Rab-mediated vesicle trafficking in cancer

Hong-Tai Tzeng and Yi-Ching Wang

Abstract
A large group of small Rab GTPases which mediate secretory and endosomal membrane transport, as well as autophagosome biogenesis, are essential components of vesicle trafficking machinery. Specific Rab protein together with the cognate effectors coordinates the dynamics of trafficking pathway and determines the cargo proteins destination. Functional impairments of Rab proteins by mutations or post-translational modifications disrupting the regulatory network of vesicle trafficking have been implicated in tumorigenesis. Therefore, the vesicle transport regulators play essential roles in the mediation of cancer cell biology, including uncontrolled cell growth, invasion and metastasis. The context-dependent role of the same Rab to act as either an oncoprotein or tumor suppressor in different cancers is found. Such discrepancies may be due in part to the interaction of specific Rab protein with different effectors or cargos in various tumors. Here, we review recent advances in the roles of Rab GTPases in communicating with other effectors in tumor progression. In this review, we also emphasize dysregulation of Rab-mediated membrane delivery shifting normal cell behaviors toward malignancy. Thus, recovery of the dysregulated vesicle trafficking systems in cancer cells may provide future directions for potential strategy to restrain tumor progression.

Keywords: Rab protein, Effector, Vesicle trafficking, Cancer

Background
Rab proteins are evolutionarily conserved with 55–75% identity across species. They are small GTPases comprising more than 70 members in humans and function as regulators of vesicles transport, proteins trafficking, membrane targeting and fusion [1–3]. Rab protein activity is controlled by cycling between the active GTP-bound and inactive GDP-bound forms. Guanine nucleotide exchange factors (GEFs) serve as the effectors of Rab GTPase by facilitating the exchange of GDP for GTP, resulting in the activation of Rabs and the downstream signaling [4]. In contrast, GTPase-activating proteins (GAPs) catalyze the hydrolysis of GTP to GDP to convert the GTP-bound Rabs to inactive GDP-bound form [5]. Some Rab small GTPases localize to the cytosol by forming complex with guanine dissociation inhibitors (GDIs) that prevent their membrane anchorage. Other effectors such as motor proteins, tethering factors and SNAREs (Soluble N-ethylmaleimide sensitive factor attachment protein receptor) are involved in the coordination of Rabs-mediated vesicle transport from donor membrane budding toward acceptor membrane fusion [6–8]. Dysregulation in Rabs level or mutations altering GTP/GDP-binding of Rabs or Rabs interaction with effectors may dampen the efficiency and specificity in membrane traffic that are implicated in disease development such as cancer.

In recent years, advanced progress in understanding the cellular functions of Rabs on vesicle trafficking has been made. Therefore, this review provides an overview of our current knowledge of regulation of Rab-mediated vesicle dynamics, and their critical roles in tumorigenesis.

Rab GTPases function as molecular switches in membrane traffic
Over the past two decades, emerging evidence has shown that distinct classes of small GTPases are involved in membrane vesicles trafficking. Individual Rab protein localizes to the surface membrane of different organelle in the cytosolic compartment and regulates a specific membrane trafficking pathway for appropriate protein sorting and targeting. Most Rabs are expressed ubiquitously, while some have tissue/cell-type specificity. For
example, Rab17 is predominantly expressed in epithelial cells and localized to apical recycling endosome (ARE) to mediate transcytosis to the basolateral plasma membrane [9]. Rab15 and Rab25 are also involved in the transportation of cargos through the ARE system [10, 11]. Rab12 is highly expressed in Sertoli cells and is responsible for the cargo delivery from peripheral to the perinuclear region to maintain centrosomes integrity [12]. Rab10 is expressed in adipocytes and implicated in mediating insulin-stimulated plasma membrane translocation of glucose transporter GLUT4 [13]. Rab8A and Rab13 are expressed in skeletal muscle cells and become active forms in response to insulin stimulation [14].

Some Rabs localize at different subcellular organelles. For instance, localization of Rab33 at the medial Golgi helps in the intra-Golgi transportation of vesicles [15]. Rab5 and Rab21 are involved in early endosome transport and mediate endocytosis pathway while Rab7 regulates cargo trafficking from early endosome to late endosome and subsequently to lysosome for degradation [16–18]. Another vesicle transport route is from trans-Golgi network (TGN) to the plasma membrane, which is mediated by secretory granules and vesicles. A lot of Rab proteins are associated with exocytic pathway including Rab3, Rab11, Rab26, Rab27, Rab37 and Rab38 [19–24]. Vesicles transport between TGN and early endosome are controlled by Rab22 and Rab31 [25, 26]. The diversity of individual Rab binding partner determines the specific vesicle transport route and creates the complexity of membrane trafficking.

Autophagy is responsible for degradation of intracellular components by transporting them to lysosomes to maintain cellular homeostasis and prevent pathogens infection. Rab proteins are also involved in the regulation of autophagy biogenesis [27]. Rab5, for example, participates in autophagy induction by the sequential signaling cascade in response to growth factor [28]. Overexpression of Rab32 promotes autophagosome biogenesis [29]. Rab33 has also been reported to regulate autophagosome formation through interaction with ATG16L, an essential factor for LC3 lipidation and membrane biogenesis in autophagy [30]. Several Rabs including Rab7, Rab11, Rab24 and Rab25 play critical roles in modulating autophagosomal maturation [31–34]. In ovarian cancer cells, knockdown of Rab25 increases the conversion of LC3-I to LC3-II, a critical step for autophagy, and induces apoptosis. These results indicate a role of Rab25 in tumorigenesis relevant to autophagy suppression [34].

Emerging evidence has shown that exosomes act as a novel mode of intercellular communication. They deliver message from cancer cells to surrounding stromal cells as well as distant metastatic sites to create a pre-metastatic niche [35]. Exosome secretion is regulated by fusion of the plasma membrane with multivesicular bodies (MVBs), which are late endosomal structure of endocytic pathway containing intraluminal vesicles. It has been observed that Rab proteins critically contribute to exosome release. For example, Rab11 regulates transferrin receptor secretion via the exosome pathway [36]. Similarly, Rab35 promotes exosome release by interacting with its effector TBC1D10A-C [37]. The role of Rabs in regulation of exosome pathway also has been explored in association with tumor progression. Indeed, Rab27-dependent exosome secretion of microRNAs is linked to tumor invasiveness in bladder cancer [38].

**Dysregulated Rab GTPases implicated in cancer**

Emerging evidence show that aberrant expression of Rab GTPases is closely associated with tumorigenesis (Fig. 1). Indeed, a set of Rab proteins including Rab1, Rab2A, Rab3D, Rab8, Rab11, Rab21, Rab23, Rab25, Rab27B, Rab35 and others (as reviewed in Table 1) promotes tumor cell migration and invasion to exhibit their effects on tumorigenesis and metastasis by regulating intracellular signal transduction [39–49]. Elevated expression of oncogenic Rab1 has been reported in several cancer types and is associated with poor survival [50–53]. Overexpression of Rab1A promotes mTORC1 signaling and oncogenic growth in response to amino acids stimulation and therefore enhances tumor progression and invasion in colorectal cancer [50, 51]. In addition, gene amplification and overexpression of Rab23 enhance cancer cell invasion and correlate with advanced-stage gastric cancer [47].

Moreover, it has been recently shown that Rabs-mediated vesicle dynamics cooperates with oncogenic signaling pathway to promote tumorigenesis. Indeed, Rab2A drives breast cancer stem cells expansion through activation of Erk signaling [44]. High expression of Rab25 has been frequently associated with poor prognosis in breast and ovarian cancer. Mechanistically, Rab25 expression promotes anti-apoptotic phosphoinositide 3-kinase (PI3K)-Akt pathway and inhibits pro-apoptotic molecules expression such as BAK thereby increasing aggressiveness of cancer cells [48]. Recently, another oncogenic Rab35 has been identified by two gain-of-function mutations in tumor cells. It is proposed that constitutively active Rab35 mediates internalization of platelet-derived growth factor receptor α to LAMP2-positive endosomal membrane, where it drives the activation of oncogenic PI3K/Akt signaling [49], suggesting that Rabs-mediated vesicle dynamics and oncogenic signaling cooperate to direct tumor progression.

Malfunction of Rabs-regulating vesicle trafficking could promote cancer invasion. For example, Rab11 is an important component for membrane proteins recycling and proteins transport from TGN to the plasma membrane [54]. Rab11-mediated αβ3 integrin trafficking has been found to contribute to increase cancer cell invasion in breast cancer [39]. Similarly, Rab25 facilitates invasive cell...
migration by controlling α5β1 integrin trafficking through the recycling endosomes [40]. Oncogenic Rab8 transports exocytic vesicles carrying membrane type 1-matrix metalloproteinase (MT1-MMP) to the plasma membrane for matrix degradation of migrating cancer cells cultured in collagen gel [41]. In a similar scenario, through mass spectrometric analysis, heat-shock protein 90a has been identified as a component of Rab27B-regulated vesicles, acting as a pro-invasive growth regulator required for activation of matrix metalloproteinase 2 (MMP2). An increased expression of Rab27B is associated with the poor prognosis of oestrogen receptor-positive breast cancer patients, supporting the role of Rab27B in tumor promotion [42].

In contrast to the roles of Rabs in promoting tumor progression, a minor fraction of Rabs is proposed to serve as tumor suppressor (Table 1). However, Rab proteins may have diverse functions in different types or subtypes of cancers. For example, in addition to its role in increasing invasiveness of cancer cells, Rab25 has also been identified to act as a tumor suppressor by inhibiting invasive and angiogenic activities in esophageal squamous cell carcinoma [55] and by increasing malignant tumor formation in the intestines of Rab25−/−;ApcMin/− mice [56]. The oncogenic or tumor suppressive functions of Rab25 are cell-type dependent. Rab25 enhances the aggressiveness in ovarian and breast cancer cells [48], while it functions as a tumor suppressor in esophageal squamous cell carcinoma and colorectal carcinoma [55, 56]. An explanation for the discrepancies is that the role of Rab25 in tumorigenesis is dependent on specific or a group of cancer type and on its interplay with cell-type specific effectors.

Rab37 is another example of diverse functions in different types of cancers. Upregulation of Rab37 and its interacting partner TMEM22 are found in renal cell carcinoma (RCC) and decrease in its level by siRNA reduces cancer cell growth, suggesting the oncogenic-like role of Rab37 in RCC [57]. However, promoter hypermethylation of Rab37 gene leading to low expression of Rab37 mRNA and protein is associated with advanced metastasis in non-small cell lung cancer patients [58]. These results may attributed to Rab-mediated cell-type specific distinct downstream pathways or cargo trafficking. Interestingly, Rab37-mediated exocytosis of tissue inhibitor of metalloproteinase 1 (TIMP1) inactivates extracellular MMP9 and thereby suppresses cell invasion signaling [59]. Of note, reconstituted TIMP1 by addition of TIMP1 recombinant protein abolishes the migration and invasion ability of lung cancer cells in vitro and in vivo [59]. In addition, 5-Aza-2-deoxycytidine treatment of a highly
metastatic lung cancer cell line shows demethylation and re-expression of the \textit{Rab37} gene and correlates with reduced cancer cell migration \cite{58}. The last-mentioned two studies provide therapeutic strategies such as DNA demethylation of \textit{Rab37} gene and increased expression of \textit{Rab37} protein and its cargos such as TIMP1 could facilitate the development of anti-cancer treatment.

\textbf{Rab GTPases regulators mediate cancer progression}

Dysregulated interaction between Rabs and their effectors could also link to tumor progression and malignancy. Effector proteins including GEFs, GAPs and GDIs together with tethering factors and SNAREs play key roles in regulating Rab GTPase function as molecular switches by cycling between active membrane-bound GTP and inactive cytosolic GDP-bound forms. For example, numerous effectors for Rab5 have been identified, including Rabaptin-5, Vac1, early endosome antigen 1 (EEA1), PI3K, and Class C core vacuole/endosome tethering (CORVET). Increased expression of Rabaptin-5, a Rab effector interacting with GTP-bound Rab5, accelerates endocytosis of epidermal growth factor receptor via Rab5-mediated endosomal fusion pathway and subsequently affects tumor progression \cite{60, 61}. The effector of Rab11, Rab11-family interacting protein 2 (Rab11-FIP2), has been implicated in regulation of recycling endosomal trafficking through interaction with Rab11a \cite{62}. Rab11-FIP2 increases epithelial-mesenchymal transition and metastasis in gastric cancer \cite{63}. Rab11-FIP2 also promotes colorectal cancer cells migration and invasion by upregulating MMP7 expression through activating PI3K/Akt signaling \cite{64}. In contrast, Rab11-FIP1C, another effector of Rab11, acts as a tumor suppressor in ErbB2-mediated breast cancer \cite{65}. DENND2B, a GEF for Rab13, activates Rab13-mediated exocytosis and enhances the invasiveness of cancer cells. Disruption of Rab13-mediated trafficking limits the spread of epithelial cancer cells \cite{66, 67}.

Moreover, alteration of SNARE complex has been shown to involve in tumorigenesis. SNARE complex are composed of vesicle associated SNAREs (v-SNARE) and SNAREs at targeting membrane (t-SNAREs). The trans-SNAREs formation by interaction of v-SNAREs with t-SNAREs allows the fusion of vesicle and acceptor membrane. Notably, an increase in interaction between Syntaxin6 and Rab11/vesicle-associated membrane protein 3 (VAMP3) on recycling endosome inhibits \(\alpha\vbeta1\) and \(\alpha\vbeta3\) integrins recycling and suppresses cell migration \cite{68}. Conversely, Rab7 and

\begin{table}[h]
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\caption{Oncogenic and tumor suppressor Rab proteins in cancers}
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Rab protein} & \textbf{Cancer types} & \textbf{Expression} & \textbf{Clinical implications} & \textbf{References} \\
\hline
Rab1 & Colon & Increased & Elevated cell invasion, poor prognosis & [50] \\
& Liver & Increased & Elevated cell invasion, poor prognosis & [51] \\
& Brain & Increased & Poor survival & [52] \\
Rab2 & Breast & Increased & Expansion of stem-like cells, poor prognosis & [44] \\
Rab3 & Breast & Increased & Elevated cell motility & [45] \\
& Brain & Increased & Tumor progression & [81] \\
Rab4 & Breast & Increased & Elevated cell motility & [82] \\
Rab5 & Lung & Increased activity & Elevated cell motility & [83] \\
Rab11 & Breast & Increased activity & Elevated cell invasion & [39] \\
Rab17 & Liver & Decreased & Elevated clinical tumor characteristics & [84] \\
Rab21 & Cervical cancer & Increased & Elevated cell motility & [46] \\
Rab23 & Stomach & Increased & Poor prognosis & [47] \\
Rab25 & Ovarian, Breast & Increased & Poor prognosis & [48] \\
& Esophagus & Decreased & Poor survival & [55] \\
& Colon & Decreased & Poor survival & [56] \\
Rab27 & Breast & Increased & Poor prognosis & [42] \\
Rab31 & Breast & Increased & Poor survival & [85] \\
Rab35 & Not applicable & Gain of function mutations & Anti-apoptosis & [49] \\
Rab37 & Lung & Decreased & Poor prognosis & [58, 59] \\
Rab38 & Brain & Increased & Poor prognosis & [86] \\
\hline
\end{tabular}
\end{table}
VAMP7 cooperatively mediate endosomal recycling of membrane type MT1-MMP to promote cancer cells migration and invasion [69]. These findings reveal that the effectors and SNAREs of Rab-mediated membrane trafficking are involved in tumorigenesis. Nevertheless, more research is needed to better understand the complexity of the interaction between Rab-effectors-SNAREs.

Rabs and Rab effectors in tumorigenic signalings
Phosphorylation of Rab proteins is important for vesicle targeting and traffic. Rab5a has been reported to be phosphorylated by PKCε to facilitate T-cell migration [70]. Mechanistically, phosphorylated Rab5a promotes Rac1 activation to facilitate actin remodeling. Conventional PKC-mediated Rab11 and Rab6 phosphorylation results in impaired endosomal recycling and redistribution in cytosolic fraction, respectively [71, 72]. Studies have shown that phosphorylation of Rab4 by p34cdc2 prevents the association of Rab4 with endosomal membrane by dissociating its binding to membrane effector during the cell cycle [73, 74]. Interestingly, dephosphorylation of Rab7 by PTEN is important for its membrane targeting and subsequent activation, suggesting that phosphorylation status is critical for regulating Rab7 endosomal localization and activity [75]. Rab8A phosphorylation on Ser111 is also observed to impair its binding to Rab8A, the GEF for Rab8A that triggers GDP exchange [76]. However, the significance of post-translational modifications in the regulation of Rab GTPase activity is poorly defined. The clinical relevance of the modifications such as phosphorylation of Rabs in human cancers still remains largely uncharacterized.

In addition, phosphorylation-dependent regulation of Rabs effectors plays important roles in coordinating Rabs-mediated vesicle trafficking. For example, connexin43/1/2 are identified as GEFs for Rab35. Akt-mediated connexin43/1/2 phosphorylation promotes the interaction of Rab35 and its GEF [77]. Unc-51-like kinases have been reported to phosphorylate DENND3 and up-regulate its GEF activity toward Rab12. Activation of Rab12 facilitates autophagosome trafficking in response to starvation [78]. Accordingly, phosphorylation of Rabin8, a GEF for Rab8, by ERK1/2 increases its GEF activity and promotes recycling of transferrin to the plasma membrane [79]. Importantly, dysregulated phosphorylation of Rabs effectors involves in tumorigenesis. For example, Rabaptin-5, a Rab5 effector in endosomal membrane fusion, is a protein kinase D (PKD) substrate. Interestingly, phosphorylated Rabaptin-5 interacts preferentially with Rab4, but not Rab5, to promote αvβ3 recycling leading to enhanced cell motility and invasion [80]. The oncogenic signaling pathways of Rab effectors in promoting tumor development or suppressing tumorigenesis need further elucidation.

Conclusion
Taken together, as key regulators of cargo transport in vesicle trafficking, it is not surprising that Rab proteins have been linked to tumorigenesis or tumor prevention. Vesicle delivery and dynamics are critical for regulation of cell behaviors associated with cell migration/invasion and tumorigenesis. Notably, specific Rab proteins may have diverse functions in different types or subtypes of cancers. Although mutations or alterations in expression of the components of vesicle transporting machinery may not directly drive cell transformation, cooperation between Rabs and effectors in mediating vesicle movement pathways has critical influences on tumor progression and malignancy. Therefore, it raises the possibility that targeting particular trafficking system may provide a new approach to cancer treatment.

Abbreviations
ARE: Apical recycling endosome; CORVET: Class C core vacuole/endosome tethering; EEA1: Early endosome antigen 1; GAPs: GTPase-activating proteins; GDIs: Guanine dissociation inhibitors; GEFs: Guanine nucleotide exchange factors; MPP2: Matrix metalloproteinase 2; MT1-MMP: Membrane type 1-matrix metalloproteinase; MVB: Multivesicular body; PI3K: Phosphoinositide 3-kinase; PKD: Protein kinase D; SNARE: Soluble N-ethylmaleimide sensitive factor attachment protein receptor; TGN: Trans-Golgi network; t-SNARE: targeting membrane SNARE; VAMP: Vesicle-associated membrane protein; v-SNARE: vesicle associated SNARE

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Data and materials related to this work are available upon request.

Authors’ contributions
HTT and YCW wrote the review. Both authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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