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REVIEW PAPER

Rabs Mediated Membrane Trafficking in Cancer Progression

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Abstract

Ras-associated binding (Rab) GTPases control diverse stages of endo and exocytic pathways. Functional impairments of Rabs and its associated proteins have been implicated in many hereditary and neurological diseases. Although Rabs are not classically considered as oncoproteins, many Rabs have been involved in tumor progression/proliferation and its aggressiveness. Rabs contribute to tumor cell migration, invasion of cancer cell to extracellular matrix (ECM) and modification of tumor microenvironment through modulation in integrin trafficking, exosomal and protease secretions. In the present review, current knowledge about the pathogenesis and tumor progression of some Rabs (Rab27, 25 & 21) has been discussed.

Keywords: Rab GTPases, SNAREs, tumorigenesis, endocytosis, exocytosis

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1. Introduction

Ras-associated binding (Rab) proteins play a master role in the proper flow of transport vesicles from their origin to target organelle which is crucial for the accurate delivery of the cargo within the cell. Emerging evidences show that numerous diseases including cancers can occur by alternations in membrane trafficking. Cancer is uncontrolled cell division due to series of successive mutations in genes that leads to atypical cellular proliferation. According to WHO, Cancer remained the second most frequent cause of death worldwide in 2018. An improved understanding covering genetic aberrations due to malfunctioning of Rab proteins may indicate potential therapeutic targets that can improve cancer survival.

Rab protein (ras-like in rat brain) was identified by Touchot in 1987 [1] and was indicated as a key player in endosomal trafficking [2]. This evolutionary conserved subgroup of Ras GTPases superfamily comprises more than 60 members in humans which are phylogenetically classified [3]. These small GTPases (20–25 kDa) play a significant role in budding, transport, tethering and fusion of endosomal vesicles to their target membrane [4]. Numerous Rabs are associated with distinct vesicles at different stages of membrane trafficking to represent them specifically to their target membrane. The activity of Rab proteins is regulated by some effectors:

guanine nucleotide exchange factors (GEFs), which facilitate the activation of Rabs by exchanging GDP with GTP; GTPase activating proteins (GAPs), which hydrolyze GTP into GDP, rendering Rabs into inactivated state; and guanine nucleotide dissociation inhibitors (GDIs), which act as negative regulators. GDI maintains the cytosolic form of Rab proteins by interacting with the isoprenylated C-terminal of Rabs [5].

Functions of other effectors of Rab proteins, e.g. SNAREs (Soluble N-ethylmaleimide sensitive factor attachment protein receptor), motor proteins and tethering factors, are summarized in figure 1. Rab escort protein (REP) presents Rabs to geranylgeranyltransferase which adds isoprenoid moieties to one or two cysteine resides on the C-terminal of Rab proteins. This process helps to attain the attachment capacity [6]. Dysregulation in Rabs function by mutations in them and their effectors may alter the vesicular transport system which can contribute to developing tumorigenesis and many inherited disorders such as choroideremia and Griscelli syndrome [7].

Recent advancements in understanding cancer progression enable us to overview the current knowledge about the role of Rabs mediated endosomal trafficking in cancer, which will be the focus of this review.

2. *Role of Rabs in pathophysiology*

Compartmentalization of organelles and the impermeable nature of plasma membrane hinder many cell sustaining molecules to enter the cell. Exchange of molecules between these organelles is mediated by vesicular transport; a series of specific steps that facilitate the accurate delivery of materials between intracellular organelles by vesicles. Rab proteins, being specific to each membranous compartment, assist in endocytic and exocytic membrane transport. Efficient trafficking is essential, because the incorrect localization of molecules can cause disastrous and even fatal effects to the cell [8, 9]. Some Rabs are tissue or cell specific, while most of the Rabs express ubiquitously and may participate in more than one step in transport. For example, Rab1 has been documented in early intra-Golgi transport as well as in vesicle budding from ER to Golgi [10]. Rab27a is involved in the exocytosis of lytic granules from cytotoxic T lymphocytes (CTL) [11] and in the peripheral distribution of intracellular vesicles called melanosomes, which are required for normal skin and hair colour development. Loss of function mutation in Rab27a is responsible for an autosomal recessive disorder of diluted pigments in skin and hair called Griscelli Syndrome subtype 2 [12, 13].

MYO5A gene encodes a motor protein myosin Va which is responsible for melanosomal arrest and its peripheral accumulation at the distal ends of melanocytes' dendrites, from where melanosomes can be transferred to

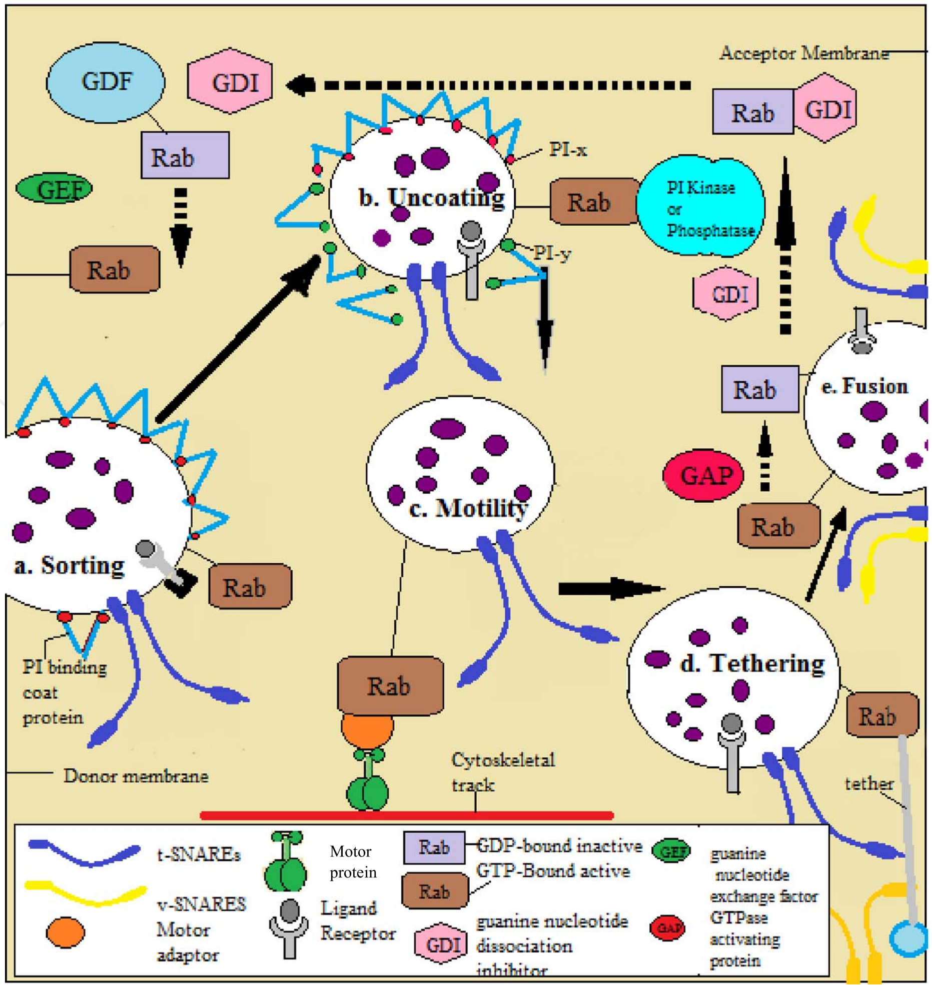

Figure 1. Steps in membrane trafficking modulated by Rab GTPases: (a) Following activation by guanine nucleotide exchange factor (GEF), Rabs can activate a sorting adaptor to aid receptor attachment to the budding vesicle. Cargo specific coat proteins are also recruited at this step. (b) Rab mediated delivery of phosphoinositide (PI) kinase or phosphatase may change the composition of transport vesicle (PI-x to PI-y where x and y are just to show the change in composition of transport vesicles) which causes the uncoating of PI binding coat protein. (c) Rabs facilitate directional vesicle transport along cytoskeletal track (actin filaments and microtubules) through motor adaptors or by interacting directly with motor proteins. (d) Rabs mediated vesicular tethering is initiated by the interaction of Rabs and tethers. These tethering factors play important functions in the activation of SNARE complex and increase the fidelity of fusion by assisting in the selection of correct acceptor membrane. (e) Rab GTPase is converted into its inactive form after vesicle fusion by GTPase activating protein (GAP). Guanine nucleotide dissociation inhibitor (GDI) removes Rabs from target membrane and maintains it in cytosolic form. GDI dissociation factor (GDF) releases Rabs from GDI and inserts it again into the target membrane for the next Rabs cycle [14].

keratinocytes, the site of making visible pigmentation. Rab27a is considered as a melanosomal membrane protein that acts, completely or partially, as a receptor for myosin Va. According to one assumption, myosin Va interacts indirectly with Rab27a and exon F in the tail domain of melanocytes-spliced isoform of myosin Va forming a complex with one of the Rab effector, melanophilin for downstream signaling. Dysregulation in any of the genes in this complex can cause Griscelli syndrome type 2. Adverse effects of this disease may result in hemophagocytic syndrome which is characterized by uncontrolled T lymphocytes production and enhanced activity of macrophages [15].

Rab11 subfamily includes Rab11a, Rab11b and Rab11c (also called Rab 25). The expression of Rab25 is specific to epithelial cells [16]. Additionally, it is involved in many cellular functions, for example, regulation of $\alpha 5\beta 1$ integrin and transferrin receptor recycling, IgA transcytosis, activation of growth promoting signaling (Akt, Wnt and Src) pathways, microtubules organization and suppression of apoptosis [17, 18].

From neurodegenerative disorders to diabetes, Rab11 has been implicated in a number of patho-physiological diseases. Neurodegeneration in Alzheimer disease is caused by accumulation of amyloid-β (Aβ) peptides. Rab11 is responsible for cellular trafficking of Aβ peptides. Blockage in Aβ recycling was observed with constitutively active Rab11 mutant [19, 20].

In case of type 2 diabetes, insulin resistance can destroy the intracellular sources responsible for translocation of GLUT4, which plays a major role as a transporter of glucose to insulin. Rab11 is functionally involved in transportation of GLUT4 from storage vesicles to recycling pathways [21]. In addition to Rab11, Rab10 also coordinates with myosin Va for translocation of GLUT4 from storage vesicle to plasma membrane in adiposities [22] whereas Rab8a and Rab13 can regulate the translocation of GLUT4 in muscles cells [23].

3. Role of Rabs in cancers

Membrane trafficking controls protein transport, cellular proliferation/invasion, differentiation and signal transduction [8]. Abnormalities in endocytic pathways, for example, disturbance in cell–cell communication and loss of morphological polarity lead to malignancies [24]. Although no Rab activated cancer causing mutation has been reported so far [25], transcriptional profiling of several cancer tissues has shown altered expression of several Rabs [26]. This suggests that being important regulators of vesicular transport, changed expression of Rabs may promote cancer development and progression [14].

4. Rab27

Rab27 exists in two isoforms, (i) Rab27a, which contributes majorly in the exocytosis of melanosomes, lytic granules and dense granules [27] (ii) Rab27b, which is mainly involved in the exocytosis of pancreatic acinar [28], targets uroplakins to urothelial apical membrane [29], and also regulates secretions of pituitary hormones [30]. Together with these functions, recent studies have shown that Rab27a and Rab27b promote exosomal secretions to augment tumor supporting microenvironment in many cancer cell lines, e.g. lung cancer cell line A549 [31], HeLa cell line [32], breast cancer cells [18, 33] and bladder cancer cells [34].

Exosomes and shed microvesicles (sMVs) are the two classes of extracellular vesicles (EVs) which can be distinguished on the basis of their sizes and the mechanism of biogenesis. Exosomes range in diameter between 30 nm and 150 nm, whereas the average diameter of sMV is between 50 nm and 1300 nm [35]. Exosomes play an important role in tumor progression. Cancer cells send soluble molecules and exosomes to the tissue microenvironment for the invasion and metastasis of cancer [36]. Tumor derived exosomes carry functional oncoproteins, micro RNAs [37] and oncogenic long non-coding RNAs [38], resulting in the activation of downstream signaling pathways, altered expression of genes and drug resistance in neighboring cells respectively [37, 38].

It was found in a study that Rab27 promotes cancer growth by enhancing exosomal release which can reduce the expression of tumor suppressor micro RNAs, namely miR-23b and miR-921. Knockdown of Rab27a or Rab27b in bladder cancer cells reduced exosomal secretion, increased the intracellular levels of miR23b and miR921 and decreased primary tumor progression [34]. Knockdown of both Rab27a and Rab27b suppress in vitro tumor growth in WM1385 and WM 1960 melanoma cells lines [35] and in vivo tumor development in xenografts of human and mouse melanoma cells [37].

Bobrie *et al.*, studied the prometastatic effect of Rab27a on 4T1 (metastatic) and TS/A (non metastatic) mouse breast carcinoma cells and found that the inhibition of Rab27a not only reduced exosomal secretions but also abolished the secretions of proMMP9 in both cell lines. Matrix metalloproteinases (MMPs) enhance the invasiveness of cancer cells by extracellular matrix (ECM) degradation and growth factors activation. They suggested that Rab27a dependent exosomal secretions are also required for the mobilization of neutrophils which enhanced the growth and metastasis in 4T1 cells [38].

Mechanism for the altered expression of Rab27 in cancer is still debatable. The expression of several Rabs involved in cancers is regulated by micro RNAs, e.g. miR-9 regulates the expression level of Rab34 in gastric cancer [39]. However, misregulation of miR is not found in the altered expression of Rab27a or Rab27b, so far. Elevated mRNA levels of Rab27a due to copy number amplification were found in many melanoma samples, which could be a reason for the upregulation of Rab27 in cancers [35].

In MCF-7 cells, Rab27b derived exosomes are reported to be regulated by V-ATPases, which create a proton gradient for vesicular trafficking. Reversible inhibition of V-ATPase abolished Rab27b vesicle accumulation and inhibited cell cycle transition from G1 phase to S phase by reducing invasive potential of ERα-positive breast cancer cells in collagen type 1 and choriallantoic membrane (CAM) tissue in fertilized chicken eggs [35]. Rab27b promotes invasion, growth and metastasis in breast cancer cells by heat shock protein (HSP 90α) secretions. Reduction in Rab27b also reduced the expression of HSP90α and activation of its receptor, pro MMP-2 [40].

5. Rab25

Studies have indicated that the oncogenic and tumor suppressor nature of Rab25 is cancer type dependent [17]. Overexpression of Rab25 in prostate cancer [17], breast cancer and ovarian cancer [28] aids tumor progression whereas Rab25 is downregulated in colon [41] and esophageal cancers [42].

Amplification in chromosome 1q is associated with breast and ovarian cancers, Wilms tumor and invasive ductal breast carcinomas. An increase in the copy number and mRNA levels of Rab25 in chromosome 1q22 was reported in almost half of the breast and ovarian cancer patients. The potential role of Rab25 in tumor progression and aggressiveness was indicated by the stage dependent expression of Rab25 in breast and ovarian cancers, because higher expression of Rab25 was found in Stage III and Stage IV as compared to early stages [28].

Rab25 can also promote tumor cell metastasis by interacting with β1 integrin. It directs the localization of integrin containing vesicles to the plasma membrane that enhance tumor cell ability to invade the ECM [43].

It was postulated that recycling of integrin to plasma membrane is governed by a pathway involving a protein, CLIC3 (chloride intracellular channel protein 3). Activated integrin can promote many processes that are linked with metastasis, such as cell migration, growth and survival, by activating Src pathway which in turn activates transcription factor, STAT3. STAT3 leads to the enhanced expression of cell cycle genes that augment tumorigenesis. Oncogenic and tumor suppressive nature of Rab25 were also inferred from the expression of CLIC3. A significantly shorter survival in pancreatic cancer patients was observed with high levels of Rab25 and CLIC3 whereas elevated Rab25 and reduced CLIC3 levels were shown with better clinical outcomes. Thus, it was hypothesized that Rab25 may act as an oncogene in the presence of CLIC3 by enhancing integrin recycling and the absence of CLIC3 makes Rab25 a tumor suppressor [44].

As described earlier, Rab25 can activate growth promoting pathway which may stimulate cellular proliferation in cancer cells. Similarly knockdown of Rab25 can reduce metastatic potential in cancer cells due to decrease in phospho-Akt levels, for example, in bladder cancer cells [45] glioblastoma multiforme cells [46], breast cancer cells and ovarian cancer cells [28]. This phenomenon supports the potential involvement of PI3K pathway in facilitating Rab25 activity. Inhibition of Rab25 in hepatocellular carcinoma cells was reported to block cell growth rate possibly due to the depletion of AKT phosphorylation, Wnt signaling pathway and its target genes (MMP7, cyclin D and c-myc) [47].

Rab25 has been documented in the alternation of expression of apoptotic molecules; where Rab25 was found to reduce pro-apoptotic proteins BAX and BAK in ovarian cancer [28], and its knockdown tends to reduce anti-apoptotic molecule Bcl-2 in tobacco carcinogen-induced lung cancer [48]. Hence, it can be concluded that, the epithelial-specific protein, Rab25, boosts cancer progression by stimulating growth promoting signaling pathways and suppressing apoptotic cell death.

With regard to the tumor suppressive nature of Rab25, it was speculated that the loss of Rab25 may cause imbalance in the distribution of some important cargoes in membrane trafficking that augment colon carcinogenesis, as genetic deletion of Rab25 in mice having intestinal and colonic neoplasms showed accelerated tumorigenesis [41]. Similarly, the expression of Rab25 was also considerably reduced in clinical specimens of esophageal squamous cell carcinoma (ESCC). Akin to the most common reason behind the downregulation of many tumor suppressors; the suppression of Rab25 in ESCC was also due to its promoter hypermethylation. Moreover, stable overexpression of Rab25 not only decreased phosphorylation of FAK and c-Raf, which reduced downstream signaling of MAPK/ERK, but also minimized invasion and angiogenesis in tumor cells [42]. In human ovarian cancer cell line (A2780), increases in cellular mobility have been observed by localization of integrin-recycling vesicles to plasma membrane by Rab25 [49].

6. Rab21

Rab21 was initially cloned and sequenced by Madin-darby Canine Kidney II cell library. This protein shows a close phylogenetic relation with Rab22 and Rab5 [50]. Constitutively expressed Rab21 is believed to localize in early endosomes [20] at plasma membrane and in Golgi complex [51].

C-terminal of Rab21 is associated with $\alpha 2$ and $\alpha 11$ integrin chains to mediate integrin trafficking for cytokinesis. Any mutation in Rab21 can disrupt cytokinesis which may cause multinucleate daughter cells to occur frequently in cancer progression. Thus, Rab21 is considered important for genetic stability, accurate cell division and inhibition of aneuploidy in dividing cells [52].

Rab21 can also localize β1 integrin to focal adhesion molecules, hence silencing of Rab21 disturbs integrin trafficking and thus impairs cellular migration and adhesion. On the other hand, higher expression of Rab21 stimulates cell motility which increases cancer cell adhesion to collagen [53].

Carcinoma associated fibroblast (CAF) and many other immune cells promote cancer cell invasion, commonly occur in distant metastasis. Matrix remodeling by CAF generates a path through ECM which is utilized by cancer cells for invasion. This process requires integrin along with other components for matrix attachment and to enable fibroblasts to move matrix molecules, e.g. collagen fiber. Hooper in 2010 suggested that Rab21 plays a vital role to promote cancer cell invasion by CAF. It facilitates the accumulation of integrin α5 at plasma membrane to force matrix remodeling. Two HMG-CoA reductase inhibitors, lovastatin and simvastatin, were found to reduce CAF induced matrix remodeling and diminished invasion of squamous cell carcinoma cells by disrupting the function of Rab21 [54].

7. Conclusion

Rab proteins are oncologically important, most of the Rabs act as tumor promoters by increasing exosomal secretions that support tumor microenvironment, directing integrins to plasma membrane that promote invasion of tumors to extracellular matrix, activating growth promoting pathways which can stimulate cancer cell proliferation and by suppressing apoptosis, while some may perform tumor suppressive functions depending upon tumor stage and cellular context [52].

Diversified mechanism of these molecular switches in tumor progression can be used in elucidating novel therapeutic targets and prognostic biomarkers in different cancers. Developing Rab specific inhibitors, which are unavailable presently, may be useful to investigate the Rabs targeted molecules that can improve cancer therapy.

The mechanism involved in the overexpression of Rab21, 25 and 27 in cancer progression is another area to study that can produce new methods for cancer prevention. Currently, increase in mRNA levels due to copy number amplification [35] and miR downregulation [39] has been documented as a reason in the overexpression of Rabs in some cancers. As the mechanisms behind the overexpression of Rab GTPase in different cancers are identified, it may present novel targets in therapeutics.

Conflict of interest

The author has no competing interest to declare that may directly or indirectly affect the content of this article.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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