosis (in macrophages and dendritic cells). In epithelia, Rab GTPases help generate polarity by regulating the trafficking of junctional proteins and integrins and by defining epithelial transport circuits to cilia (connecting with intraflagellar transport, IFT), the apical (AM) and basolateral (BM) membranes, and apical recycling endosomes (AREs). They thus play major regulatory roles maintaining compartment identity, regulating cargo delivery, controlling protein and lipid storage/degradation and modulating specialized trafficking functions.

Rab proteins are increasingly found downstream of signaling cascades and can impact gene expression and growth control. Rab5, for example, is implicated in EGF signaling and thought to sequester APPL1, an adaptor protein

Table 1. The Rab family

Rab	Localization	Function	References
(1) Rab23			
Rab23	Plasma membrane and endosomes	Trafficking of sonic hedgehog signaling components; embryogenesis; ciliary trafficking	Evans et al., 2003
(2) Rab29, Rab32, Rab38, Rab7L1			
Rab32	Perinuclear vesicles; mitochondria	Post-Golgi trafficking of melanogenic enzymes; binds PKA and regulates mitochondrial dynamics	Alto et al., 2002; Wasmeier et al., 2006
Rab38	Tyrosinase-positive vesicles	Post-Golgi biogenesis of melanosomes	Wasmeier et al., 2006
(3) RabL2, RabL3, RabL5			
(4) Ran			
Ran	Nucleus, cytoplasm	Nucleocytoplasmic transport	Joseph, 2006
(5) Rab7, Rab7b, Rab9			
Rab7, Rab7b	Late endosomes, lysosomes	Transport from early to late endosomes; lysosome biogenesis; b) transport to lysosomes, TLR4 signaling	Feng et al., 2001; Bucci et al., 2000; Wang et al., 2007
Rab9a,b,c	Late endosomes	Lysosomal enzyme and cholesterol trafficking; late endosome to trans-Golgi transport	Ganley et al., 2004; Lombardi et al., 1993; Narita et al., 2005
(6) Rab28, RabL4			
(7) Rab34, Rab36			
Rab34	Cell surface membrane ruffles, lysosomes	Regulation of spatial distribution of lysosomes; Formation of macropinosomes	Colucci et al., 2005; Sun and Endo, 2005; Sun et al., 2003; Wu et al., 2005
(8) Rab6, Rab41			
Rab6a,a′,b,c	(a,a′,b) Golgi, (b) ERGIC-53-positive vesicles and neuronal cell specific	Retrograde transport; (a,b) Golgi to ER and intra-Golgi tranport,Golgi stress response (a′) endosome to Golgi transport; (c) multi-drug resistance regulation	Jiang and Storrie, 2005; Martinez et al., 1994; Del Nery et al., 2006; Opdam et al., 2000; Shan et al., 2000
(9) Rab5, Rab17, Rab20, Rab21, Rab22a/Rab31, Rab24			
Rab5a,b,c	Clathrin coated vesicles, caveosomes, and early endosomes.	Endocytosis, early endosome fusion, caveolar vesicle targeting to early endosomes; (a) EGF receptor activation; (b) neuroprotection	Pelkmans et al., 2004; Barbieri et al., 2000; Arnett et al., 2004; Bucci et al., 1995
Rab17	Epithelial specific; apical recycling endosome	Transport through apical recycling endosomes; polarized sorting	Zacchi et al., 1998
Rab20	Epithelial specific; kidney dense apical tubules	V-ATPase trafficking	Curtis and Gluck, 2005
Rab21	Early endosomes	Endocytosis of integrins, cell-extracellular matrix adhesion and motility	Pellinen et al., 2006
Rab22a,b,c/ Rab31	Early endosomes and trans-Golgi	Biosynthetic pathway; (a) endosome to Golgi transport; phagosome maturation (b) trans-Golgi to endosome transport	Kauppi et al., 2002; Mesa et al., 2001; Roberts et al., 2006; Rodriguez-Gabin et al., 2001
Rab24	Autophagosomes, nuclear inclusions	Induction of autophagy, tyrosine phosphorylated	Munafó and Colombo, 2002; Overmeyer and Maltese, 2005

Table continued on next page

involved in chromatin remodeling, apoptosis and gene expression, on endosomes so it cannot enter the nucleus until activation signals are received (Bucci and Chiariello, 2006; Miaczynska et al., 2004). Rab family members that signal to the nucleus (Rab5, Rab8, Rab24 and possibly others) might work in concert with the Ran GTPase (also a Rab family member), which controls nucleocytoplasmic shuttling, to bring about rapid responses to signaling that require changes in cell growth or differentiation (Joseph, 2006; Miaczynska et al., 2004; Wu et al., 2006). Rab32, which regulates mitochondrial fission, may participate in adaptation to changing energy requirements during growth (Alto et al., 2002; Hood et al., 2006). Cell growth and differentiation may in turn be modulated through the coordinated actions of Rab GTPases regulating cell-matrix and cell-cell adhesion (Rab4a, Rab8b, Rab13 and Rab21) and those involved in growth-regulatory signaling and mitosis or apoptosis (Rab6a′, Rab11, Rab12, Rab23, Rab25, Rab35, Ran and likely others) (Bucci and Chiariello, 2006; Del Nery et al., 2006; Fan et al., 2006; Iida et al., 2005; Kouranti et al., 2006; Wang et al., 2006; Yu et al., 2007).

Rab proteins temporally and spatially control vesicular transport

Rab GTPases must both cycle between GTP-bound active and GDP-bound inactive forms and oscillate between different subcellular locations to carry out their functions (Stein et al., 2003; Stenmark and Olkkonen, 2001; Zerial and McBride, 2001). They sequentially interact with specific effectors to facilitate vesicular transport from vesicle budding to fusion. In addition, interfaces with intracellular signaling cascades can serve to up- or downregulate transport, depending on cellular requirements.

Table 1. Continued

Rab	Localization	Function	References
(10) Rab18			
Rab18	Dense apical tubules (kidney) and basolateral membrane (intestine); ER/lipid droplets; neuroendocrine secretory granules	Formation of lipid droplets from ER; negative regulator of neuroendocrine secretion	Lütcke et al., 1994; Ozeki et al., 2005; Vazquez-Martinez et al., 2007
(11) Rab2, Rab4, Rab11, Rab14, Rab25, Rab39, Rab42			
Rab2a,b	Endoplasmic reticulum	ER to Golgi transport	Tisdale et al., 1992
Rab4a,b,c	Early and recycling endosomes	Rapid endocytic recycling to plasma membrane; (a) adherens junction disassembly	van der Sluijs et al., 1992; Mruk et al., 2007; Bottger et al., 1996
Rab11a,b	(a) Golgi and recycling endosomes; (b) neuronal specific	(a) Transport from Golgi to apical endocytic recycling endosomes; phagocytosis in macrophages; (b) Ca^{2+}-dependent secretion	Ullrich et al., 1996; Wilcke et al., 2000; Khvotchev et al., 2003
Rab14	Rough ER; Golgi/trans-Golgi and early endosomes	Phagosome and early endosome fusion; trafficking between early endosomes and Golgi	Junutula et al., 2004; Kyei et al., 2006; Proikas-Cezanne et al., 2006
Rab25	Epithelial specific; apical recycling endosome	Transport of apical recycling endosomes	Casanova et al., 1999; Wang et al., 2000
(12) Rab19, Rab30, Rab33, Rab43			
Rab33a,b	Medial Golgi	Retrograde Golgi transport to ER	Valsdottir et al., 2001
(13) Rab1, Rab3, Rab8, Rab10, Rab12, Rab13, Rab15, Rab35, Rab40			
Rab1a,b	Endoplasmic reticulum	ER to Golgi transport	Tisdale et al., 1992; Allan et al., 2000
Rab3a,b,c,d	Synaptic and secretory vesicles.	Regulated exocytosis; (a-d) Ca^{2+}-dependent secretion and vesicle docking; dense-core vesicle docking to the plasma membrane (with Rab27)	Rupnik et al., 2007; Schlüter et al., 2002; Tsuboi and Fukuda, 2006
Rab8a,b	Golgi region, endosomes, dendrites, basolateral plasma membrane	Trafficking between Golgi, endosomes and plasma membrane; cholesterol degradation; Extension of primary ciliary membrane (a) basolateral transport in epithelia and dendritic transport in neurons; (b) adherens junction assembly	Nachury et al., 2007; Peränen et al., 1996; Chen et al., 2001; Chen and Wandinger-Ness, 2001; Hattula et al., 2006; Linder et al., 2007
Rab10	Golgi	Polarized membrane transport from Golgi to basolateral membrane, may co-operate with Rab8	Babbey et al., 2006; Chen et al., 1993; Schuck et al., 2007
Rab12	Centrosomes	Transport from cell periphery to perinuclear centrosomes	Iida et al., 2005
Rab13	Tight junctions and endosomes	Tight junction biogenesis	Marzesco et al., 2002
Rab15	Early/sorting and recycling endosomes	Trafficking through recycling endosomes; coordinates rapid and slow recycling; attenuates Rab5 function	Elferink and Strick, 2005; Zuk and Elferink, 2000
(14) Rab26, Rab27, Rab37, Rab44, Rasef			
Rab26	Secretory granules	Regulated secretion of granules	Yoshie et al., 2000
Rab27a,b	Epithelial specific; melanosomes	Exocytosis; (a) Transport of secretory granules, dense-core vesicles (with Rab3a) and lysosome-related organelles; myosin recruitment to melanosomes; (b) platelet specific, regulated secretion	Barral et al., 2002; Futter, 2006; Tolmachova et al., 2007; Tsuboi and Fukuda, 2006
Rab37	Secretory granules (insulin and mast cell granules)	Mast cell degranulation	Masuda et al., 2000; Brunner et al., 2007

Uncharacterized Rab family members are highlighted in red.

The membrane association/dissociation and nucleotide binding/hydrolysis cycles are intimately connected and regulated by specific chaperones. Rab family members are modified by a prenyl moiety at their C-termini (Rab44, Rab-like proteins and Ran are notable exceptions) (Colicelli, 2004; Leung et al., 2006; Leung et al., 2007). The increased hydrophobicity due to prenylation necessitates delivery to the appropriate membrane by accessory factors such as Rab escort protein (REP) after synthesis (Goody et al., 2005). Once delivered to the membrane, Rab proteins are activated by the exchange of GDP for GTP, triggered by guanine nucleotide exchange factors (GEFs). Once an individual transport step is completed, GTPase-activating proteins (GAPs) accelerate Rab GTP hydrolysis allowing recognition by a GDP dissociation inhibitor (GDI), which sequesters the Rab in the cytosol until it is recruited to a membrane and begins the transport cycle again (Goody et al., 2005).

Regulation of Rab activation and inactivation may be linked to signaling in order to allow dynamic responsiveness to cellular trafficking needs. Rab regulatory proteins (GEFs, GAPs and GDIs) are phosphorylated in response to stress and growth factor signaling, thereby enhancing or diminishing Rab activity and resulting in up- or downregulation of constitutive and regulated trafficking (Bucci and Chiariello, 2006; Roach et al., 2007). For example, in insulin signaling, phosphorylation of the Rab GAPs Tbc1d4/AS160 and Tbc1d1 by Akt (protein kinase B) results in heightened levels of activated Rab proteins involved in trafficking and fusion of glucose transporter (Glut4) vesicles with the plasma membrane.

Activated Rab proteins serve as molecular scaffolds to coordinate three main membrane-trafficking steps: vesicle budding, cytoskeletal transport, and targeted docking and fusion (Grosshans et al., 2006; Stein et al., 2003). Consequently, Rab proteins interact sequentially with many downstream effector proteins in a temporally and spatially regulated manner. To induce vesicle budding, Rab proteins promote cargo selection. Rab9, for example, binds to tail-interacting protein 47 kDa (TIP47), which mediates Golgi recyling of the mannose 6-phosphate receptor from endosomes (Carroll et al., 2001). Rab GTPases also cooperate with Arf GTPases to recruit vesicle coats. Rab11, for example, may regulate protein coat recruitment via ARF4 and the Arf GAP ASAP1 and enable rhodopsin transport from the TGN to the rod outer segment of photoreceptor cells (Deretic, 2006). Following budding, a number of Rab proteins (e.g. Rab6, Rab7, Rab11 and Rab27) are known to recruit actin- or microtubule-based motor protein complexes (MPCs) that transport vesicles along cytoskeletal filaments (Jordens et al., 2005). Finally, Rab proteins help recruit tethering factors, which help target the carrier to the appropriate membrane, as well as SNARES, which may directly promote homotypic or heterotypic membrane fusion (Grosshans et al., 2006; Markgraf et al., 2007). On the endocytic pathway, Rab proteins also scaffold lipid kinases and phosphatases to control budding and fusion (the micrograph illustrates colocalization of the myotubularin phosphatase MTM1, the lipid kinase hVPS34 and Rab7) (Cao et al., 2007; Shin et al., 2005).

The Rab family tree

The human Rab family includes multiple paralogs (e.g. Rab5a, Rab5b and Rab5c) which probably arose through gene duplication (Colicelli, 2004; Stenmark and Olkkonen, 2001). Further isoform diversity is generated through ongoing mRNA processing in the form of alternative splicing (Dou et al., 2005). Ran, a GTPase initially thought to define a separate family, and several recently identified Rab-like GTPases are categorized as part of the Rab family on the basis of comparative sequence analyses (Colicelli, 2004). Dendrogram clustering suggests 14 Rab subfamilies (Table 1). One must exercise caution, however, in making structure/function predictions about uncharacterized members (denoted in red in Table 1) on the basis of these sequence-derived clusters. For any given subfamily the alignments do not differentiate whether the sequence similarity underlies a common basic structure, effector binding, regulatory protein interactions, subcellular localization or another aspect of the protein. Many Rab isoforms bind different effectors and have unique subcellular localizations. Hence, one must consider a number of other factors when extrapolating Rab functions.

Rab proteins as scaffolds

The rapidly expanding RCSB Protein Data Bank (www.rcsb.org) contains the crystal structures for 26 mammalian Rab GTPases and eight Rab-effector complexes. Rab7 was the first GTPase structure to be solved both in its GTP- and in its GDP-bound states (Brachvogel et al., 1997). The Rab7 structure has also been solved in a complex with a regulatory protein (REP1) and an effector (RILP) and therefore serves as an instructive example (Rak et al., 2004; Wu et al., 2005). The GDP- and GTP-bound forms of Rab7 demonstrate the significant conformational changes in the Switch I (blue) and II (pink) regions that occur as a consequence of GTP binding and hydrolysis (Goody et al., 2005; Pereira-Leal and Seabra, 2000). So far, comparison of Rab7 in complexes with RILP and REP1 reveals two overlapping surfaces that are important for protein-protein interactions. At least two disease-causing mutations, outside the nucleotide-binding pocket of Rab7, disrupt effector interactions (Mukherjee and Wandinger-Ness unpublished observations), which suggests that additional protein-interaction surfaces exist. Rab7 and other Rab proteins have discrete protein-protein interaction surfaces that enable them to play pivotal roles as molecular scaffolds. Structural overlays of Rab GTPases and analyses of protein-protein interaction surfaces will be crucial if we are to understand how Rab GTPases and their effectors function and contribute to human disease when mutated (Pfeffer, 2005; Stein et al., 2003).

Rab proteins in disease and as drug targets

Given the importance of Rab GTPases in many cellular functions, it is not surprising that altered expression or mutation of Rab proteins and/or their effectors may underlie human diseases such as cancer (Rab25, Rab5 and Rab7), neuronal dysfunction (Rab1 and Rab7), retinal degeneration (Rab8) and immune and pigmentation disorders (Rab27 and Rab38) (Cheng et al., 2005; Chua and Tang, 2006; Di Pietro and Dell'Angelica,

2005; Inglis et al., 2006). Thus, the Rab GTPases are prime drug targets, prompting our group and others to undertake high-throughput screens. The wealth of functional assays and structural data are expected to enable discrimination of specific and effective compounds in the near future.

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Note added in Proof

A link between Ran and apicobasal polarity and ciliogenesis has recently been established suggesting the interconnections between Rab-regulated membrane transport and nuclear signaling will be an important area for further study (Fan S. et al., 2007).

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