

Role of Rab GTPases in Hepatocellular Carcinoma

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Abstract: The Rab GTPase family contains almost 70 genes in the human genome and acts as the key regulator of intracellular membrane trafficking in human cells. The dysregulation of Rab GTPase has been shown to be associated with multiple human diseases, ranging from neurodegeneration, and infection to cancer. Rab GTPases not only play important roles in genome replication, morphogenesis and the release of hepatitis B virus (HBV) or hepatitis C virus (HCV), but also contribute to hepatitis-related hepatocarcinogenesis and hepatocellular carcinoma (HCC) progression. The alteration of Rab GTPase expression in HCC plays an important role in tumour cell proliferation, invasion and migration. Notably, the expression of Rab genes can be regulated by some noncoding RNAs, such as miRNAs and circRNAs. Thus, Rab GTPases can serve as promising rational and therapeutic targets for HCC treatments. In this review, we summarized recent advancements in this field focusing on Rab GTPases in HCC.

Keywords: Rab GTPase, membrane trafficking, hepatocellular carcinoma, therapeutic target

Background

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the fifth most common neoplasm. It accounts for approximately 8% of all cancer-related deaths and more than 800,000 new cases and deaths globally each year.¹ HCC has been recognized as the leading cause of death among patients with cirrhosis. In recent decades, there has been great progress in the diagnosis and treatment of HCC, but the prognosis of HCC patients is still unsatisfactory.^{2,3} The prevention and treatment of HCC are still some of the most serious public health problems in the world. It is urgent to look for early diagnostic markers and therapeutic targets, especially those that can be exploited to inhibit angiogenesis and alter the oxygen-deficient environment, to improve HCC patient prognosis and quality of life.^{4–6}

Intracellular membrane trafficking is crucial for regulating membrane transport and dynamics for a variety of membranous organelles in eukaryotic cells. Rab GTPases, which include almost 70 highly evolutionarily conserved genes in the human genome, play important roles in intracellular membrane trafficking. They are localized to different membrane compartments and exert their function by recruiting effector molecules to control the specificity and directionality of membrane protein trafficking, vesicular transport, membrane targeting and fusion.⁷

Notably, Rab GTPases can be involved in tumour cell migration, invasion, proliferation, stromal cell communication, and drug resistance.⁸ The activity of Rab GTPases can be regulated by guanine nucleotide exchange factors (GEFs) or GTPase-activating proteins (GAPs) through the interconversion of the active GTP-bound form

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and the inactive GDP-bound form.⁹ Intracellular transport dysfunction induced by aberrant Rab GTPases in cancers has attracted growing concern. Our review delineates recent advances regarding the molecular mechanism of Rab GTPases and the roles of these GTPases in hepatocarcinogenesis and HCC progression.

The Molecular Mechanism of Rab GTPases as Switches in Membrane Trafficking

As they are molecular switches, Rab GTPases can be active when GTP is bound and inactive when GDP is bound. The oscillation between these two distinct conformations is tightly controlled by specific proteins, such as guanine nucleotide exchange factors (GEFs) and GAPs.¹⁰ In detail, GEFs facilitate GTP binding with GTPases and contribute to the conversion to an active state, whereas the inactive form is coordinated by GAPs, which catalyse

GTP hydrolysis.¹¹ To anchor to correct internal membranes, Rab GTPases need to be prenylated at their C-termini.¹² As a Rab-specific effector, guanine nucleotide dissociation inhibitor (GDI) has a high affinity for GDP-bound Rab proteins and plays an important role in mediating the dissociation of membrane-bound Rab GTPases from membranes to the cytosol (Figure 1).¹³

The role of GTP-bound Rab protein in facilitating specific and accurate transport depends on biological interactions with multiple effectors, including tethering factors, motor linkers, Rab regulators, and sorting adaptors.¹⁴ These effectors coordinate with Rab GTPases to complete the consecutive processes of vesicle trafficking along endocytic and exocytic paths, such as receptor cargo selection, vesicle formation and movement along the cytoskeleton, accurate docking and further fusion with their target membrane compartments. For instance, Rab coupling protein (FIP1C) and Rab11 family interacting protein 2 (Rab11-FIP2) are the effectors of Rab11; Rab11-FIP2 was found to regulate endosome

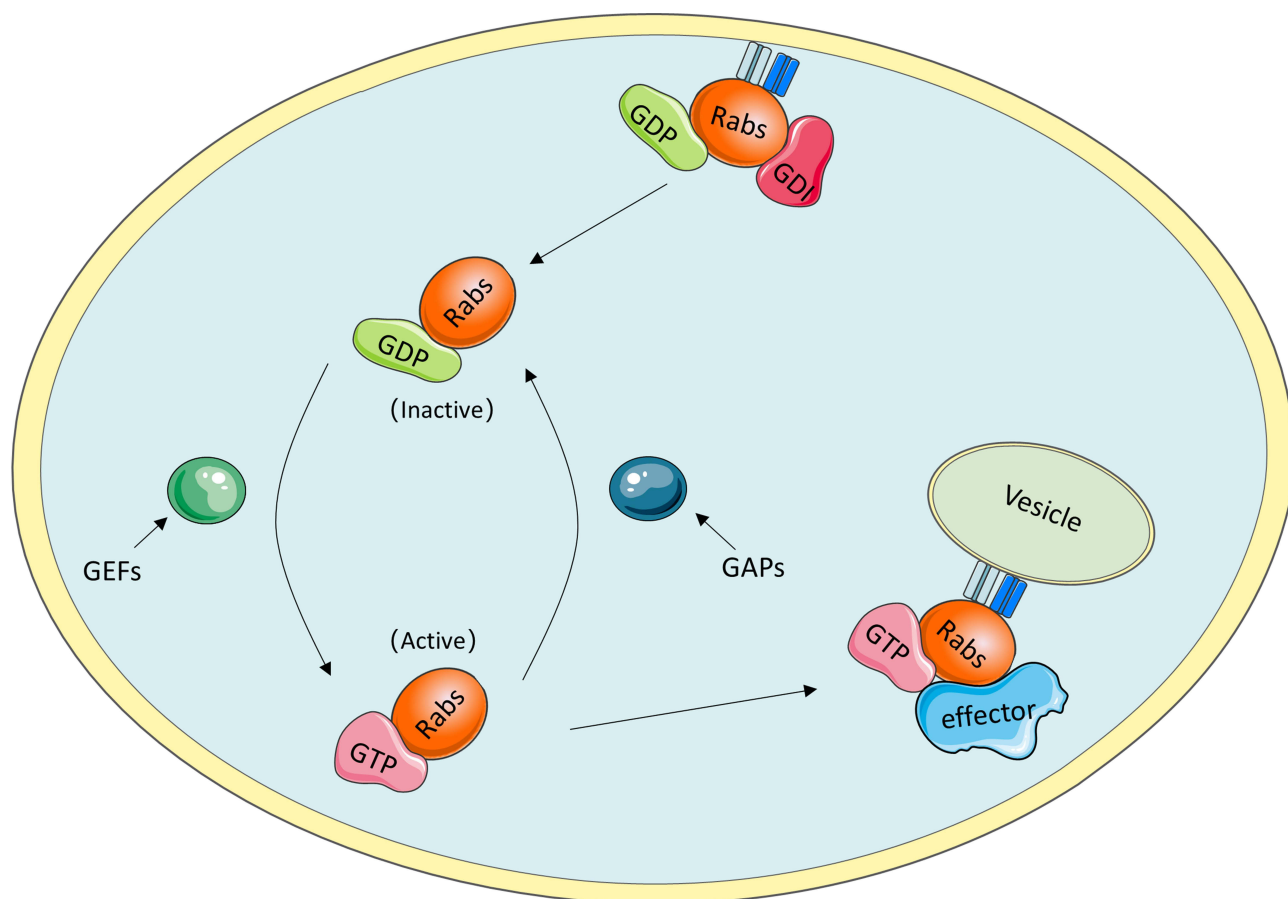


Figure 1 Rab GTPases cycle. i) GDI binding with GDP-bound Rab proteins mediates the dissociation of membrane-bound Rab GTPases from membranes to the cytosol. ii) GEFs facilitate the conversion to active GTP-bound Rab proteins, whereas the transition to inactive GDP-bound Rab proteins is coordinated by GAPs through catalyzing GTP hydrolysis. iii) GTP-bound Rab proteins interact with multiple effectors to execute specific functions.

trafficking and promotes cellular motility in nasopharyngeal carcinoma, and targeted deletion of FIP1C led to accelerated tumour onset in the context of ErbB2-positive breast cancer.^{15,16}

The localization of Rabs to their appropriate intracellular membranes after prenylation requires Rab escort protein (REP), which includes two components: choroideremia (CHM) and choroideremia-like (CHML).¹⁷ The expression of CHML is increased in HCC tissues and is associated with prognosis in HCC patients. A mechanistic study revealed that CHML facilitates constant Rab14 recycling by escorting Rab14 to the membrane and then promoting HCC migration, invasion and metastasis. Thus, the CHML-Rab14 axis has been established as a potential promoter of HCC progression and may be employed as a promising therapeutic target for HCC treatment.^{18,19}

Effects of Rab GTPase Dysregulation

Due to their regulation of the indispensable process of membrane trafficking, Rab proteins are crucial for the maintenance of cell homeostasis and concrete cellular functions. The dysregulation or mutation of Rab proteins or their

related effectors not only affects the process of membrane transport but also causes disorders of multiple cellular processes, such as cell division, migration, apoptosis and survival.²⁰ Several genetic diseases, such as diabetes, immune deficiency and cancer, are driven by mutations in Rab GTPases, and their interacting proteins have been identified.²¹ The abnormal function of Rab GTPases is associated with a variety of HCC pathophysiologies (Figure 2).

Autophagy plays a crucial role in resistance to nutrient deficiency and the removal of intracellular misfolded proteins and damaged senescent organelles.²² As a kind of self-protective mechanism, autophagy is indispensable for the maintenance of cellular proteostasis and homeostasis. Dysregulation of autophagy can lead to the development of a variety of diseases, including cancers.²³ As the main regulators of autophagy, Rab GTPases can link autophagic degradation with the intracellular membrane dynamics network and facilitate tumorigenesis and cancer development.^{24,25} Dysregulation of autophagy has been noted in the pathogenesis of HCC.²⁶ Rab GTPases can affect the process of autophagy and play a driving role in the occurrence and progression and even the metastasis of HCC. As an LRRK2 substrate, Rab GTPases can not only

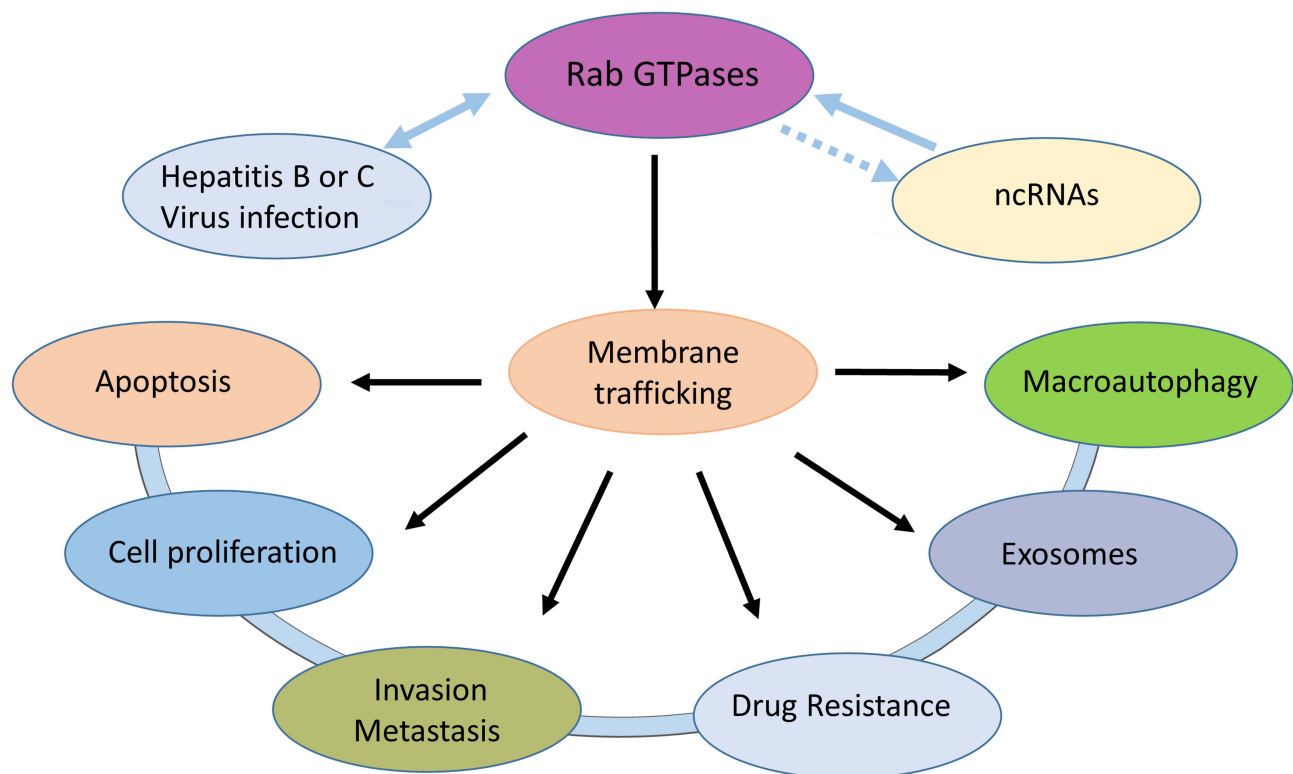


Figure 2 Rab GTPases can affect cell proliferation, apoptosis, invasion, metastasis, exosomes and autophagy by mediating membrane transport. Hepatitis B or C virus can interact with Rab GTPases. Some noncoding RNAs can regulate Rab GTPases expression in HCC.

indirectly regulate phagocytosis, cell signal transduction and autophagy in immune cells,²⁷ but they also serve as regulators of cilia formation and immune synaptic assembly.²⁸

As mediators of intercellular communication that carry hereditary material and molecular information, exosomes have been demonstrated to be involved in a variety of processes, including immune responses, cytokinesis, neurite outgrowth, blood coagulation, angiogenesis, and cancer metastatic dissemination and migration, based on their unique structure and distinct origins.^{29–31} Rab GTPases have been identified to critically regulate exosome biogenesis and secretion.³² Recent studies have found that knock-down of Rab27a inhibits exosome secretion and thus promotes the migration and invasion of parental MHCC97H cells. Further study showed that exosomes extracted from MHCC97H cells can promote the process of epithelial-mesenchymal transition (EMT) by activating the MAPK/ERK signalling pathway.³³

Relationship Between Rab GTPases and Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV)

HCC appears frequently in the context of cirrhosis and HBV or HCV infections.³⁴ Over 50% of HCC cases worldwide are attributed to HBV, which makes HBV one of the most common carcinogens. HBV can promote hepatocyte transformation, HCC development and progression through a series of driving stimuli, including DNA damage, chronic inflammation, senescence, epigenetic modifications, telomerase reactivation and chromosomal instability. Recent studies have revealed that HBV can promote hepatocarcinogenesis and HCC progression by regulating Rab GTPase expression and activity.³⁵ HBV can promote HCC cell proliferation and migration by downregulating the expression of miR-101-3p targeting Rab5a.³⁶ Emerging evidence has revealed that HBx can induce the upregulation of oncogenic Rab18 in HCC and then enhance hepatocarcinogenesis, contributing to the abnormal lipogenesis and hyperproliferation in HBV-associated hepatomas.³⁷

Rab GTPases are also involved in the processes of infection, genome replication, morphogenesis and HBV or HCV release. After endocytosis, HBV travels through a complex network of endocytic pathways to the nucleus and begins to replicate. Endosomal vesicles may play a key role in infection, providing the right environment for viral uncoating and

nucleocapsid release. Rab GTPases play an important role in vesicular transport, which is involved in different stages of the viral life cycle. First, HBV requires Rab5- and Rab7-dependent transport through the endosomal compartment to initiate a successful infection.³⁸ On the other hand, HBV can suppress autophagosome maturation and escape autophagic degradation via the negative regulation of Rab7 expression.³⁹ In addition, Rab33B is necessary for the reproduction of HBV and controls HBV assembly by regulating core membrane binding and nucleocapsid processing.⁴⁰

Membrane transport is also involved in the life cycle of the hepatitis C virus (HCV). The Rab protein is an important host factor for HCV RNA replication. First, Rab13 regulates the endocytic cycle of tight junction-associated proteins, whose downregulation inhibits HCV infection. Therefore, Rab13 plays an important role in the entry of HCV.⁴¹ Second, the formation of the HCV replication complex requires RAB-associated proteins such as RAB5 and RAB7.⁴² In addition, Rab5, Rab7, Rab18 and Rab27a are important for HCV genome replication. Rab1b, Rab3d, Rab7, Rab9 and Rab27a are involved in the release of HCV.⁴³ RAB18 and RAB32 are required for the viral assembly of HCV.^{44–46}

Relationship Between Rab GTPases and HCC

As Rab-mediated membrane transport affects many cellular functions, Rab GTPases can also indirectly control several cell signalling pathways involved in cell division, migration, apoptosis, survival, tumorigenesis, and cancer progression.²⁰ Given their pivotal roles in membrane trafficking and the maintenance of cellular homeostasis, Rabs and Rab-associated factors are implicated in a myriad of human diseases, particularly HCC. Previous studies have demonstrated that several Rab GTPases are involved in hepatocarcinogenesis and HCC progression (Table 1). Most aberrant Rab GTPases, such as RAB11A, are over-expressed in HCC and can activate tumour growth, survival, invasion and metastasis via various signalling pathways, such as the phosphoinositide 3-kinase (PI3K) pathway and the mitogen-activated protein kinase (MAPK) pathway.⁴⁷

Rab GTPases are rarely downregulated in HCC tissues and function as tumour suppressors. Studies reveals that Rab17 plays an unexpected role as a tumour suppressor whose overexpression in HCC cells attenuates tumorigenic properties, including cell proliferation, migration and invasion, by deactivating the Erk pathway.^{48,49} RAB43 is

Table I Rab GTPases Functions and Prognostic Implications in HCC

Gene Name	Function	Prognostic Implication
Rab5a	Promoting cell growth, differentiation, apoptosis and angiogenesis	Tumour promoter factor
Rab10	Regulating cell survival and proliferation	Tumour promoter factor
Rab11a	Promoting migration and invasion	Tumour promoter factor
Rab17	Inhibiting migration and invasion and promoting G1 arrest	Tumour suppressor factor
Rab18	Enhancing hepatocarcinogenesis and cell proliferation	Tumour promoter factor
Rab25	Promoting migration and invasion	Tumour promoter factor
Rab27a	Inhibiting migration and invasion	Tumour suppressor factor
Rab31	Promoting migration and invasion	Tumour promoter factor
Rab40b	Promoting migration and invasion	Tumour promoter factor
Rab43	Inhibiting cell proliferation and EMT	Tumour suppressor factor

another downregulated Rab GTPase in HCC tissues. Overexpression of RAB43 can inhibit the proliferation of HCC cells, while knockdown of RAB43 can promote the EMT process in HCC.⁵⁰

Rab GTPases Regulate HCC Cell Proliferation, Apoptosis, Invasion and Metastasis

Rab GTPases have been reported to regulate HCC cell proliferation and apoptosis. First, high RAB10 levels in HCC cells are correlated with a poor prognosis in HCC patients. In vitro and in vivo studies have shown that RAB10 plays an oncogenic role in regulating cell survival and proliferation through multiple oncogenic, cell stress and apoptosis pathways in HCC.⁵¹ Rab13 is also a valuable marker for the prediction of HCC progression and a prognostic indicator for HCC patient prognosis. Overexpression of Rab13 can significantly enhance the proliferation and growth of hepatoma cells.^{52,53} Rab31 is another Rab GTPase that intensively inhibits apoptosis and accelerates growth by activating the PI3K/AKT pathway and increasing the Bcl-2/BAX ratio in HCC.^{54,55}

Increasing evidence has revealed that there are some Rab GTPases that not only promote HCC proliferation, but also promote HCC invasion and metastasis. As a highly expressed Rab GTPase in HCC tissues that is associated with poor clinical prognosis, Rab11a can promote HCC cell proliferation, migration and invasion and inhibit apoptosis by activating the PI3K/AKT pathway and regulating matrix metalloproteinase 2 (MMP2) expression.⁵⁶ As a newly identified mammalian target of rapamycin complex 1 (mTORC1) activator, Rab1A is reported to be frequently overexpressed in HCC samples and can promote HCC growth and metastasis and increase rapamycin

treatment sensitivity by enhancing hyperactive amino acid-mTORC1 signalling in vitro and in vivo.^{57,58}

Rab5a, Rab25 and Rab40 are also upregulated in HCC tissues compared with paratumour tissues. The level of Rab5a in HCC samples has been associated with tumour-node-metastasis (TNM) stage and lymph node metastasis. Mechanistically, Rab5a promotes cell proliferation, invasion and migration by activating the EGF receptor and FAK signalling pathways.⁵⁹ Rab25 promotes HCC cell malignant proliferation and invasion by activating the AKT and Wnt signalling pathways.⁶⁰ Overexpression of Rab40b upregulates cyclin D1, cyclin E1 and MMP2 to promote HCC proliferation and metastasis through the PI3K/AKT signalling pathway.⁶¹

Rab27a is another important and unique Rab GTPase that regulates the process of HCC cell exosome secretion. The knockdown of Rab27a can inhibit MHCC97H-derived exosome secretion, which then promotes the migration, chemotaxis and invasion of MHCC97H cells by regulating EMT via the MAPK/ERK signalling pathway.⁶² Rab34 can also augment cell migration and invasion properties by regulating the G1 phase of the cell cycle and promoting the EMT process.^{63,64}

Rab Family Genes are Regulated by Noncoding RNAs

Aberrant expression of noncoding RNAs in cancer samples has been reported to be correlated with clinicopathological parameters and prognosis in patients with malignancies, including HCC. As expected, some altered noncoding RNAs, including miRNAs, in HCC can regulate cell proliferation, invasion, and metastasis and influence HCC patient prognosis by targeting Rab family genes (Table 2).⁶⁵ For example, miR-101-3p, a downregulated miRNA in HCC tissues, can regulate HCC cell growth and

Table 2 Rab GTPases-Associated Noncoding RNAs in HCC

Gene Name	Non-Coding RNA	Pathway	Function in HCC	Reference
Rab5a	MiR-101-3p	NA	Cell growth and migration	[66]
Rab1(Rab1a)	MiR-223 Circ-UGGT2 MiR-5226B-5P	mTOR	Cell proliferation, migration, invasion and apoptosis	[67,72]
Rab1b	MiR-541	NA	Positive modulator of autophagy	[68]
Rab18	MiR-145-5P	NA	Promote proliferation and migration and inhibit the apoptosis	[69]
Rab23	MiR-429	EMT	Promotes cell growth and invasion and represses apoptosis	[70]
Rab24	MiR-615-5p	Rab-RAS	Retarding cell cycling processes and accelerating apoptosis	[71]
Rab35	Long non-coding RNA HOTAIP	mTOR	Promotes exosome secretion	[73]

migration by targeting the Rab5A gene.⁶⁶ MiR-223, a well-identified downregulated miRNA in HCC samples, modulates cell proliferation through regulation of cell apoptosis in a Rab1-mTORC1-dependent manner.⁶⁷ As a miRNA associated with malignant clinicopathologic phenotypes and prognosis and sorafenib treatment sensitivity of HCC patients, miR-541 inhibits the malignant properties and autophagy of HCC cells both in vitro and in vivo by partly downregulating the expression of Rab1B which serves as an oncogene and important modulator of autophagy in HCC.⁶⁸ Wang et al also reported that miR-145-5p acts as a new tumour suppressor by specifically targeting RAB18 whose ectopic expression can promote proliferation and migration and inhibit the apoptosis of HCC cells.⁶⁹ More interestingly, miR-429 decreases the migratory ability and reverses the process of EMT (thus promoting mesenchymal-epithelial transition [MET]) in HCC by targeting RAB23.⁷⁰ In addition, miR-615-5p inhibits HCC cell malignant growth abilities, such as cell motility and metastasis, by retarding cell cycling processes and accelerating apoptosis with a direct inhibitory effect on Rab24.⁷¹

The expression of Rab family genes can be regulated by other noncoding RNAs, such as circRNAs and long noncoding RNAs. For example, the silencing of circUGGT2 inhibits HCC growth in vivo and restrains the proliferation, colony formation, cell cycle progression, migration, and invasion of HCC cells in vitro by competitively binding to miR-526b-5p which targets RAB1A.⁷² Long noncoding RNA HOTAIR promotes exosome secretion by regulating RAB35 expression and localization in HCC.⁷³ Long noncoding RNA HULC promotes HCC cell

growth and invasion and represses apoptosis by regulating the miR-372-3p/RAB23 axis.⁷⁴

Conclusion

Considering the prominent role in endomembrane dynamics, Rab GTPases indeed occupy a dominant position not only in the maintenance of proteostasis and homeostasis but also in cell type-specific functions. It is not surprising that altered expression of Rab GTPases correlates with various human diseases, particularly cancer. Alterations in expression rather than mutations of Rab genes play master regulatory roles in HCC pathological processes, including cell motility, proliferation, metastasis and survival, via the vital impact on vesicle trafficking, signalling cascades, and receptor recycling. Intriguingly, Rab GTPases play bidirectional roles in the physiology of tumour processes. Most Rab GTPases are viewed as oncogenic drivers and are associated with tumorigenesis, progression and metastasis, and the underlying molecular mechanisms are not well recognized and need further research.

A new type of tumour biomarker based on abnormal alterations of Rab GTPases in HCC patients may be used for the early diagnosis of HCC. The expression levels of numerous Rab GTPase have been verified to be closely associated with tumour progression and HCC patient prognosis and thus probably serve as putative prognostic indicators. In addition, identification of the physiologic and pathophysiologic characteristics of Rab GTPases may offer innovative perspectives to exploit effective small molecule inhibitors and therapeutic strategies related to Rab GTPases for HCC treatment.

Abbreviations

HCC, hepatocellular carcinoma; GEF, guanine nucleotide exchange factors; GAP, GTPase-activating proteins; GDI, guanine nucleotide dissociation inhibitor; CHML, choriocarcinoma-like; HBV, hepatitis B virus; HCV, hepatitis C virus; MAPK, mitogen-activated protein kinase; EMT, epithelial-mesenchymal transformation; MMP2, matrix metalloproteinase 2.

Data Sharing Statement

All data are included in the article.

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Disclosure

The authors report no conflicts of interest in this work.

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