Emerging roles for Rab family GTPases in human cancer

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Abstract

Members of the Ras-associated binding (Rab) family of small GTPases function as molecular switches regulating vesicular transport in eukaryotes cells. Their pathophysiological roles in human malignancies are less well-known compared to members of Ras and Rho families. Several members of the Rab family have, however, been shown to be aberrantly expressed in various cancer tissues. Recent findings have also revealed, in particular, Rab25 as a determinant of tumor progression and aggressiveness of epithelial cancers. Rab25 associates with α5β1 integrin, and enhances tumor cell invasion by directing the localization of integrin-containing vesicles to the leading edge of matrix invading pseudopodia. We summarized here recent findings on Rab25 and other Rabs implicated to be involved in a variety of human cancers, and discussed plausible mechanisms of how dysregulation of Rab expression could be tumorigenic or tumor suppressive.

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1. Introduction

The RABs, with more than 60 genes in the human genome (and multiple functionally distinct, splice variants of each gene), are the largest subfamily of the Ras superfamily of small GTPases [1–6]. The Rab play essential roles in various aspects of membrane traffic control, and like other members of the Ras superfamily, function as molecular switches through changes in its guanine nucleotide binding status. In its active, GTP-bound form, Rab could mediate vesicular transport by allowing transport carriers or vesicles to engage specific effectors such as motor proteins and tethering factors, as well as vesicle fusion with the engagement of soluble N-ethylmaleimide sensitive factor (NSF) [7] attachment receptor (SNARE) [8–9] proteins.

Rab are found both in the cytosol and membrane-associated fractions, with the latter being the active, functional fraction. Synthesized in the cytosol, Rabs are subjected to C-terminal prenylation (geranylation) by Rab geranylgeranyl transferase (RabGGT) [10] with the aid of Rab escort protein (REP), which enables its membrane attachment [11]. Guanine nucleotide dissociation inhibitors (GDIs) act as negative regulators of Rabs. It extracts Rab-GDP from membranes and interacts with the isoprenylated C-terminus of Rabs, thus blocking GDP dissociation and keeping these Rabs cytosolic [4, 12]. The guanine nucleotide-binding status of Rabs is more directly modulated by two different classes of regulatory proteins, namely the guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). Rab GEFs activate Rab by promoting GDP-GTP exchange [13–17]. On the other hand, Rab GAPs inactivate active Rab by enhancing their intrinsically weak GTPase activity, and accelerates the conversion of GTP-bound Rab to the inactive, GDP-bound state [18–23].

Rabs’ functions are defined by a myriad of effector proteins which they bind to when activated [24], and which facilitates either motor protein-mediated vesicle transport, docking or fusion. Actin-
dependent motor adaptors such as myosin Va is recruited by Rab27A to melanosomes via melanophilin in the regulation of melanosomal dynamics [25], while microtubule-dependent motors such as Rabkin–nesin-6 interacts with Rab6 [26]. Tethering complexes such as p115/GM130 [27], the transport protein particle (TRAPP) complex [28], and the early endosomal antigen 1 (EEA1) [29] mediate transport carrier or vesicle docking at the target membranes of the exocytic and endocytic pathways. Some Rab binding-regulated regulatory complexes may perform cell type specific functions. The protein complex of RIMx/Munc13/α-liprins, for example, interacts with Rab3A to regulate synaptic vesicle exocytosis in neurons [30].

Knowledge of human hereditary disorders that results directly from Rab mutations are limited [31–33]. Rab27A mutations underlie the symptoms of Griscelli syndrome type II, an autosomal recessive condition characterized by pigment disorder and immunological dysfunctions [34]. The hereditary peripheral neuropathy Charcot–Marie–Tooth disease type IIB is known to result from mutations in Rab7 [35–36]. Diseases could also arise from mutations in proteins that regulate Rab activity, or mutations in their downstream effectors. Griscelli Syndrome type I and III are caused by mutations in the actin motor Myo5A and melanophilin [37], both of which interact with Rab27 [38]. Inefficient geranylgeranylation of Rab27A resulting from mutations in the type 1 isoform of REP (REP-1) could underlie the X-linked retinal degenerative disease Choroideremia [39]. Mutations in GD1A cause X-linked non-specific mental retardations [40], while mutations of the catalytic subunit of Rab3-GAP cause Warburg Micro syndrome [41]. Altered function of Rab geranylgeranyl transferase can cause the Hermansky–Pudlak syndrome (HPS, a type of albinism which includes a bleeding tendency and lung disease), which is a genetically heterogeneous collection of related human autosomal recessive disorders [42–43], and defects in the various genetic mutants in HPS indirectly affect Rab27-mediated traffic and biogenesis of lysosomal-related organelles.

Carcinogenesis is usually a multistep process involving activation/elevation of growth and/or survival-promoting oncogene products, as well as inactivation of tumor suppressing genes, as a result of cumulative mutations or gene amplifications/deletions. The RAS family genes (H-RAS, K-RAS and N-RAS), the founding members of the Ras superfamily small GTPase, are prototypic oncogenes [44–45], where mutant Ras could transform cells through persistent and dysregulated mitogenic signaling. Oncogenic roles of two other Ras-related subfamilies such as Ral [46] and Rho [47] are also well-known. Dysregulation of membrane traffic in the exocytic and endocytic pathways could plausibly lead to aberrant cell proliferation, but implication of involvement of Rab family members in human cancers has been rather scarce until recently. In the last few years, aberrant expressions of several members of the Rab family are now known to be associated with various cancer tissue types. One reason for these revelations is the advent of high throughput and high resolution microarray transcript profiling and array-based comparative genome hybridization (aCGH) technologies. In the following paragraphs, a summary of findings in which aberrant Rab expressions had implicated these proteins in the malignant pathology of human cancers is first presented. These shall be followed by a discussion on known and possible mechanisms whereby certain Rab could be involved, directly or indirectly, in tumorigenesis.

2. Dysregulated Rab expression implicated in human cancer

Dysregulated expression of several other Rabs have been shown in expression analysis of cancer tissues. A summary of known Rab family members implicated in human cancers is shown in Table 1. Microarray analysis coupled to immunohistochemical analysis had revealed a high prevalence of transcript and protein over-expression of the key ER-Golgi traffic regulator Rab1A in tongue squamous cell carcinomas (98%), as well as in premalignant lesions (93%) [48]. Levels of Rab2, Fig. 1. A cartoon depicting generalized and hypothetical situations in which Rabs may participate in tumorigenesis/metastasis. Rab membrane association and function is regulated by proteins which modulate its guanine nucleotide binding status (guanine nucleotide exchange factors, GEFs and GTPase activating proteins, GAPs). Guanine nucleotide dissociation inhibitors (GDIs) associate with cytosolic, GDP-bound Rabs. GTP-bound Rab regulates endocytosis and endocytic trafficking of growth factor receptors, and changes in levels and activity of certain Rabs may change the strength and duration of growth factor receptor-ligand complex from signaling endosomes, which is qualitatively different from signaling from the cell surface (represented green and red block arrows, respectively), leading to enhanced cell proliferation and survival. In some cases (such as that of Rab25), enhanced modulation of the dynamics of cell adhesion components (such as integrin) by elevated levels of Rabs may enhance filopodia formation, tumor invasion and metastasis.
another Rab protein mediating ER-Golgi transport, are often found elevated in peripheral lymphocytes of patients with hematological and solid tumors [49]. The levels of brain-enriched Rab3 is often found elevated in cancers of the nervous system and neuroendocrine cells [50], as well as insulinoma tissue [51].

Rab5 is a key regulator of growth factor receptors-mediated endocytosis, and would, in theory, be a prime candidate of genes whose dysregulated expression could be tumorogenic. Upregulation of Rab5 has been correlated with the degree of malignancy and metastatic potential of human lung adenocarcinoma [52]. Another study shows that Rab5A expression was higher in resected hepatocellular carcinoma (HCC) tissue compared to non-tumorous tissues, and a dominant-negative Rab5A mutant attenuated EGF-mediated signaling and cell migration of a human hepatoma cell line [53]. Both Rab5A and Rab7 are upregulated in autonomous thyroid adenomas compared to quiescent surrounding tissues, and the levels of these Rabs are apparently enhanced by thyroid stimulating hormone [54]. Interestingly, another report indicated that the expression level of Rab5B was lower in the surrounding tissues, and the levels of these Rabs are apparently upregulated in autonomous thyroid adenomas compared to quiescent surrounding tissues, and the levels of these Rabs are apparently enhanced by thyroid stimulating hormone [54].

Rab25 overexpression also led to decreases in anchorage-dependent colony forming activity, cell proliferation and serum deprivation, anchorage deprivation, UV irradiation and chemotherapy treatment. Rab25 over-expression also led to decreases in squamous cell carcinomas (eg. carcinoma), hepatocellular carcinoma and thyroid adenoma, as well as preneoplastic pancreatic intraductal neoplasia lesions [57]. Our recent analysis with Rab22B/Rab31 specific antibodies shows that it is abundant in the brain and also found in other tissues such as spleen and intestine [59]. Rab22B/Rab31 is apparently upregulated in breast tumor samples with high expression of an uPA receptor splice variant (uPAR-del4/5), and may be associated with a worse metastasis free survival endpoint in patients [60]. Rab32 has been found to be frequently hypermethylated in microsatellite-unstable gastrointestinal adenocarcinomas [61]. Both Rab32 and Rab38 are key regulators of post-Golgi trafficking of melanogenic enzymes in melanocytes [62]. RAB38 is the gene mutated in coat color mutants in mouse and rats, and is a prominent autoimmunogen in a significant portion of melanoma patients [63].

A recently identified small GTPase, known as Rab-like protein 1 (RBEL1) because of its closer homology to Rab than other members of the Rab superfamily, is found to be over-expressed in about two thirds of primary breast samples examined [64].

Rab23 is a prominent example of a Rab protein with a specific function during mammalian development. Sonic hedgehog (Shh) functions as a morphogen at the early neural tube to specify the expression of ventral cell markers. The open brain (opb) mutation was first identified as a natural mouse mutation resulting in severe defects in the developing neural tube [65]. The neural patterning defects of opb appear to be opposite that of shh. The opb gene acts downstream of shh, as shh phenotype is at least partially rescued in a shh/opb double mutant. opb encodes mouse Rab23 [66], and recent findings indicate that several nonsense mutations of human Rab23 underlie Carpenter’s syndrome [67], a autosomal recessive disorder with anatomical and physiological deformities. The exact role of Rab23 in antagonizing shh signaling is unclear at the moment [68]. Rab23 levels had been recently shown to be elevated in hepatocellular carcinoma cell lines and tissues, and silencing of Rab23 by siRNA in some of these cell lines could reduce survival and increase the basal rate of apoptosis [69]. Rab23 levels were also reported to be elevated in atrophic gastritis and intestinal metaplasia [70]. Another recent report has provided a further connection between Rab23 and gastric cancer. Using high resolution array-based comparative genomic hybridization, Rab23 is identified as one of the genes focally amplified in the gastric cancer cell line Hs746T [71]. Silencing of Rab23 in this cell line reduced invasiveness. Rab23 amplification was also found in primary gastric tumors, and its elevated expression is significantly associated with diffuse-type compared to the intestinal type gastric cancer [71]. Rab23’s implication in cancer is of considerable mechanistic interest, and shall be discussed further in sections below.

Rab23 is perhaps the Rab family member whose association with human cancer is best documented and best defined in terms of possible underlying molecular mechanisms. Phylogenetically, it belongs to the Rab11 subfamily (Rab11A, Rab11B and Rab25/Rab11C) [1]. When first cloned, it was shown that Rab23 is enriched in organs with epithelial cells, with prominent expression throughout the gastrointestinal mucosa (and with the highest expression seen in the ileum and colon). High Rab23 expression is also found in lung and kidney. These findings indicated that Rab25 has an epithelial-restricted expression profile [72]. It was later shown that Rab25 is associated with the apical recycling system in MDCK cells [73] and regulates apical endocytosis and transcytosis [74]. More recent papers reported detection of Rab25 expression in ovarian and breast cancers [75–76]. As described in the next section, it later became clear that Rab25 plays important pathogenic roles specifically in epithelial cancers.

### 3. Rab25 in epithelial cancer

In using aCGH to investigate amplifications in chromosome 1q in ovarian and breast cancer, Mills et al. [75] delineated an increase in DNA copy number of a region on chromosome 1q22 of advanced epithelial ovarian cancers. Ovarian cancer patients with elevated 1q22 copy number are associated with poor disease-free survival following surgical and chemotherapy procedures. Of the 34 open reading frames in this region, the authors identified RAB25 as the most markedly elevated gene. Furthermore, increase in Rab25 expression was shown to be higher in late stage tumors (such as stage III and IV) than early stage cancers, indicating that it may be involved in tumor progression. Interestingly, no mutation in the Rab25 gene itself was identified, which suggests that high levels of wild type Rab25 alone may be cancer promoting.

To evaluate the effect of elevated Rab25 levels on ovarian and breast cancers, cell lines stably over-expressing Rab25 were generated. Rab25 over-expression resulted in a marked increase in anchorage-dependent colony forming activity, cell proliferation and cell survival under several different apoptotic stress conditions, such as serum deprivation, anchorage deprivation, UV irradiation and chemotherapy treatment. Rab25 over-expression also led to decreases...
in the levels of the pro-apoptotic proteins Bax and Bad, while elevating Akt phosphorylation. Silencing of Rab25, on the other hand, increased sensitivity to apoptotic stress, and reversed the decrease in Bax and Bad levels as well as Akt phosphorylation. It is possible that phosphoinositide-3-kinase pathway (PI3K pathway), together with Bcl-2 proteins, are involved in mediating Rab25's action.

When introduced in vivo, Rab25 over-expressing cells formed tumor in nude mice much more efficiently compared to parent cells, forming larger tumors in shorter times. However, Rab25 over-expressing non-tumorigenic immortalized ovarian epithelial cells did not form tumor in nude mice. Increase Rab25 expression therefore appears insufficient for tumor initiation, or the primary transformation of ovarian epithelial cells, but instead participate in tumor progression by increasing tumor growth and aggressiveness of already transformed tumor cells [75].

How exactly does high level of Rab25 enhance growth and aggressiveness of epithelial tumors? Caswell et al. found that the β1 subunit of integrin and α5β1 heterodimers co-immunoprecipitated with over-expressed epitope-tagged Rab25 in ovarian cells [77]. Further pull-down analysis with various recombinant proteins indicated that an interaction occurs between Rab25 and β1 integrin in a specific (neither Rab11A nor Rab11B interact likewise), as well as GTP-dependent manner in vitro through Rab25's C-terminal hyper-variable region. Fluorescence resonance energy transfer (FRET) microscopy showed that the proteins interact in vivo in membrane puncta near the plasma membrane.

Although the interaction between Rab25 and α5β1 integrin immediately suggests an effect on cell migration, over-expression of Rab25 did not significantly change cell migration parameters on a 2-dimensional growth surface. However, when presented with a 3-dimensional (3D) environment (matrigel or fibrillar type I collagen gel), Rab25 over-expression augmented invasion through the 3D matrix in a manner that is enhanced by fibronectin. Invasion was attenuated by Rab25 silencing, and dependency of the Rab25-mediated invasion on α5β1 integrin could be specifically blocked by antibodies against the α5 or the β1 integrin subunit, as well as the α5β1-binding site in fibronectin. Fibronectin was known to be anti-invasive and anti-metastatic. The invasive phenotype of v-fos transformed rat fibroblasts, for example, could be reversed by fibronectin incorporated into the 2D substratum or 3D matrix in a α5β1-dependent manner. Intriguingly, Rab25 expression could overcome this invasion inhibitory effect of fibronectin.

The authors further investigated the cellular localization and dynamics of Rab25-α5β1 integrin containing vesicles. To aid imaging, they used a less dense cell-derived matrix composed mainly of fibrillar collagen and fibronectin. Rab25 slowed the speed, but enhanced the persistence of cell migration on the matrix, which occurred through the extension of pseudopods. FRET indicate that association between Rab25 (Cherry-Rab25) and α5β1 (GFP- β1) is strongest within the pseudopods. In Rab25 over-expressing cells, vesicles containing both Rab25 and α5β1 are slower moving and colocализed at the pseudopodal tips, whereas vesicles carrying α5β1 alone are more rapid in their movements are seldom found at the tips. Photocitation and time-lapse observation showed that these Rab25-α5β1-containing vesicles are responsible for delivering α5β1 to the plasma membrane of pseudopodal tips. A discrete pool of α5β1 was rather effectively retained at the pseudopodal cell migration front by Rab25. This pool appears to result from rapid and effective recycling of α5β1 from the plasma membrane.

The observations of Caswell et al. [77] are interesting, but the full implication of these observations remains to be worked out. In the 3D cell matrix invasion experimental set up for ovarian tumor cells, Rab25 expression appears to sustain the availability of a distal pseudopodal α5β1 pool via a plasma membrane recycling mechanism. This α5β1 pool in turn presumably stabilizes the pseudopods and provided robustness and persistence to cell invasion. Another point of interest is that matrix fibronectin interaction with cell surface α5β1 is usually anti-invasive for non-epithelial cells with little or no Rab25 expression. It is not yet entirely clear how Rab25-mediated trafficking of α5β1 could overcome this anti-invasive mechanism, but it is likely to reduce strong, permanent adhesion and aid migration.

From the preceding discussion, it is clear that Rabs, although not usually considered oncogene products, could profoundly alter the proliferative, survival and invasiveness of cancer cells. Rabs' loss or gain-of-function resulting from gene amplification or deletion could therefore impact on the tumoragic/metastatic parameters above. It is also conceivable that Rabs' influences in tumorigenesis/ metastasis could go both ways. Another recent report, for example, showed that a loss of Rab25 expression in some breast cancer cell lines and breast cancer tissues from patients [78]. Using fifteen breast cancer cell lines, the authors detected Rab25 in all 6 non-tumorigenic cell lines, and loss of Rab25 were found in 4 out of 9 tumorigenic cell lines. Furthermore, about one-third of the breast cancer tissues were detected to have loss of Rab25 expression. The authors pointed out an interesting fact which may offer an explanation of how loss of Rab25 could influence tumorigenesis. Interestingly, 3 out of the 4 breast cancer cell lines with a loss of Rab25 expression also had H-Ras or K-Ras mutations. The GTP-binding site of Rab25, DTAGLE, is different from other Rab proteins (DTAGQE); and is interestingly identical to the GTP-binding site of the oncogenic Q61L mutant of Ras [79] in the switch II region. Hence, it is possible that the two similar GTP-binding sites of Rab25 and Q61L mutant of Ras compete for locally available GTP, and loss of Rab25 may therefore enhances Ras-driven breast tumorigenesis.

In the ensuing discussions, we shall look at various possible ways of how Rabs might be tumorigenic/metastatic, or conversely, tumor suppressive under certain circumstances.

4. Rabs' influence on endocytic trafficking and mitogenic signaling of growth factor receptors

One of the most obvious ways by which changes in Rabs' expression levels could affect cell growth and proliferation is through their influence on growth factor receptor trafficking and consequentially, signaling. This notion is particularly applicable to those Rabs controlling the endocytic itineraries of the various membrane receptors of mitogenic ligands, such as the epidermal growth factor receptor (EGFR) and other members of the ErbB receptor tyrosine kinases family [80–81]. Many tumors are known to have increase activities of receptor tyrosine kinases, either through aberrant over-expression or constitutive activation by various regulation-impairing mutations [82–83].

It is now known that internalized EGFR-ligand complexes continue to signal from intracellular “signaling endosomes” [84–89]. Signaling from intracellular compartments differs quantitatively and qualitatively from that at the cell surface as the association of the EGFR with different signaling adaptors is compartment specific. Regulated trafficking of EGFR could thus potentially affect the pattern as well as the duration of signal transduction. Rab mutants have been shown to influence EGFR signaling and degradation at different stages of the endocytic route [80, 90–91]. It is therefore theoretically plausible that somatic gene amplification of endocytic Rabs could enhance or prolong mitogenic EGFR signaling in ways that could contribute to tumorigenesis. Furthermore, influences on EGFR signaling need not come solely from those Rab proteins that are essential EGFR's endocytic itinerary (such as Rab4, Rab5, Rab7 and Rab11). Any Rab whose over-expression could perturb the trafficking and mitogenic signaling of growth factor receptors.

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There is a further possible connection between Rab-mediated trafficking and growth factor signaling — that molecules downstream of growth factor receptors could regulate Rab activity and growth factor receptor endocytosis. The phosphatidylinositol 3 (PI3)-kinase and its downstream target Akt kinase constitutes a major axis of growth and survival signaling in most cells, and is therefore a major contributor to tumorigenesis of various cancers [96–98]. Mutations of the p110 catalytic subunit of PI3-kinase could induce a gain of function of its enzymatic activity that drives tumorigenesis [99]. The regulatory p85 subunit of PI3-kinase has a breakpoint cluster region homology (BH) domain with sequence homology to GAPS, and has GAP activity towards certain members of the Rho and Rab family (Rab4 and Rab5) [100]. A single point mutation (p85-R274A) abolishes the GAP activity, but does not apparently alter its role in PI3-kinase function. It was recently shown that expression of this mutant p85 could result in the transformation of NIH3T3 fibroblasts, with loss of contact inhibition, growth in soft agar and tumor formation in nude mice [101]. These observations suggest that expression of the RabGAP activity-defective p85-R274A may have somehow deregulated PDGF receptor endocytosis, and this had altered its downstream signaling in a PI3-kinase-independent manner that resulted in cellular transformation. This notion is supported by the finding that co-expression of a Rab5 dominant-negative mutant (Rab5-S34N, with a preferential binding to GDP) could revert the enhanced MAP kinase and Akt activation, as well as the transformed phenotype induced by p85-R274A.

Other than affecting cell growth and proliferation through influencing growth factor receptor trafficking and signaling, Rab can also affect cell survival through influencing cell surface expression of nutrient receptors. Rab7 is shown to mediate endocytosis and degradation of glucose and amino acid transporters in growth factor-deprived cells, where it functions as a pro-apoptotic protein by limiting cellular nutrient uptake and nutrient-dependent cell survival [102]. A dominant-negative Rab7 could cooperate with the viral oncopogene E1A to promote the transformation of p53-deficient mouse embryonic fibroblasts.

5. Rabs' influence in other known tumorigenic signaling pathways

Other than growth factor receptors, aberrant Rab-mediated trafficking of components of some other signaling pathways could also be potentially tumorigenic. One of these is the Wnt signaling pathway which has been extensively implicated in cancer [103–104]. It is unclear if the canonical Wnt signaling requires Rab, but Xenopus Rab40 has been recently shown to participate in the noncanonical Wnt pathway [105]. A firm connection between Rab and Wnt signaling awaits further work. Notch signaling has also been implicated in both tumorigenesis and cancer suppression [106–107]. A role in modulating Notch signaling has been shown for Rab6 [108] and Rab11 [109] homologues in Drosophila. However, a connection between mammalian Rab and Notch-mediated tumorigenesis has yet to emerge.

Dysregulated signaling of another developmentally important morphogen, sonic hedgehog (Shh), has been implicated in multiple human cancers [110], including gastric cancer [111], prostate cancer [112], pancreatic cancer [113], skin cancer [114] and childhood medulloblastoma [115]. The reports on several recent associations between Rab23, which appear to antagonize Shh signaling during development [66], and cancer [69–71], as discussed earlier, is therefore noteworthy. At the moment, the exact mode of function of Rab23 in the Shh pathway is unclear [68], but genetic analysis indicate that it does not work directly on the membrane receptor components, namely Patched and Smoothened [116]. Rather, it appears to affect unknown factors downstream of Smoothened but upstream of the Gli transcription factors. Regardless of its mechanism of action, Rab23 may have a role in several Shh-dependent or independent human cancers.

6. Concluding remarks

With widespread use of high throughput genomics technologies, one could expect more associations between aberrant Rab gene expression and human cancers to be revealed in the near future. This could provide further examples of how deregulated membrane transport could contribute to tumorigenesis (or metastasis). Thus far, most association between Rabs and cancers involves transcript and/or protein up-regulation. More extensive efforts such as those planned by International Cancer Genome Consortium (ICGC) could yet uncover Rab mutations that might directly affect cell proliferation and survival.

A simplistic view of how Rab might help drive tumorigenesis is that increase Rab expression presumably results in heightened activation of cell proliferative or survival pathways through modulation of growth factor receptor endocytosis and signaling through signaling endosomes Fig. 1. Also, as in the case of Rab25/Rab11C, modulation of the dynamics of cell adhesion components and/or cytoskeleton (perhaps in conjunction with the Rho family members) may also enhance tumor invasion and metastasis. There may in fact be a connection between growth factor receptor and integrin recycling. A very recent report suggests that the Rab11 family interacting protein 1 (Rab11-FLP1) (or Rab coupling protein, RCP), a Rab11 effector, could under certain circumstances interact with both α5β1 integrin and EGFR and mediate their coordinated recycling in a manner which increases downstream AKT phosphorylation [117]. Rab11A has been previously shown to be increased in ductal carcinoma in situ compared to normal ducts [118]. Overexpression of wild type Rab11A increased, while a S25N dominant-negative mutant delayed EGFR recycling, and inhibited proliferation and anchorage-dependent growth of a breast cancer cell line MCF10A [118]. Rab11 family-mediated recycling of multiple factors could therefore collectively contribute to tumor pathogenesis.

In some cases, however, the mechanistic basis of Rab-enhanced tumorigenesis may not be so straightforward. For example, the mode of action of Rab23 in terms of tumorigenesis and progression remains unclear. Since Rab23 is known to antagonize tumorigenic Shh signaling, that its upregulation could contribute to tumorigenesis appears to be counter intuitive. Rab23 may therefore have other unknown, perhaps non-Shh signaling related activities that contributes towards tumorigenesis.

As the underlying mechanisms of Rab-mediated tumorigenesis/metastasis come to light with further investigations, it is conceivable that expression profiling of some Rabs might become useful as stage indicators or prognostic markers of the respective cancers. Some of these might even represent novel targets for therapeutic intervention of malignancies.

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