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Rab GTPases, Membrane Trafficking and Diseases

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Abstract

The Rab family of GTPases contains over 60 genes in the human genome and contributes to regulation of intracellular membrane trafficking along endocytic and exocytic pathways as well as specialized pathways in specific cell types. It has become increasingly clear that disruption of the intracellular membrane trafficking system at different stages can cause various diseases. In the past decade, altered expression levels and mutations of Rab GTPases have been associated with such diseases as cancer, Alzheimer's disease, and various genetic disorders. This review discusses the specific Rab GTPases and their involvement in the diseases.

Keywords

Rab; GTPase; GTP-binding protein; cancer; genetic disorder

INTRODUCTION

The intracellular membrane trafficking system is essential for transport of proteins and membranes in all eukaryotic cells via vesicular carriers along endocytic and exocytic pathways. Transport vesicles are formed and pinched off from donor membrane compartments, move along cytoskeleton via recruiting motor proteins, and fuse with target membrane compartments via recruiting tethering factors and engaging SNAREs. Rab proteins are important regulators at each of the vesicular transport steps. The Rab family of GTPases belongs to the Ras GTPase superfamily and contains over 60 20–30 kDa monomeric proteins [1] that specifically target to each of the membrane compartments and transport vesicles in the cell [2, 3]. Each Rab binds and hydrolyzes GTP and consequently cycles between GTP- and GDP-bound forms, with the GTP-bound form being biologically active and interacting with multiple effectors to promote specific transport functions. For example, the well characterized Rab5 is localized to the plasma membrane and early endosomes and interacts with over 20 effectors [4] to promote the formation and uncoating of endocytic vesicles [5, 6], vesicle movement [7], and endosome fusion [8]. Some of the Rab5 effectors promote signal transduction processes on endosomes that regulate cell growth and differentiation [9].

Rab proteins like Rab5 are ubiquitously expressed in all cell types and promote highly conserved transport functions along the endocytic and exocytic pathways that exist in all eukaryotes, but most Rabs in human exhibit tissue-specific expression and regulate specialized transport pathways in a cell-type specific fashion. For example, Rab27 is highly expressed in secretory cells of endocrine and exocrine tissues, cytotoxic T cells (CTLs) and melanocytes [10, 11], and is known to regulate cytotoxic granule secretion in CTLs [12] and melanosome transport in melanocytes [13]. It is the tissue-specific Rabs that are linked to recessive genetic disorders some of which were reviewed nearly a decade ago [14]. This review provides an update on additional Rab mutations linked to genetic disorders and further emphasizes the association of altered expression levels of both ubiquitous and cell type-specific Rabs with cancer and Alzheimer's disease.

RAB GTPASES AND CANCER

Unlike Ras, no activating mutations in Rab GTPases have been found in any cancers thus far. However, most Rabs show altered expression levels in various types of cancers [15, 16], suggesting altered membrane trafficking activities in cancer cells. Among them, Rab25 is best documented for its association with cancers of epithelial origin. Rab25 co-localizes with Rab11 in subapical vesicles and regulates apical recycling in MDCK cells [17]. Overexpression of Rab25 is linked to aggressiveness of ovarian and breast cancers [18, 19], via gene amplification and/or other unknown mechanisms that up-regulate Rab25 mRNA levels. Indeed, nude mice injected with A2780 and HEY cells overexpressing Rab25 more readily develop tumors that grow larger in a shorter time than control cells without Rab25 overexpression [19], while RNAi-mediated Rab25 knockdown inhibited tumor growth [20]. Ectopic overexpression of Rab25 in cultured ovarian and breast cancer cell lines lead to anchorage-independent growth, reduced BAX expression, increased Akt phosphorylation and cell survival, while RNAi-mediated Rab25 knockdown has opposite effects and increases apoptosis induced by serum starvation or UV [19]. Furthermore, overexpression of Rab25 in the ovarian cancer cell line A2780 is shown to promote recycling of $\alpha 5 \beta 1$ integrin, via interaction with the $\beta 1$ subunit, and cell invasion in 3-D matrix [21], with implication in cancer metastasis.

In addition to ovarian and breast cancers, overexpression of Rab25 has been associated with other types of cancers, including testicular tumors [22], wilms tumors [23], bladder and hepatocellular carcinomas [24, 25]. Interestingly, however, there is loss of Rab25 expression in basal and triple-negative breast cancers [26], suggesting differences of cancer subtypes. In addition, reduced Rab25 expression is found in human colorectal adenocarcinomas and correlates with poor prognosis of colon cancer patients [27], suggesting a tumor suppressor function for Rab25. In support of this contention, loss of Rab25 in mouse models of colon cancer significantly increases colonic tumor formation [27]. The mechanism is unclear. The data that overexpression and loss of Rab25 contribute to the aggressiveness of different types of cancers remain to be reconciled. Rab25 is closely related to Rab11 and belongs to the Rab11 subfamily. Indeed, Rab25 can interact with the Rab11 effector Rab11FIP1/RCP [28], which is suggested to contribute to $\alpha 5 \beta 1$ integrin recycling and cell migration [29]. In this regard, Rab11 itself has been reported to play a role in $\alpha 6 \beta 4$ integrin recycling and hypoxia-induced breast cancer cell invasion [30].

Two other Rabs, Rab5 and Rab21, also regulate the cell surface remodeling of $\beta 1$ integrins [31]. In contrast to Rab25, however, both Rab5 and Rab21 interact with the tails of α subunits ($\alpha 1$, $\alpha 2$, $\alpha 5$, and $\alpha 6$) instead of the $\beta 1$ subunit of the integrins [31]. Rab5 and Rab21 show close phylogenetic relationship and belong to the Rab5 subfamily [1, 32]. They are localized to early endosomes and plasma membrane, and promote endocytosis and redistribution of the $\beta 1$ integrins, which is shown to facilitate cell adhesion and migration of breast and prostate cancer cells (MDA-MB-231 and PC3) [31]. Furthermore, a recent report shows that depletion of Rab21 or Rab5 in carcinoma-associated fibroblasts decreases $\alpha 5$ integrin at the plasma membrane and reduces the remodeling of extracellular matrix that is necessary for the invasion of squamous cell carcinoma [33]. In addition, Rab5 and Rab21 interact with other effectors such as APPL1 [34, 35], which promotes EGF-mediated signal transduction and cell proliferation [34]. Consistently Rab5 expression is increased in lung adenocarcinoma [36] and hepatocellular carcinoma [37]. On the other hand, Rab5 activity is suppressed during the cell differentiation process in PC12 cells and inhibition of Rab5 activity via dominant negative mutant enhances NGF-mediated neurite outgrowth, a hallmark of neuron differentiation [38]. Another Rab associated with the endocytic pathway, Rab23, is up-regulated in gastric cancer and is linked to cancer invasion [39]. Rab23 is localized to the plasma membrane and endosomes and is a negative regulator of hedgehog signal transduction [40], possibly by regulation of the endocytosis and/or recycling of the signaling proteins involved in the pathway. Rab23 mutations including truncation and missense mutations have been linked to Carpenter syndrome, a pleiotropic genetic disorder with autosomal recessive inheritance [41], which is discussed in more detail below.

Cancer microarray analysis reveals that most Rabs are either up-regulated or down-regulated in all cancers examined except Myeloma [15, 16]. Remarkably, a Rab may be up-regulated in certain cancers but down-regulated in other cancer types. Rab31 (also called Rab22B) is a good example. Rab31 is another member of the Rab5 subfamily for its sequence similarity to Rab5, Rab21, and Rab22. In contrast to the early endosomal localization of the other Rab5 subfamily members, however, Rab31 is mostly localized at TGN and is suggested to regulate the membrane trafficking from TGN to early endosomes [42]. Rab31 is highly up-regulated in breast cancer samples and is suggested to serve as a prognostic marker for breast cancer metastasis [43]. In addition, Rab31 expression is increased in cancers of brain, skin, salivary gland, pancreas, kidney, head and neck, and gastric origins [16]. However, its expression is decreased in leukemia, lung and colon cancers [16]. Furthermore, Rabs associated with the exocytic pathway have also been implicated in various cancers. Rab1 and Rab2 that regulate the membrane transport between ER and the Golgi complex are up-regulated in tongue squamous carcinomas [44] and peripheral blood mononuclear cells from patients with solid tumors [45], respectively. Overexpression of Rab20 has been associated with pancreatic carcinoma [46] and triple negative breast cancer [47]. Each Rab controls a specific membrane transport pathway and up- or down-regulation of the Rabs may have great impact on the transport of cargo proteins, including the signaling proteins involved in regulation of cell proliferation, adhesion, and migration. Investigation into how altered expression of Rab GTPases may contribute to tumorigenesis and metastasis has emerged as an important area of cancer research.

RAB GTPASES AND ALZHEIMER'S DISEASE

Alzheimer's disease represents a major form of dementia that is associated with amyloid plaques in the brain [48, 49]. The core component of the amyloid plaque is amyloid- β peptide (A β) [50], which is derived from the amyloid precursor protein (APP) [51–53] via proteolytic cleavages by β - and γ -secretases [54–58]. Mutations in APP and other genes (e.g., γ -secretase) that enhance the production of toxic A β can cause early onset of Alzheimer's disease [59–62]. Along this line, the APP gene is mapped to chromosome 21 [51] and it's known that Down syndrome (trisomy 21 with an extra copy of the APP gene) is associated with early onset Alzheimer's disease [63]. However, the late onset or "sporadic" form is most common and accounts for more than 95% of Alzheimer's disease. The disease etiology is not well understood and may involve multiple factors associated with aging.

Both APP and β -secretase (also called BACE or memapsin) are type I transmembrane proteins and there are data suggesting that β -secretase cleaves at the β -site of APP in endosomes where the acidic pH favors β -secretase activity [64–67]. The γ -secretase is also a membrane-associated enzyme complex that cleaves at the γ -site in the transmembrane domain of APP after the β -cleavage, releasing the A β peptide into the lumen of endosomes and eventually to extracellular space. Sorting APP and the secretases into the same endosomes represents the initiation of A β production and requires endocytosis and endosome fusion, which are regulated by endocytic proteins including endosome-associated Rab GTPases. Indeed, Rab5 and Rab7, which control early and late endosomal fusion respectively, are selectively up-regulated in hippocampal neurons of individuals with mild cognitive impairment and Alzheimer's disease [68]. In this regard, both Rab5 and Rab7 are also up-regulated and associated with enhanced endocytic activity in aged monkey brains in an age-dependent manner [69]. The data are consistent with the contention that enhanced endocytosis represents an endocytic dysfunction that promotes production and accumulation of A β in the early stage of Alzheimer's disease [70]. Along this line, Rab5-containing early endosomes are significantly enlarged in neurons of early stage Alzheimer's disease [70], which results from overexpression of APP and increased β -cleavage in the endosomes [71], suggesting that the cleaved products of APP may increase Rab5 activity to promote endosome fusion, which further facilitate the cleavage of APP and production of A β in a positive feedback loop.

RAB GTPASES AND GENETIC DISORDERS

Mutations in five Rab GTPases have been linked to genetic disorders. Among the five Rabs, only Rab7 is ubiquitously expressed in all tissues, while the other four (Rab23, Rab27, Rab38, and Rab39b) exhibit tissue-specific expression. The Rab7 mutations are point missense mutations that appear to enhance Rab7 activity/function. In contrast, the mutations in the other four Rabs are either nonsense mutations leading to premature termination or other inactivating mutations, resulting in loss-of-function phenotypes. In addition, mutations in the gene coding for GDP dissociation inhibitor α (GDI α), which interacts with Rab proteins and regulates the cycling of Rabs between membranes and cytosol, also cause one form of genetic disorders termed X-linked mental retardation [72], possibly due to defective cycling of one or more Rabs.

Rab7 and Charcot-Marie-Tooth Type 2B (CMT2B) Disease

CMT includes various forms of inherited neuropathies affecting the peripheral nervous system [73]. CMT2B is one of the disease forms that is also called hereditary motor and sensory neuropathy type IIB, reflecting clinical symptoms of sensory loss and distal muscle weakness and high frequency of foot ulcers and infections, which eventually lead to amputation of the toes [74]. Genetic linkage studies have identified four missense mutations in the Rab7 gene at the CMT2B locus, which are predicted to produce mutant Rab7 proteins with single amino acid changes including L129F, K157N, N161T, and V162M [75–77]. These mutations cluster around the third and the fourth GTP/GDP-binding motifs (–NKXD¹²⁸ and –ETSA¹⁵⁶) and are shown to reduce the affinity for both GTP and GDP, leading to enhanced nucleotide exchange rate independent of GEFs [78–80]. As a result, the Rab7 mutants are more active than the wild-type protein and are mostly in the active GTP-bound state because of higher concentrations of GTP than GDP in the cell [78–80]. In addition, the Rab7 mutants are also shown to have reduced GTP hydrolysis activity, which is suggested to contribute to the higher ratio of GTP/GDP on the mutants [78, 80, 81]. However, a recent structural and biochemical study of the L129F mutant shows no difference between the mutant and wild-type proteins in the GTP hydrolysis rate, suggesting that the unregulated nucleotide exchange alone may account for the enhanced activity of the mutant [79]. It's important to note that although Rab7 is ubiquitously expressed in all tissues, the excessive Rab7 activity due to the mutations in CMT2B affects only the peripheral neurons and the clinical symptoms develop slowly over years.

Rab23 and Carpenter Syndrome

Rab23 is predominantly expressed in the brain and is expected to function in neurons [82]. In mouse embryos, Rab23 is expressed at low levels in all tissues but is highly expressed in spinal cord, somites, limb buds and cranial mesenchyme [83]. Rab23 is localized to the plasma membrane and early endosomes [40] and is suggested to regulate the transport and activity of signaling proteins involved in Sonic Hedgehog signaling pathway [83, 84]. The mouse *open brain* (*opb*) gene negatively regulates the Sonic Hedgehog signal transduction and is mapped to Rab23 [83]. The *opb* phenotype (open neural tube and embryonic lethality) results from nonsense mutations in Rab23 that lead to premature termination and loss of Rab23 function [83]. Recently four nonsense mutations and one missense mutation have been linked to human Carpenter syndrome [41], which is an autosomal recessive disorder of cranio-synostosis, obesity, and limb malformation. The four nonsense mutations occur at residues Glu⁴⁸, Tyr⁷⁸, Glu¹³⁷, and Leu¹⁴⁵ and all are predicted to produce truncated Rab23 proteins with no activity, while the missense mutation occurs at Cys⁸⁵ downstream of the switch II region and the change to Arg is suggested to disrupt protein folding [41]. Taken together, the genetic studies suggest that excessive Sonic Hedgehog signaling due to the loss of Rab23 function may play a role in Carpenter syndrome.

Rab27 and Griscelli Syndrome

Rab27 contains two isoforms (Rab27a and Rab27b) both of which are expressed in various exocytic cells of endocrine and exocrine origins, in CTLs, and melanocytes [10, 11]. However, the relative abundance of each isoform varies in different tissues [11].

Functionally the Rab27 isoforms appear redundant and can compensate for each other in mice [85]. Rab27a is localized on secretory granules in CTL and facilitates the transport of the granules to immunological synapses for secretion of cytotoxic enzymes such as granzyme A and hexosaminidase [86], while it is localized on melanosomes in melanocytes and promotes the transport of the melanosomes from perinuclear region to cell periphery via recruiting MyoVa [87–89].

Griscelli syndrome is an autosomal recessive disorder characterized by pigment dilution of the skin and hair, defective melanosome transport and cluster of melanosomes near the perinuclear region in melanocytes [12, 13]. In addition, Griscelli patients often show defects in the immune system with uncontrolled T lymphocyte and macrophage activation, termed haemophagocytic syndrome [90]. The genetic mutations responsible for the partial albinism and haemophagocytic syndrome in Griscelli patients have been mapped to the Rab27a gene [12]. The mutations lead to three missense (W73G, L130P, and A152P), one nonsense, and six frameshift changes all of which are predicted to produce inactive or truncated Rab27a proteins [12]. Rab27a, but not Rab27b, is highly expressed in melanocytes and CTLs [85] and inactivation of Rab27a in these two cell types results in defective melanosome transport [13] and cytotoxic granule release [12], which are believed to contribute to the clinical symptoms of partial albinism and haemophagocytic syndrome, respectively, in Griscelli patients. Consistently the defects in melanocytes and CTLs are recapitulated in a mouse model containing an inactivating mutation in Rab27a (the *ashen* mice) [86, 88, 89, 91].

Rab38 and Hermansky-Pudlak Syndrome

Hermansky-Pudlak syndrome (HPS) represents a group of autosomal recessive disorders characterized by albinism and prolonged bleeding, due to dysfunctions of melanocytes and platelets, respectively, and multiple genes have been linked to the disease [92]. A number of mouse and rat models for HPS have been established and each is defined by a particular gene mutation. In this regard, mutations in the Rab38 gene have been identified to be associated with the phenotypes of *chocolate* mice [93] and *Fawn-hooded and Tester-Moriyama* rats [94], two of the HPS models. The *chocolate* mutation is a missense mutation (G19V) in the highly conserved phosphate-binding motif of Rab38 and is predicted to affect GTP binding [93], while the *Fawn-hooded and Tester-Moriyama* mutation is a missense mutation at the start codon of Rab38 (from ATG to ATA), leading to failed translation initiation and synthesis of Rab38 [94]. A detailed cell biology study on Rab38 shows that the *chocolate* mutation (G19V) indeed inactivates Rab38 [95]. Rab38 is localized on mature melanosomes [93, 95] as well as perinuclear vesicles involved in transport of melanogenic enzymes such as tyrosinase to melanosomes, suggesting that Rab38 plays a role in the biogenesis of melanosomes [95].

Rab39b, GDI- α , and X-linked Mental Retardation (XLMR)

XLMR contains many forms caused by mutations in dozens of genes on the X chromosome and most of the genes encoding proteins localized at the neuronal synapses, suggesting synaptopathy-like disorder in XLMR patients [96]. Recently two loss-of-function mutations (one nonsense mutation and another point mutation affecting the 5' splicing site) in Rab39b were found to be responsible for one form of XLMR [96]. Rab39b is specifically expressed

in the neuronal cells of the brain, as determined by qRT-PCR and in situ hybridization analyses [96]. In hippocampal neurons, Rab39b appears to localize to the Golgi complex as well as endosomes, and shRNA-mediated knockdown of Rab39b can reduce the number of growth cones at the neuronal terminal as well as synapse formation [96]. In addition, mutations in GDI- α also contribute to XLMR. A nonsense mutation and a missense mutation (L92P) in the GDI1 gene, which encodes GDI- α , have been associated with XLMR, and the L92P mutant protein is shown to reduce interaction with Rab3a, a Rab on the synaptic vesicles [72]. Taken together, the data suggest that Rab39b and possibly other neuronal Rabs affected by GDI- α play an important role in the neuronal development in the brain.

CONCLUDING REMARKS

Rab GTPases regulate the formation, movement along cytoskeleton, and fusion of transport vesicles to promote transport of proteins and membranes along endocytic and exocytic pathways as well as specialized transport pathways in a cell type-specific fashion. As such, the Rabs that regulate endocytosis and exocytosis are ubiquitously expressed in all tissues, while the Rabs involved in specialized transport pathways are expressed only in specific cell types. It's now clear that loss-of-function mutations in some Rab proteins can cause autosomal recessive disorders and these Rabs are cell type specific. On the other hand, gain-of-function mutations in the ubiquitous Rab7 lead to dysregulated, overactive Rab7 activity, which contributes to the autosomal dominant disorder CMT2B. Although Rab7 is expressed in all tissues, the Rab7 mutations affect mainly neuronal functions with clinical symptoms of neuropathy in CMT2B, reflecting the sensitivity of neurons to alterations in the intracellular membrane trafficking system [81, 97].

In addition to mutations, the expression levels of Rab GTPases also have great impact on diseases such as cancer and Alzheimer's disease discussed here. Alterations in Rab25 expression are well documented in cancers of epithelial cells and shown to promote the aggressiveness of cancer cell invasion. Interestingly, Rab25 is overexpressed in ovarian cancer but reduced in colorectal adenocarcinomas both of which contribute to the tumorigenesis of the respective cancers [19, 85]. The up-and down-regulation of the same gene in different cancers appears a common theme for many Rabs [16], reflecting distinct growth requirements by different cancer types. Rab25 and Rab5 subfamily members are known to regulate integrin endocytosis and recycling [29, 31], but how the Rab-mediated cell surface remodeling process contributes to cancer cell invasion remains to be established. In most cases, however, it's unclear if altered expression of Rab proteins is a result, rather than a cause, of pathological processes such as cancer and Alzheimer's disease. Identification of specific cargo proteins affected by altered expression of Rab proteins should provide further insight into the mechanisms of disease processes.

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