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RAB7A: THE MASTER REGULATOR OF VESICULAR TRAFFICKING

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The membrane flow of eukaryotic cells occurs through vesicles that bud from a donor compartment, move and fuse with an acceptor compartment. Rab (Ras-related in brain), which belong to the Ras superfamily of small GTPases, emerged as a central player of vesicle mobility in both secretory and endocytic pathway, Rab7a being a master regulator of late endocytic trafficking. Elucidation of how mutant or dysregulated Rab7 GTPase and accessory proteins contribute to organ specific and systemic disease remains an area of intensive study and an essential foundation for effective drug targeting. Mutation of Rab7 or associated regulatory proteins causes numerous human genetic diseases. Cancer and neurodegeneration represent examples of acquired human diseases resulting from the up- or down-regulation or aberrant function of Rab7. The broad range of physiologic processes affected by altered Rab7 activity is based on its pivotal roles in membrane trafficking and signaling. The Rab7-regulated processes of cargo sorting, cytoskeletal translocation of vesicles and appropriate docking and fusion with the target membranes control cell metabolism, growth and differentiation. In this review, role of Rab7 in endocytosis is evaluated to illustrate normal function and the consequences of dysregulation resulting in human disease. Selected examples are designed to illustrate how defects in Rab7 activity alter endocytic trafficking that underlie neurologic, lipid storage, and bone disorders as well as cancer.
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INTRODUCTION

Mammalian Rab7 was first identified in a rat liver cell line as BRL-Ras (X12535;NM_023950) and subsequently named Rab7a upon recognition as a distinct member of Ras related GTPases now well known as the Rab family of GTPases (NP_004628.4;P51149;P09527). Rab7a is the most widely studied form and encoded on human chromosome 3q21.3 (mouse chromosome 6) as two splice variants differing in 3' untranslated region. The most intensively studied mammalian forms of Rab7a (mouse, canine, rat and human) are 99.5% identical with only a single conservative change among 207 amino acids (D/E196). A more recently discovered homolog,

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Rab7b/Rab7L1, is encoded on human and mouse chromosome 1q32 and functions in late endosome to Golgi trafficking (1). Human Rab7b is only 47% identical and 82% homologus to Rab7a across its 199 amino acid length. Following the initial demonstration of Rab7a function in regulating membrane transport from early to late endosomes, Rab7a has established roles in autophagy, lipid metabolism, growth factor signaling, bone resorption and phagolysosome biogenesis (2).

RAB7A: THE GOOD, THE BAD AND THE UGLY

Rab7a belongs to the family of Ras superfamily of GTPases that plays a critical role in diverse cellular processes. The identification of the Ypt1p as a GTP binding protein in yeast led to the discovery of more than 70 Rab GTPases in the human genome (3-5). Rab7a was first cloned from a MDCK cell cDNA library (6) and later mapped in the mouse genome (7). Rab7a was conclusively shown to orchestrate membrane transport from early to late endosomes (8). This generated considerable interest to investigate the functionality of the protein and it is now known to play an important role in endocytic trafficking and other degradative pathways like phagocytocis and autophagy (9, 10). Rab7a regulates internalization and degradation of growth factor receptors (11, 12). This regulation is critical as overexpression of epidermal growth factor receptor (EGFR) is characterized in different types of cancer (13-15). Rab7a is pivotal in the trafficking of multivescicular bodies, melanosomes and exosomes (16, 17). It is also associated with lipid homeostasis that modulates membrane structure and organization, cell signaling, regulation of growth, cell cycle and differentiation (18). Osteoclasts involve Rab7a vesicular trafficking in bone resorption to maintain bone integrity (19). Rab7a is vital for axonal retrograde trafficking (20). At neuromuscular junction, Rab7a regulates neurotrophin traffic (21). Inhibition of Rab7a activity cause endosomal accumulation of TrkA and pronounce enhancement of TrkA signaling in response to nerve growth factor (NGF) stimulation (21a). NGF has been implicated in a host of different cardiometabolic and neurological disorder (22). The endocytic role of Rab7a was further demonstrated in regulating trafficking of EGF-EGFR complex by controlling its lysosomal degradation (11, 12, 23-25). Similarly, ligand stimulated lysosomal degradation of platelet activating factor receptor (PAFR) depends on Rab7a in its delivery to the lysosomes (26). In concert with Rab5 and Rab11, Rab7a regulates intracellular trafficking patterns of angiotensin II type 1A receptor as exemplified by increased AT(1A)R degradation and AT(1A)R targeting to lysosomes in cell types with over-expressed Rab7a (27). In Chinese hamster ovary cells, agonist induced down regulation of the human kappa-opiod receptor (hkor) and inverse agonist upregulation of mutant rat μ-opioid receptor is thought to be dependent on the endocytic pathway regulated by Rab7a (28, 29). Rab7a is indispensable in the delivery of autophagic cargo for degradation from autophagosomes to lysosomes (9, 30). It is thought to play a critical role in the final maturation of late autophagic vacuoles but not the initial maturation of early autophagosomes (31). Rab7a effects the degradation of autophagosomes by fusing the autophagosomes with the lysosomes and rapidly delivers of a complex of Beclin-1 binding UVRAG with class C Vps to lysosomes via late endosomes (32). Phagocytosis plays a vital role in development and immunity (33), and the maturation of phagosome to phagolysosome occurs by recruitment of Rab7a (34). Complete maturation is thought to be mediated by retrograde emission of tubular extensions generated by activation of Rab7a and its accessory proteins (35). Rab7a plays a role in melanosome biogenesis by sorting and associating with early and intermediate stage melanosomes (36). It is in the T22N dominant negative form in human amelanotic melanoma cells (SK-mel-24) impairs vesicular transport of tyrosinase and TRP-1 proteins from the trans-Golgi network to maturing melanosomes (37, 38). In MMAc melanoma cells, GTP bound (active) form of Rab7a promotes melanogenesis by regulating gp100 maturation (39). In a similar way, exosomal transport uses established endocytic pathway machinery to deliver cargo to extracellular environment of the cell. Exosomes help in the elimination of undegraded endosomal or lysosomal proteins and membranes (40). In dendritic cells, Rab7a is associated with exosome biogenesis and function that involve antigens transfer (41). Improper lipid homeostasis associated with disorders such as Niemann-Pick Type C (NPC) disease characterized by accumulation of lipids within late endosomes and lysosomes in tissues such as liver spleen and brain (42, 43). Overexpression of Rab7a in NPC disease fibroblasts dramatically improves intracellular trafficking of cholesterol and sphingolipids (44). Similarly accumulation of cholesterol in endosome membranes increases the amount of membrane associated Rab7a and inhibits Rab7a membrane extraction by guanine nucleotide dissociation inhibitor (45). Rab7a gene is also distinctly upregulated within hepatic and aortic tissues in a rabbit in response to cholesterol loading (46). In another scenario, Rab7a together with MTM1 are thought to serve as molecular switches controlling the sequential

synthesis and degradation of endosomal PI_3P (47, 48). During cell differentiation, epithelial cells undergo epithelial-mesenchymal transition (49). The change is marked by down-regulation and inward sequestering of E-cadherin which is later trafficked *via* endocytic pathway to the lysosomes (49). Enhanced transport of the ubiquitinated E-cadherin to the lysosomes is accomplished by activated Rab7a catalyzed by Src kinase (50). Like E-cadherin transport, formation of ruffled border during bone resorption processes is usually accompanied by transport of acidic intracellular vesicles to the plasma membrane. This has been shown to involve regulatory role of Rab7a (19, 51). This is further confirmed by presence of Rab7a in rat osteoclasts which implies late endosomal nature of the plasma membrane domain in resorbing osteoclasts (52).

Rab7a is exploited to create a niche for the survival of many intracellular pathogens. Intracellular bacterial pathogens are thought to manipulate Rab function in the formation of vacuoles in their bid to colonize host cells during infection (53). Rab7 has a fundamental role in cellular vacuolation and vacuole growth (54, 55). In HeLa cells transfected with Rab7a mutants and then exposed to VacA cytotoxin, dominant-negative mutants of Rab7a prevent vacuolation confirming that membrane flow along the endocytic pathway is pertinent to vacuole growth (55, 56). In another study it is shown that interactions with the endocytic pathway controlled by Rab7a are key to *Salmonella* containing vacuole (SCV) biogenesis (57). Once entered into mammalian cells, *Brucella abortus* occupies *Brucella* containing vacuole (BCV) followed by acquisition of Rab7a and its effector Rab-interacting lysosomal protein to facilitate lysosomal delivery (58). Expression of dominant negative Rab7a or overexpression of RILP impairs the ability of bacteria to convert BCV into an ER-derived organelle thereby interfering with replication process (58). Like in higher organisms, the role of Rab7a in phagocytosis in lower organisms is quite prominent. In the enteric protozoan parasite *Entamoeba histolytica*, expression of either EhRab7aA or EhRab7aB-GTP mutant triggers a defect in phagocytosis accompanied with disturbed formation and disassembly of prephagosomal vacuoles (59).This implicates the two Rab7a isotypes in lysosome and phagosome biogenesis. In *Dictyoselium discoideum*, Rab7a homolog is thought to regulate fluid phase influx, efflux, retention of lysosomal hydrolases and phagocytosis (60-62). Phagosomes in cells overexpressing dominant negative Rab7a mature to form multiparticle spacious phagosomes which allude to Rab7a's role in regulating early and late steps of phagosomal maturation (61). In yeast, endocytosed pheromone alpha-factor accumulates in late endosomes in delta ypt7 cells, implicating Ypt7p (homolog of mammalian Rab7a protein) in endocytic pathway from late endosomes to the vacuole (63). Another report suggests the role of YPT7 GTPase in the uptake of the fluorescent styryl dye FM4-64 via the endocytic pathway to the vacuolar membrane (64). Transport fidelity is indispensable as evidenced by the increasing number of human diseases attributable to defects in endosomal trafficking and Rab7a specifically like Charcot-Marie-Tooth disease which is an autosomal dominant peripheral neuropathy (65-75). Rab7a sorts cargo on early endosomes by recruiting retromer complex (Vps26/29/35) that enables retrieval of cation independent mannose 6-phosphate receptor, TGN 38, Wntless among other cargo from early endosomes to the Golgi (76-78). Dysregulation of retromer is associated with other neurologic diseases like Alzheimer's disease (79, 80). In a macroscopic scale, its role in growth regulation is potentially important to the overall survival of the organism. The significant role it plays in pathogen entry, presents Rab7a as a potential therapeutic target.

In sum, Rab7 is indispensable in intracellular trafficking and signaling. However its role in diverse physiological processes is only beginning to be appreciated.

REGULATION OF RAB7A ACTIVITY

Typical of all Rab GTPases, Rab7a activity is modulated by membrane association and nucleotide binding (81) (Fig. 1). Membrane recruitment is dependent on the hypervariable, isoprenylated C-terminus (10, 82-84). Like all other Rabs, the presence of GDI on GDP bound Rab7a renders its delivery to the membrane a reversible process unless guanine nucleotide exchange factor (GEF) converts Rab7a into GTP bound form (5, 85). Unlike Rab5 with a known GEF as Rabex5, Rab7a GEF is still under investigation. The hVps39 protein whose yeast homolog Vps39 acts as a Ypt7GEF is premised to be a putative Rab7a GEF (86).Termination of nucleotide binding and Rab7a activation is achieved by GTPase activating protein (GAP). TBC1D15 was found to stimulate the intrinsic GTPase activity of Rab7a (87). Another regulatory mechanism with significant control on Rab7a activity is Rab5-Rab7a conversion. It confers directionality to membrane trafficking events leading to membrane maturation (85). It involves HOPS complex mediated recruitment of Rab7a on the Rab5 positive vesicles (86, 88).Vps39 may also form a part of the complex (85). An increase in GFP-Rab7a density on endosomes of

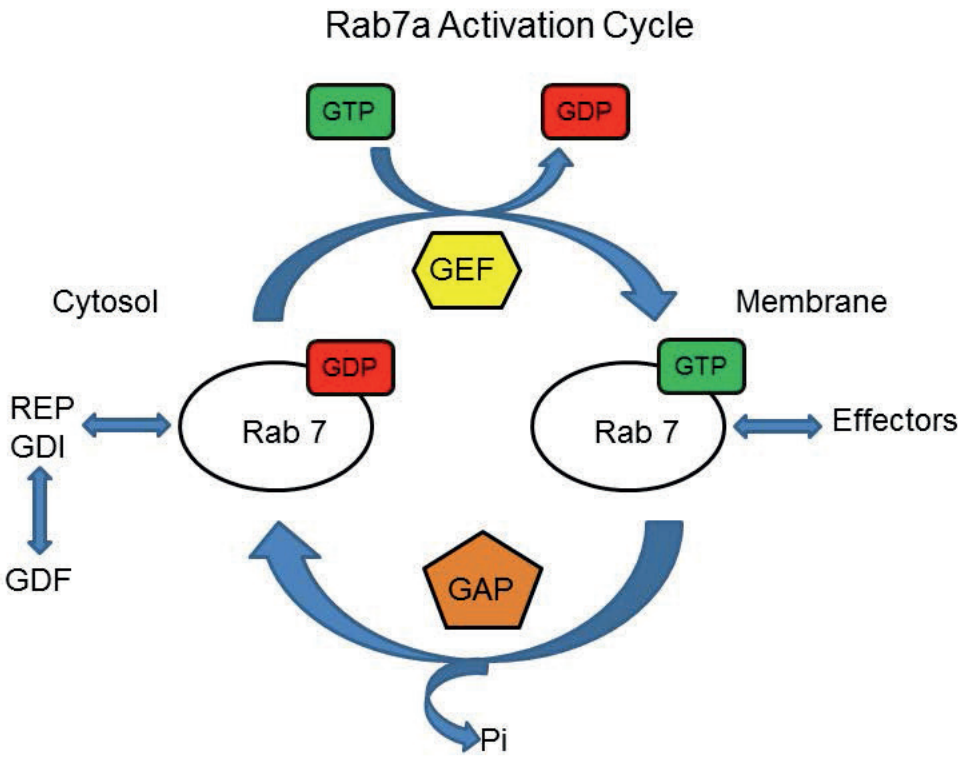

Figure1. *Rab7a activation cycle. Newly synthesized Rab7a is prenylated by geranylgeranyl transferase (GGT) and delivered to endosomal membranes by rab escort protein (REP), thereafter Rab7a membrane cycling is facilitated by GDP dissociation inhibitor (GDI); pathways that are common to all Rab GTPases. A GDI displacement factor (GDF) has been implicated in membrane transfer by displacing the GDI. A guanine exchange factor (GEF) promotes activation and a GTPase activating protein (GAP) promotes hydrolysis and inactivation. Active, GTP-bound Rab7a act as a scaffold for sequentially binding multiple effectors (see Table1) to promote cargo selection, cytoskeletal translocation and membrane fusion.*

A431 cells occurred with concomitant decay of GFP-Rab5 decay (89). Phosphorylation is a common activity regulation. Large scale proteomics analyses have identified Rab7a to be both serine and tyrosine phosphorylated. In mouse liver extracts, Rab7a was found phosphorylated on serine 72 within a highly conserved sequence near the GTP binding pocket (90). Rab7a was phosphorylated in response to EGF stimulation on tyrosine 183 in the C terminal region. Enhanced tyrosine 183 phosphorylation of Rab7a was also associated with mutant EGFR and HER2 expression in non-small cell lung carcinoma and mammalian epithelia respectively (91-93). Regulation of Rab7 activity has also been achieved by small molecule intervention of its nucleotide binding capacity. The small chemical molecule 2-(benzoylcarbamothioylamino)-5, 5dimethyl-4,7-dihydrothieno (2,3-c)pyran-3-carboxylic acid (PubChem CID 1067700) was shown to inhibit Rab7 activity *in vitro* (94, 95). This was the first report of inhibition of Rab7 activity and has potential therapeutic implications.

RAB7A EFFECTORS CONTROL ENDOCYTIC TRAFFIC

To date several effector proteins of Rab7a have been identified to interact specifically with the active GTP bound Rab7a (Table 1, Fig. 2). Rab7a effectors regulate events ranging from cargo selection to microtubule translocation to downstream membrane tethering and endosomal membrane fusion. Rab7a activation leads to dynamic assembly of large

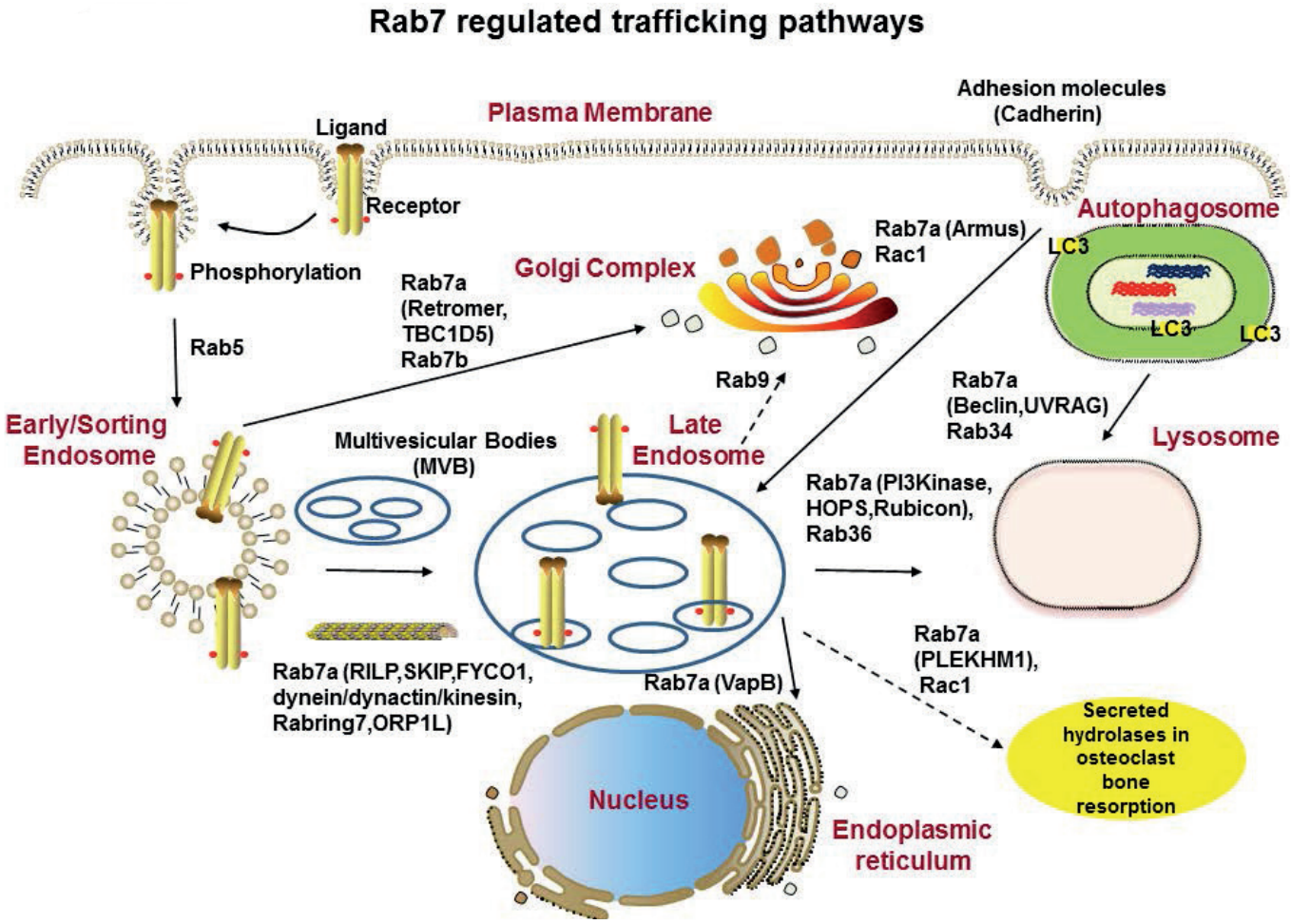

Figure2. *Rab7a regulated trafficking pathways. Rab7a regulated trafficking from early to late endosomes in a process requiring Rab5 to Rab7a conversion. Rab7a also cooperates with other Rab GTPases to facilitate late endosome-lysosome fusion and autophagolysosome formation (Table1). Key Rab7a effectors involved on individual pathways are noted in parentheses. Rab7a cooperates with Rac1 in epithelia promote internalization of cell adhesion molecules and in osteoclasts to promote localized hydrolase secretion for bone resorption.*

protein complexes in a spatially and temporally regulated manner (96). Specific protein complexes serve discrete functions in the transport process yet handoffs and multiple layers of regulation are common. On multivescicular bodies and late endosomes Rab7a regulates cargo sorting and bidirectional transport by interacting with effectors that modulate kinesin and dynein activity. Lysosomal sorting and perinuclear transport are mediated by Rab7a interacting lysosomal protein (RILP) effector (97). RILP interacts with endosomal sorting complex components (ESCRT II, Vps22 and Vps36) and based on depletion studies, RILP is shown to participate in the sorting of ubiquitinated receptors into intraluminal vesicles (98). RILP facilitates the sorting and sequestration of cytosolic signaling machinery and targets them for lysosomal degradation. RILP is also targeted by bacterial pathogen to create a niche for its replication (99, 100). In a tripartite complex, Rab7a, RILP and ORP1L recruit a dynein/dynactin motor complex that in association

Table1. *Rab7 effectors and their roles in vesicular trafficking*

Rab7a isoform and nucleotide bound state	Rab7a effector/ binding partner	Regulator/effector function
Rab7a	ANKFY1(ankyrin repeat andFYVEdomainprotein1)/ ANKHZN/Rabankyrin-5	Possible role in vesicular trafficking. Novel interactor of Rab7. Specific role yet to be established (70, 113).
Rab7a	ATP6 V0A1	Component of vacuolar ATPase that regulated organelle acidification required for protein sorting, receptor mediated endocytosis, zymogen activation and synaptic vesicle proton gradient. Novel Rab7 interactor (70, 114).
Rab7a-GDP	Ccz1 (vacuolar protein trafficking and biogenesis associated homolog)	Recruited to endosomes by Mon1a/Mon1b and acts as Rab7 GEF in yeast. Possible human homolog C7orf28B also some similarity to HPS4 involved in biogenesis of lysosome related organelles (115).
Rab7a-GTP	FYCO1(FYVE and coiled coil domain containing 1)	Promotes microtubule plus end transport of autophagosomes presumably by functioning as a kinesin adaptor (116)
Rab7a	GNB2L1 ((guanine nucleotide binding protein,G protein),beta polypeptide)	Role in intracellular signaling and activation of protein kinase C and possible interaction with Rab7 via WD40 domain. Novel interactor of Rab7. Specific role yet to be determined (70).
Ypt7p/ Rab7a-GTP	HOPS complex (Vps11,-16,-18,-33,-39 and -41)	Involved in vacuolar tethering and fusion in yeast and conserved mammalian homologs function in mammalian endolysosomal fusion. Interfaces with CORVET complex to promote Rab5 to Rab7 conversion in yeast. Vps39 sub unit binds Mon1-Ccz1 complex that serves as Rab7 GEF in C.elegans and yeast (89, 117, 118).
Rab7a	hVps39	In yeast Vps39p, cooperates with Mon1-Ccz1 complex to promote Ypt7p nucleotide exchange. Function of mammalian protein remains to be determined (118, 119).
Rab7a	IMMT (Mitofilin)	Maintains mitochondrial morphology and suggested role in protein import. Novel interactor of Rab7 (70).
Rab7a	KIF3A (kinesin+adapter?)	Kinesin2 heavy chain associates with late endosomes along with dynein, Rab7 and dynactin. Possible mediator of Rab7-regulated anterograde transport coordinated by Rab7 interacting adapter such as FYCO1 or other as yet unidentified protein (120).
Rab7a-GDP	Mon1a-Mon1b	Mammalian homologs of C. elegans SAND1. Mon1a-Mon1b causes Rab5 GEF displacement and Mon1b interacts with the HOPS complex. Mon1 is an effector of Rab5, but only interacts with Rab7 when complexed with Ccz1 (115, 121-123).
Rab7a-GTP	ORP1L ((oxysterol-binding protein,OSBP)-related protein 1)	Required for cholesterol sensing and regulation of dynein/dynactin motor with Rab7 and RILP, regulates late endosome/lysosome morphogenesis and transport (101).
Rab7a-GTP	Phosphoinositide 3-kinase complex (hVps34/hVps15)	TypeIII-PI3-kinase that generates phosphoinositide 3-phosphate to control endosomal trafficking and signaling. Forms complex with myotubularins for negative regulation (124).
Rab7a-GTP	Plekhm1 (Pleckstrin homology domain containing family M(with RUN domain member)	Regulates lysosomal secretion in osteoclasts for bone resorption by interacting with LIS1 to control microtubule transport and Rab7 and PI3Kinase to recruit effectors for fusion (125).
Rab7a	Prohibitin	Negative regulator of cell proliferation and a possible tumor suppressor. Novel interactor of Rab7, specific role yet to be established (70).
Rab7a-GTP	Rabring7	Rab7-interacting ring finger protein, functions as E3 ligase that ubiquitylates itself and controls EGFR degradation (126).

Table 1 continued.

Rab7a isoform and nucleotide bound state	Rab7a effector/ binding partner	Regulator/effector function
Rab7a-GDP	REP1 (Rab Escort protein1)	Presents Rab7 to Rab geranylgeranyl transferase for addition of prenyl group that acts as a membrane anchor (96).
Rab7a-GTP	Retromer (Vps26,Vps29,Vps35)	Regulates retrograde transport from late endosome to trans-Golgi network (TGN) through direct interaction with Vps26 (127).
Rab7a-GTP	RILP (Rab7 Interacting Lysosomal Protein)	Involved in late endosomal/lysosomal maturation. Recruits dynein/dynactin motor protein complex (128).
Rab7a-GTP	Rubicon	Regulates endosomal maturation through differential interaction with UVRAG and Rab7. Rubicon binding inhibits UVRAG by binding to active Rab7 frees UVRAG to activate the hVps34/hVps15 complex and HOPS thereby simultaneously increasing the active pool of Rab7 and PI3P signaling (129).
Rab7a-GTP	SKIP (SifA and kinesin interacting protein)	Homolog of PLEKHM1 that binds Rab7, Rab9 and kinesin-1 and may regulate anterograde motility of late endosomes. Target of Salmonella SifA protein (130, 131).
Rab7a	Spg21	Loss of function causes autosomal recessive hereditary spastic paraplegia. Involved in vesicular transport. Novel interactor of Rab7. Specific role yet to be established (70).
Rab7a	STOML2 (Stomatin-like 2)	Negatively modulates mitochondrial sodium/calcium exchange. Novel interactor of Rab7. Specific role yet to be established (70).
Rab7a-GTP	TBC1D2 ((tre-2/ USP6,BUB2,cdc16) domain family,member5)/Armus and Rac1	Regulates cytoskeletal organization, ruffled border formation in osteoclasts and E-cadherin/adherens junction degradation in conjunction with Rac1, inactivates Rab7 through C-terminal GAP activity (132, 133).
Rab7a-GTP	TBC1D5 ((tre-2/ USP6,BUB2,cdc16) domain family,member 5)	Negatively regulates retromer recruitment and causes Rab7 to dissociate from membrane and may have Rab7GAP activity (77).
Rab7a-GTP	TBC1D15 ((tre-2/ USP6,BUB2,cdc16)domain family,member 15	Functions as Rab7 GAP and reduces interaction with RILP, fragments lysosomes and confers resistance to growth factor withdrawalinduced cell death (87, 119).
Rab7a-GTP	TrkA (neurotrophic tyrosine kinase receptor)	Interacts with Rab7 and regulates endocytic trafficking and nerve growth factor signaling as well as well as influencing neurite outgrowth (22, 68).
Rab7a-GTP	UVRAG (UV radiation resistance associated gene)/Beclin1	UVRAG/C-Vps complex positively regulates Rab7 activity via PI3kinase complex during autophagic and endocytic maturation (32).
Rab7a-GTP	VapB ((Vesicle associated membrane protein)-associated protein B)	Involved in mediating endosome-ER interaction in response to ORP1L conformation sensing low cholesterol levels (102).
Rab7a	Vps13c (vacuolar protein sorting 13c)	Vacuolar protein sorting and novel interactor of Rab7. Specific role yet to be established (70).
Rab7a-GDP,GTP	XAPC7/PSMA7 (proteasome subunit, alpha type7)	Negative regulator of late endocytic transport. Overexpression inhibits EGFR degradation (110).
Rab7b	SP-A (Surfactant protein A)	Transiently enhances the expression of Rab7 and Rab7b and makes them functionally active to increase the endolysosomal trafficking in alveolar macrophages (134).

with betaIII spectrin transports endosomes to the perinuclear region on microtubules (101-103). Endosomal lipids like cholesterol and phosphoinositides are critical regulators of cargo sorting and transport on the late endosomal pathway that are integrated with transport through the Rab7a effector ORP1L. When cholesterol levels are low, ORP1L promotes association of late endosomes with endoplasmic reticulum by dissociating minus end motor proteins. The ER protein VAPB contributes to motor dissociation and the peripheral movement of late endosomes. Being more peripherally localized, late endosomes are poised to receive cholesterol from early endosomes or ER. When cholesterol levels are high the conformation of ORP1L is altered and perinuclear transport is favored. In NPC disease where endosomal cholesterol levels are high the bidirectional motility of endosomes are perturbed that contribute to disease pathology and can be reversed by overexpressing Rab7a and Rab9 (107, 108). Membrane associated scaffolding protein huntingtin (Htt) helps in dynein/dynactin mediated perinuclear positioning. The mutant form of this protein causes Huntington's disease (2, 104). Huntingtin and Htt-associated protein of 40kD (HAP40) are known Rab5 effectors that orchestrates transport between tubulin- and actin-based networks, though the link with Rab7a remains unclarified. Anterograde movement of endosomes to the cell periphery along the microtubular network is incompletely characterized. Plus end motility of the autophagosomes is coordinated by FYVE and coiled coil domain protein1 FYCO1 and an unknown kinesin (96). Late endosomal movement depends on kinesin2-KIF3A heavy chain while the Rab7a link and effector remain unknown (105). Rab9 and Rab7a have been shown to interact with distinct domains on SifA and kinesin interacting protein (SKIP), implicating kinesin-1 in anterograde motility and late endosomal sorting (106). Similar to Rab5 on early endosomes, GTP bound Rab7a is required for classIII phosphatidyl inositol 3-kinase (consisting of hVps34 catalytic, the hVps15/p150 Rab7a adaptor and Rubicon regulatory subunits) activation on late endosomes (2, 109). The synthesis of PI_3P on endosomes recruit FYVE domain containing protein that promote membrane remodeling (including intraluminal vesicle formation) and eventually terminate the signal. Together these downstream effectors control endolysosome morphology, membrane trafficking, acidification among other functions. Rab7a together with the early endosomal myotubularin lipid phosphatases (MTM1) and late endosomal myotubularin related protein 2 (MTMR2) acts as a molecular switch regulating the sequential synthesis and degradation of endosomal PI_3P (47). The phosphatases bind directly to the phosphatidyl inositol 3-kinase complex leading to inactivation of the myotubularins. The interaction of lipid kinase to myotubularin precludes the interaction of Rab7a with lipid kinase illustrating the importance of protein hand-offs in phosphoinositide 3-phosphate homeostasis on late endosomes. Together the examples cited provide evidence for a Rab7a function in endosomal lipid homeostasis in both metabolism and signaling, disruption of which leads to human disease. Rab7a interacting proteins like Rabring7 (Rab7a interacting ring finger protein) and XAPC7 have been reported to facilitate cargo degradation. Rabring7 functions as an E3 ligase in conjunction with the Ubc4 and Ubc5 as E2 proteins (96, 108). Overexpression of Rabring7 leads to degradation of EGFR and lysosome biogenesis. The proteasome subunit XAPC7 or PSMA7 in mammals interacts specifically with Rab7a and is recruited to late multivescicular endosomes (110). Overexpression of XAPC7 impairs late endocytic transport of EGFR and hence is a negative regulator of trafficking (111). Together Rabring7 and XAPC7 may coordinate the degradation of ubiquitinated growth factor receptors via a link to the proteasomal degradation machinery. There are many more putative effectors of Rab7a whose functions remain to be established. Therefore further complexity in Rab7a mediated sorting, cytoskeletal transport and membrane fusion will emerge. An important area that calls for attention is the interaction of Rab7a with the tethering factors and SNARE proteins in the endosomal fusion events that have been primarily characterized for yeast homolog Ypt7p (112).

CONCLUSION

Ever since Rab7a was discovered its role in endosomal trafficking have remained under investigation. The indefatigable interest is attributed to its diverse role in human disease. The list of Rab7a effectors continue to grow although their functions remain to be established. Elucidating regulation of Rab7 nucleotide exchange and hydrolysis and the mechanism of its recruitment to specific macromolecular complexes to regulate individual pathways remain important areas for further investigation.

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