Rab27: Molecular switch of tumor exosome secretion (Review)

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Received February 10, 2026; Accepted April 24, 2026

DOI: 10.3892/ijmm.2026.5853

Abstract. Rab proteins are core regulators of vesicle trafficking during membrane transport. As key members of this family, Rab27 comprises two functionally distinct isoforms, Rab27a and Rab27b, and participates in the regulation of exosome secretion by mediating the selective anchoring of multivesicular bodies to the plasma membrane. In tumor cells, Rab27 promotes malignant progression by modulating exosome secretion. Aberrantly expressed Rab27 is associated with the prognosis of patients with cancer, suggesting its potential as a prognostic biomarker for various malignant tumors. Furthermore, the development of novel small-molecule drugs targeting Rab27 is promising because these drugs can exert antitumor effects through interference with the exosome secretory pathway. The present review systematically summarizes the molecular mechanisms underlying the Rab27-mediated regulation of exosome secretion and its role in tumorigenesis and cancer progression and discusses the application prospects and challenges of Rab27-targeted antitumor therapeutic strategies, aiming to provide a reference for basic research and clinical translation of Rab27.

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Key words: Rab27, exosomes, transport, secretion, biomarker, antitumor treatment

Contents

1. Introduction

The Rab family consists of small G proteins within the Ras superfamily (1). They possess structural characteristics, including a GTPase-folded structure and a C-terminal anchored structure (1,2). The GTPase-folded structure generally consists of six β-folded sheets and five α-helices, which form the essential structure for its biological function (3). The C-terminal anchoring structure refers to the process of attaching to the membrane through a lipid moiety (such as an isoprenoid group) that is covalently linked to two cysteines at the C-terminus. This anchoring mechanism creates a close connection between Rab family proteins and the structural composition of lipid membranes (4,5). Typically, Rab family proteins are bound to GDP and are in an inactivated state. The guanine nucleotide exchange factor (GEF) promotes the conversion of Rab proteins to the active form by replacing GDP with GTP in a dynamically reversible process (6-8). To date, ~60 Rab proteins have been identified in humans, and one of their main functions is to regulate vesicular transport (9,10).

Due to their biological stability and diverse cargo, exosomes facilitate intercellular communication, thereby remodeling the tumor microenvironment (TME) and driving disease progression (11-17). Furthermore, exosomes offer dual potential as diagnostic biomarkers for cancer and as drug delivery vehicles (18-20). While various Rab proteins isoforms perform specific regulatory functions at different stages of exosome biogenesis (21). Among these, Rab27 is recognized as a key molecular switch that directly governs exosome secretion and is widely implicated in the progression of diverse pathological conditions, including cancer, immune-related disorders

(for example, rheumatoid arthritis and inflammatory bowel disease), neurological conditions (for example, Parkinson's disease), metabolic and endocrine diseases (for example, diabetes) and cardiovascular diseases (22-26). Although the role of Rab27 in regulating exosome secretion has been reported, a systematic overview of how Rab27 contributes to tumorigenesis and cancer progression via exosome secretion, as well as its translational potential as a diagnostic biomarker and therapeutic target, is lacking. The present review systematically summarizes the molecular mechanisms underlying Rab27-mediated exosome secretion in tumors and highlights critical issues that must be addressed to achieve therapeutic benefits by targeting Rab27.

2. Structural characteristics and localization of Rab27

Rab27 belongs to the Rab protein family and exists in two isoforms in humans: Rab27a and Rab27b (27,28). Rab27a (221 aa) shares 61% identity with Rab27b (218 aa) at the nucleotide level within the open reading frame and 71% identity at the amino acid level (29). The differences are located mainly at the carboxy terminus (30). Structurally, both Rab27a and Rab27b contain four GTP binding sites (16-24 aa, 74-78 aa, 133-136 aa and 163-165 aa) (31). Moreover, they have a shared effector region (38-46 aa). The first structural distinction between Rab27a and Rab27b lies in the disordered regions (31). Compared with Rab27a, Rab27b has a longer disordered region, mainly at the carboxy terminus. Second, slight disparities in the post-translational modification (PTM) sites of Rab27a and Rab27b exist. Compared with Rab27b, Rab27a has more ubiquitination sites (31,32). Moreover, the expression patterns of Rab27a and Rab27b differ markedly across various cancer types. For example, in certain malignancies, the expression of Rab27a is upregulated, whereas that of Rab27b is downregulated, and in other malignancies, the opposite pattern is observed. This differential expression highlights the heterogeneity of the regulation of Rab27 expression in cancer (33) (Fig. 1 and Table I).

As previously reported, Rab family proteins can be anchored to membrane-structured suborganelles, and Rab27a and Rab27b are no exception (30,34-36). However, some subtle differences exist. Rab27a is distributed in a relatively large number of subcellular organelles (30). Specifically, Rab27a is localized to melanosomes, secretory granules, late endosomes and lysosomes (37,38), whereas Rab27b is considered to be localized to the membrane of Golgi stacks and vesicles located in the trans-Golgi network (TGN) area, secretory granules and late endosomes (30,39). The distinct subcellular localization of Rab27 contributes critically to exosome biogenesis and secretion by mediating specific interactions with a range of effector proteins (23) (Fig. 2).

3. Exosome secretion and biogenesis mechanisms

Small extracellular vesicles (EVs), including exosomes, microvesicles and small ectosomes, are generated through the outward growth of the plasma membrane (PM) (40-42). Currently, there is no clear demarcation between EVs and exosomes (43,44). In the present study, the term 'exosomes' was used to denote EVs with biological activity. Exosomes are small vesicles with a diameter of 40-160 nanometers and are characterized by a bi-layered lipid membrane (45). They play a critical role as mediators of intercellular communication by transferring bioactive cargo. The proteins, nucleic acids, lipids, metabolites, and even organelles such as mitochondria within them are transported to recipient cells, thereby influencing their biological functions (46-52). The production of exosomes is linked to the formation of multivesicular bodies (MVB) within cells (53-55). Initially, the PM undergoes endocytosis, or 'inward budding', to form early-sorting endosomes (ESEs); the TGN and the endoplasmic reticulum also contribute to their biogenesis. ESEs subsequently mature within the cell into late-sorting endosomes and MVBs. These MVBs then fuse with the cell membrane, and the intraluminal vesicles (ILVs) are expelled from the cell through exocytosis; subsequently, the expelled ILVs become exosomes (56-58).

Exosome biogenesis primarily involves endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent mechanisms (57,59-61). ESCRTs consist of five complexes, including ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III and VPS4 (62,63). First, ubiquitinated cargo is recognized and bound by the ESCRT-0 complex. It is then transferred to the ESCRT-I and ESCRT-II complexes for sorting and processing, ensuring the selective incorporation of specific cargo into the ILV. The ESCRT-III complex subsequently mediates membrane curvature and scission of the endosomal membrane, leading to ILV formation (60,64-66). Additionally, VPS4 supplies energy for this process by hydrolyzing ATP (67).

Rab protein-mediated exosome secretion is among the important steps in the ESCRT-independent mechanism (21,68,69). For instance, Rab5 is involved in the formation and transport of early endosomes, whereas Rab7 is involved in the maturation of MVBs and serves as a critical regulator of the fusion of MVBs with lysosomes, playing an essential role in lysosome biogenesis (70-73). Rab proteins can interact with the cytoskeleton and mediate the transport of exosomes along the cytoskeleton (74,75). Rab proteins collaborate with other proteins involved in membrane fusion, such as soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) proteins (an essential family of proteins that mediate the fusion of MVBs with the PM), to promote the fusion of exosomal membranes with cell membranes (76,77). Moreover, Rab family proteins are associated with the cell membrane regions involved in exosome secretion (78,79). Studies have shown that Rab11 and Rab35 function in early or recycling endosomes (80-82). Rab11 can regulate calcium-dependent MVB-PM fusion, thereby promoting the secretion of exosomes (83). Interestingly, a recent study has shown that accessory ESCRT-III can regulate the formation of Rab11 and exosomes containing Rab11a through an ESCRT-dependent mechanism and does not rely on the ubiquitination/deubiquitination cycle for cargo loading (84). Rab35 and its GTPase-activating protein (GAP) can mediate the binding of endocytic vesicles to the PM, thereby regulating the secretion of exosomes (85). Research has indicated that Rab37 is involved in apical exosome secretion, whereas Rab39 is a specific regulator of basolateral exosome secretion (86).

Notably, the role of Rab27 in exosome secretion cannot be ignored. Rab27 can mediate the binding of MVBs to the

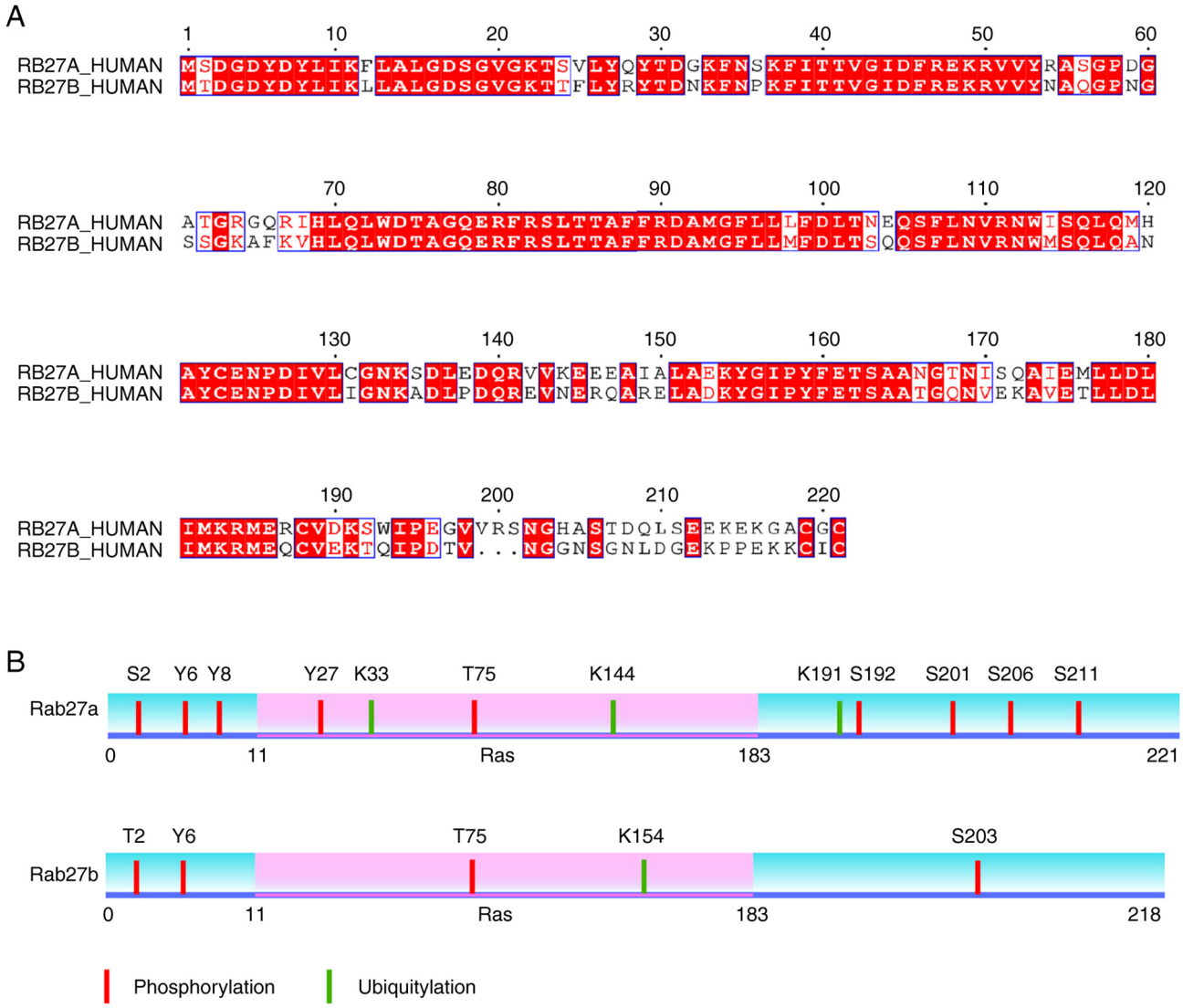

Figure 1. Structural characteristics of Rab27a and Rab27b. (A) Sequence alignment of the region between the Rab27a and Rab27b domains. Identical amino acids are highlighted with a red background and white font; functionally similar amino acids are indicated with a white background and red font; and divergent amino acids are shown in black font. (B) Post-translational modification sites of Rab27a and Rab27b.

PM and the secretion of exosomes (87,88). Research has demonstrated that Rab27a mediates the transport of MVBs to the PM (89). Moreover, Rab27a is localized to peripheral CD63-positive MVBs, preventing MVBs from fusing with one another or with other types of vesicles. This, in turn, promotes the fusion of MVBs with the PM (30). Rab27a can regulate the dynamics of cortical actin at the docking sites of MVBs by inhibiting the localization of coronin 1b (90). Rab27b is localized in the perinuclear region and mediates the transfer of MVBs from the TGN to the membrane. Additionally, Rab27b can promote the maintenance of MVBs at the cell periphery by regulating their transfer from microtubules to the actin-rich PM (57). The regulation of exosome secretion mediated by Rab is also intertwined with autophagy, resulting in the formation of a complex and coordinated regulatory network. Rab-dependent intracellular trafficking controls the sorting and transport of MVBs, which not only directs the transport and release of exosomes at the cell surface but also promotes the fusion of autophagosomes with MVBs through the recruitment of autophagy-related proteins (ATGs). This process mediates the selective loading of exosomal cargoes, including inflammatory factors, microRNAs and ATGs (91-94).

Rab27 typically requires cooperation with other Rab proteins to perform its functions. For instance, in tumor cells, Rab5 mediates the sorting of PD-L1 into endocytic vesicles, whereas Rab27 facilitates the subsequent secretion of exosomal PD-L1. Their synergistic action reduces the surface expression of PD-L1, thereby enhancing the cytotoxic activity of T cells against tumors (87). Evidence has suggested that the cooperative interaction between Rab27a and Rab3a may represent a critical step in vesicle trafficking. Rab27a can bind to Rabphilin3A to form a complex, which mediates the transport of vesicles toward the PM while recruiting a GEF to catalyze the activation of Rab3a. Activated Rab3a then associates with Rabphilin3A, further recruiting the SNARE complex, which ultimately triggers the fusion of vesicles with the PM (95,96). Furthermore, Rab27 can cooperate with Rab35 to promote the formation of MVBs (97). Conversely, Rab27 also has antagonistic interactions with certain Rab proteins. In mast cells, Rab37, Munc13-4 and Rab27 can

Table I. Differential expression of Rab27a and Rab27b across various cancer types in the GEPIA database.

Cancer type	Number of tumor samples	Number of normal samples	Rab27a expression	Rab27b expression
ACC	77	128	Down	-
BLCA	404	28	-	-
BRCA	1085	291	-	Up
CESC	306	13	-	Up
CHOL	36	9	-	-
COAD	275	349	-	-
DLBC	47	337	-	-
ESCA	182	286	-	-
GBM	163	207	Up	Down
HNSC	519	44	-	-
KICH	66	53	-	Up
KIRC	523	100	-	-
KIRP	286	60	-	-
LAML	173	70	-	-
LGG	518	207	-	-
LIHC	369	160	-	-
LUAD	483	347	-	-
LUSC	486	338	Down	-
MESO	87	-	-	-
OV	426	88	-	-
PAAD	179	171	Up	Up
PCPG	182	3	-	-
PRAD	492	152	-	-
READ	92	318	-	-
SARC	262	2	-	-
SKCM	460/461	558	Up	Down
STAD	408	211	-	-
TGCT	137	165	-	Down
THCA	512	337	Up	-
THYM	118	339	Down	-
UCEC	174	91	-	-
UCS	57	78	Down	-
UVM	79	-	-	-

ACC, adrenocortical carcinoma; BLCA, bladder cancer; BRCA, breast cancer; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal adenocarcinoma; GBM, glioblastoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, low-grade gliomas; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian carcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

form a complex, counteracting the vesicle-priming activity of Rab27-Munc13-4 (98). In the context of Sjögren's syndrome, an antagonistic relationship between Rab3D and Rab27 has been identified, in which the relative activities of these two proteins in secretory vesicles correlate with the enzymatic activity of secretory vesicle cathepsin S in the tears of patients (99). In addition, the abundance of ceramides, a class of lipid signaling molecules, is positively correlated with exosome biogenesis. Proteins in the tetraspanin family, which form a complex with syntenin and participate in the sorting of exosomal cargo and modulate membrane curvature, are both critically involved in the exosome secretion process (100-104) (Fig. 3).

In the TME, exosomes serve as critical mediators of intercellular communication between tumor cells and non-tumor cells (105,106). They not only reshape the extracellular matrix, tumor vasculature and immune microenvironment but also modulate the physical and chemical properties of the TME and induce the malignant differentiation of nontumor cells (such as

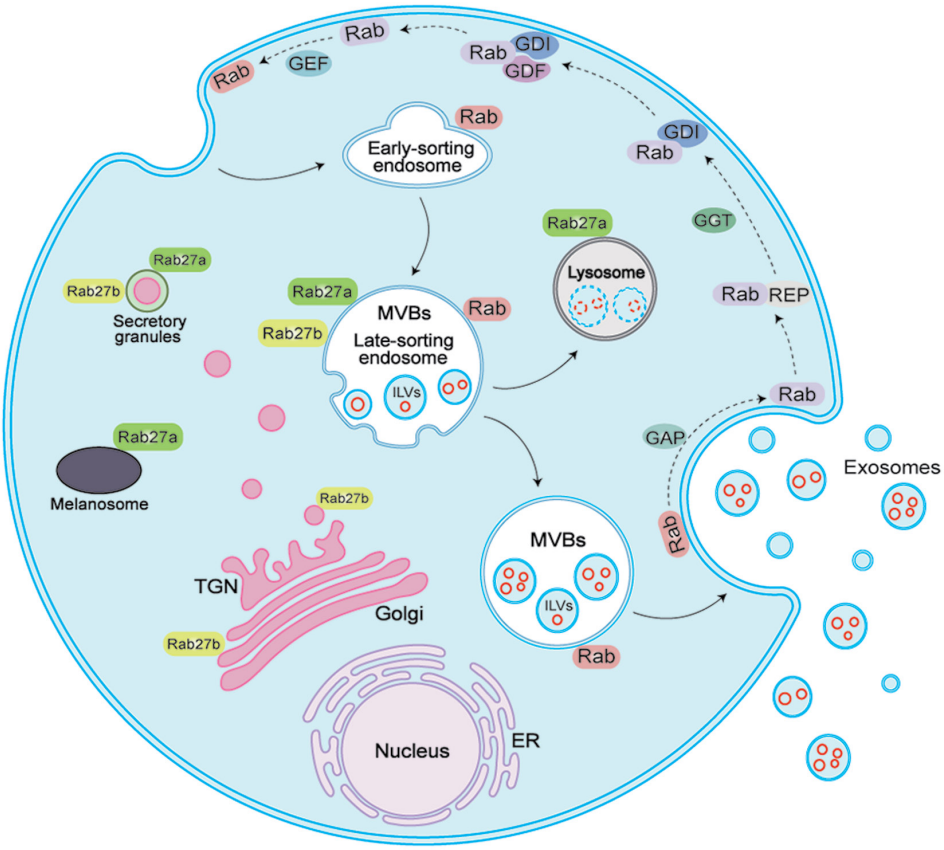

Figure 2. Rab switch form and subcellular localization of Rab27. Rab proteins exist in two reversible states: The inactive GDP-bound form and the active GTP-bound form. In the inactive state, Rab is bound to GDP. GEFs catalyze the exchange of GDP with GTP, thereby activating Rab. The GTP-bound active form of Rab plays a crucial role in vesicular transport. Subsequently, GAPs promote the hydrolysis of GTP to GDP, returning Rab to its inactive state. Inactive GDP-bound Rab is then recognized by the REP, and in the presence of geranyl-geranyl-transferase, it associates with GDIs and GDFs, which regulate the membrane cycling of Rab proteins. Rab27a is localized to melanosomes, secretory granules, late endosomes and lysosomes. Rab27b is predominantly found in the membrane of Golgi stacks and in vesicles located in the TGN area, secretory granules, and late endosomes. GEFs, guanine nucleotide exchange factors; GAPs, GTPase-activating proteins; GDIs, guanine nucleotide dissociation inhibitors; REP, Rab escort protein; GDFs, GDP dissociation stimulator factors; TGN, trans-Golgi network; ER, endoplasmic reticulum; MVBs, multivesicular bodies.

stellate cells and adipocytes) (107-113). Given the pivotal role of exosomes in intercellular communication within the TME, the role of Rab27 as a key regulator of exosome secretion indicates that not only is it a molecular switch for exosome secretion from tumor cells but also it may be a key molecule in regulating the overall communication of the TME.

4. Role of Rab27-mediated exosome secretion in tumors

Although the molecular mechanism of exosome biogenesis remains incompletely understood, the expression of the Rab27 protein as a key molecular switch that governs exosome biogenesis has emerged as an important approach for constructing a cell model of differential exosome secretion. Research has indicated that in hepatocellular carcinoma (HCC) cells, overexpression of Rab27a increases exosome secretion (114). Conversely, the inhibition of SDC4 and Rab27a by mutant β-catenin reduces exosome secretion, thereby facilitating immune escape and cancer cell communication in HCC (115). Moreover, in primary breast cancer (BC) cells, the suppression of Rab27a or Rab27b expression can reduce the secretion of exosomes by primary BC cells (116). Similarly, Hannafon *et al* (117) reported that in BC, silencing Rab27a expression significantly decreased the secretion of exosomes, inhibited the antiangiogenic effect of docosahexaenoic acid on endothelial cells, and promoted tumor angiogenesis. In melanoma, silencing Rab27a was also shown to reduce exosome secretion (118). In addition to its role in tumor diseases, Rab27 also plays a role in regulating exosome secretion in other disorders. For instance, enterovirus A71 interacts with Rab27a through non-structural protein 3A, which can decrease Rab27a ubiquitination and promote exosome secretion (119). In cardiomyocytes, activation of the AKT/Rab27a signaling pathway can promote the secretion of inflammatory exosomes (120). These findings indicate that Rab27 plays a crucial role in the regulation of exosome secretion. Because exosome secretion is a complex physiological process, altering the expression or interaction of Rab27 with other exosome marker proteins (for example, tetraspanin superfamily members and the Rho family of small GTPases) could be more effective for regulating exosome secretion. For instance, Linc01703 can facilitate the secretion of $CD81^+$ exosomes via the formation of the Rab27a/SYTL1/CD81 complex (121).

Rab27a and Rab27b are oncogenes. They can regulate diverse malignant biological behaviors of cancer cells via different molecular mechanisms (122,123). Research on melanoma revealed that silencing Rab27 expression significantly decreased the levels of various intracellular proteins associated

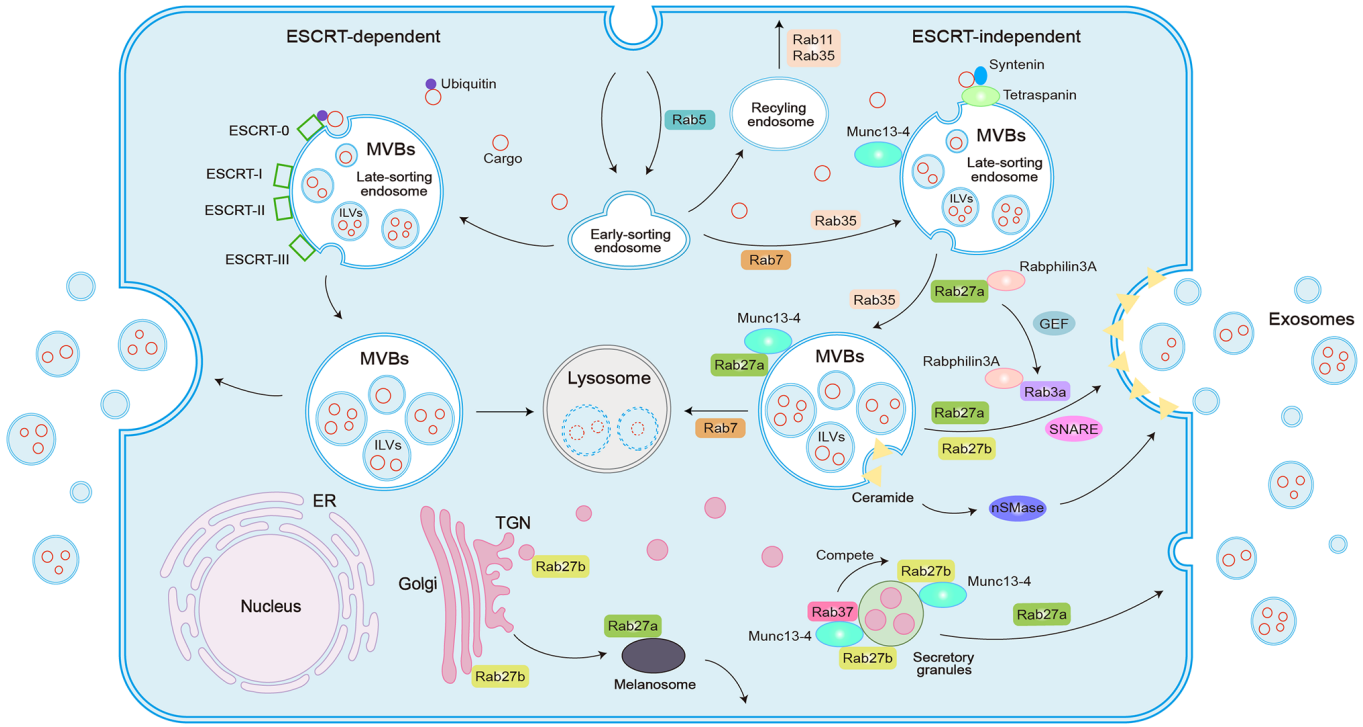

Figure 3. Mechanisms of exosome biogenesis and the functional role of Rab27 in exosome formation. Exosome biogenesis primarily involves two distinct pathways: The ESCRT-dependent mechanism and the ESCRT-independent mechanism. The ESCRT machinery comprises five essential complexes, namely, ESCRT-0, ESCRT-I, ESCRT-II and ESCRT-III, which orchestrate the formation of ILVs and facilitate cargo sorting. VPS4, an ATPase, provides the requisite energy for this intricate process through ATP hydrolysis. The ESCRT-independent pathway predominantly involves a ceramide-dependent mechanism and tetraspanin and Rab proteins. Specifically, Rab27 regulates the binding of MVBs and subsequent exosome secretion and acts in concert with other Rab proteins to orchestrate the entire process of exosome secretion. Rab5 is instrumental in the formation and trafficking of early endosomes, whereas Rab7 plays a crucial role in MVB maturation and lysosome biogenesis. Additionally, Rab37 is involved in the secretion of apical exosomes. During exosome secretion, Rab5, Rab3a and Rab35 act synergistically with Rab27, whereas Rab37 and Rab3D have antagonistic effects on Rab27 function. ESCRT, endosomal sorting complex required for transport; ILVs, intraluminal vesicles; TGN, trans-Golgi network; ER, endoplasmic reticulum; MVBs, multivesicular bodies; GEFs, guanine nucleotide exchange factors.

with cancer cell proliferation, invasion, angiogenesis, adhesion and epithelial-mesenchymal transition (EMT). These findings indicate that Rab27 is closely linked to a variety of malignant biological behaviors of cancer cells (124). The aforementioned study demonstrated that silencing Rab27 in mice bearing brain tumors induced vascular malformations and increased tumor vascular permeability, thereby facilitating immune cell infiltration across the blood-brain barrier and enhancing the efficacy of anti-brain tumor immunotherapy (125). Most studies have demonstrated that Rab27 is closely associated with the proliferation, migration and invasion of cancer cells. Li *et al* reported that Rab27a promoted the proliferation, migration and invasion of colorectal cancer (CRC) cells (126). *In vitro* experiments have shown that Rab27a can increase the proliferation, migration and invasion of oral squamous cell carcinoma cells. The underlying molecular mechanism might be related to the regulation of ZDHHC13-mediated epidermal growth factor receptor palmitoylation and membrane retention by Rab27a (127). Moreover, Rab27a can increase the proliferation and migration of bladder cancer cells by activating the NF-κB pathway. It can also inhibit apoptosis, thereby inducing chemotherapy resistance (128). Rab27b can interact with ZDHHC9 to regulate NRAS palmitoylation and facilitate the progression of myeloid leukemia (129). Interestingly, in a xenograft mouse model, Nambara *et al* (130) demonstrated that Rab27b promoted the peritoneal metastasis of gastric cancer (GC) cells. However, it did not affect the proliferation or invasion of cancer cells *in vitro* (130). These findings suggest that in a mouse model, Rab27 may promote peritoneal metastasis through exosome-mediated remodeling of the TME rather than through its direct effect on the cancer cells themselves.

Rab27 can affect tumor progression in an exosome-dependent manner (122). In triple-negative BC (TNBC) cells, silencing Rab27a significantly reduced exosome secretion, whereas silencing Rab27b did not significantly affect exosome secretion. The inhibition of Rab27a inhibited cell proliferation, invasion and adhesion (131). Alt *et al* (132) demonstrated that in TNBC, silencing Rab27a reduces exosome secretion and suppresses the interaction between tumor cells and mesenchymal stem cells, thereby inhibiting tumor growth and metastasis. A study regarding non-small cell lung cancer (NSCLC) showed that Rab27b mediates exosome secretion by NSCLC cancer stem cells (CSCs) and proposed that Rab27b is required for the maintenance of a highly tumorigenic, cancer-inducing and aggressive stem cell population (133). A study on HCC has shown that CSCs secrete exosomes in a Rab27a-dependent manner and promote the development of HCC resistance to regorafenib (134). Furthermore, Rab27 knockout has been shown to decrease the secretion of macrophage-derived exosomes, which increases the sensitivity of pancreatic ductal adenocarcinoma (PDAC) to gemcitabine (135). Although these studies suggest that Rab27 can induce tumor progression by promoting the secretion of exosomes, the underlying molecular mechanisms remain

unclear. The genetic material contained in exosomes may be important for the ability of Rab27 to promote the occurrence and development of tumors. Song *et al* (136) reported that Rab27a overexpression could increase the migration and adhesion of renal cell carcinoma (RCC) cells, promote exosomal miR-127-3p secretion, and promote the metastasis of RCC. Moreover, silencing Rab27 in bladder cancer cells significantly decreases the secretion of exosomal miR-23b and miR-921, leading to the suppression of tumor cell invasion (137). In BC cells, the suppression of Rab27 expression can reduce the secretion of exosomal mitochondrial DNA, leading to inhibition of receptor cell invasion and delaying the progression of this disease (138). Upregulated Rab27a promotes the secretion of exosomes and induces the production of IFNα in the culture medium, which then activates the TYK2/STAT/HSPA5 signaling pathway to promote NSCLC cell proliferation and metastasis (139). Rab27 is regulated by upstream regulatory genes, which modulate exosome secretion through Rab27 signaling, thereby influencing tumorigenesis and tumor progression. In lung adenocarcinoma, Linc01703 has been demonstrated to suppress lung cancer metastasis through the formation of the Rab27a/SYTL1/CD81 complex, which facilitates the secretion of $CD81^+$ exosomes (121). Furthermore, Zhang *et al* (140) revealed that PRR34-AS1 upregulates Rab27a expression by recruiting DDX3X, thereby promoting the secretion of vascular endothelial-derived growth factor and TGF-β-containing exosomes in HCC cells and enhancing their malignant phenotype.

Nevertheless, the function of Rab27 is not absolute. Its tumor-suppressive role in PDAC contrasts sharply with its aforementioned tumor-promoting functions, indicating its remarkable functional plasticity and dependence on the TME. The expression level of Rab27a in PDAC gradually decreases with disease progression. Ablation of Rab27a in genetically engineered mouse models promotes liver metastasis of cancer cells, supporting a tumor-suppressive role for Rab27a in PDAC (141). This may be closely linked to PDAC-specific epigenetic regulation. Hypermethylation of the SMC3 gene in PDAC tissues represses its expression, thereby weakening the binding of SMC3 to the promoter and enhancer regions of Rab27a and reducing the transcriptional activity of Rab27a, ultimately resulting in downregulated Rab27a expression in PDAC (141). In addition, disparities in the genetic background of different tumor cell types may also contribute to the divergent functions of Rab27. Collectively, these findings suggest that Rab27 acts neither as a pure oncoprotein nor as a strict tumor suppressor and that its function is coordinately modulated by the intrinsic properties of tumor cells, the TME, and disease stage. These findings provide a theoretical basis for targeting Rab27 and exosome-mediated intercellular communication for precision cancer therapy. Clinical intervention should consider tumor type-specific microenvironmental characteristics and molecular regulatory mechanisms to develop individualized therapeutic regimens, thereby overcoming the limitations of conventional single-target therapies (Table II).

5. Diagnostic and therapeutic potential of Rab27 in tumors

The expression of Rab27 in tumor tissues is a valuable biomarker for predicting poor prognosis across various malignant neoplasms. In gastric carcinoma research, Rab27b expression has been found to be negatively correlated with both overall survival and recurrence-free survival, indicating its potential as a prognostic biomarker for adverse outcomes (130). With respect to lung squamous cell carcinoma, increased Rab27b expression has been identified as a potential negative prognostic indicator for patients with NSCLC (142). In pancreatic cancer studies, Rab27b expression has been shown to be associated with poor survival outcomes in a subgroup of patients who may exhibit favorable responses to adjuvant chemotherapy (143). Notably, the roles of Rab27a and Rab27b are distinct in cancer tissues with different pathological characteristics. A study by An *et al* (144) further indicated that Rab27a and Rab27b may serve as potential biomarkers for predicting lymph node metastasis and prognosis in patients with GC. In GC tissues, Rab27a is highly expressed and predominantly localized in the nucleus, and its expression level is significantly positively correlated with lymph node metastasis. Rab27b is also globally overexpressed, is distributed mainly in the cytoplasm and PM, and has pathological subtype-specific prognostic value (144). In well-differentiated GC, high Rab27b expression is associated with reduced patient survival, whereas in poorly differentiated adenocarcinoma, low Rab27b expression predicts a worse prognosis (144). However, the aforementioned study lacked comparative analyses of Rab27a and Rab27b expression and localization in paired adjacent non-tumor tissues, which may explain the divergent prognostic performance of these two proteins in GCs with distinct differentiation statuses. In a study by Kottorou *et al* (145), the expression of both Rab27a and Rab27b was shown to be downregulated in CRC tissues and correlated with poor patient prognosis. Notably, low Rab27b expression is closely associated with advanced tumor stage, lymph node metastasis, and distant metastasis, whereas high Rab27b expression is linked to poor tumor differentiation and high malignancy (145). These findings suggest that Rab27 may act as a double-edged sword in relation to cancer progression. This phenomenon may be attributed to tumor heterogeneity and the bidirectional nature of signaling networks downstream of Rab27a and could also involve differential responses of tumor cells to diverse external stimuli, including chemotherapy and targeted therapy (Table III).

In the field of cancer therapy, as a key regulator of exosome secretion, Rab27 holds great promise for targeted therapeutic applications. By mediating exosome secretion and remodeling the TME, targeting Rab27 may not only directly suppress the malignant phenotypes of tumor cells but also improve vascular function and reverse the immunosuppressive state (125). Currently, therapeutic strategies targeting Rab27 are under active development and are expected to provide new breakthroughs for precision cancer therapy.

Given the critical role of Rab27 in tumor progression and its complex downstream regulatory networks, downregulating Rab27 expression using gene silencing technologies is theoretically associated with favorable antitumor effects. Researchers have strategically utilized the unique tropism of Epstein-Barr virus (EBV) for human B cells by incorporating Rab27a small interfering RNA into inactivated EBV particles, which effectively reduces the release of $CD19^+$ exosomes from B cells, consequently enhancing the antitumor efficacy of chemotherapeutic interventions (146). Furthermore, targeting Rab27 in

Table II. Rab27/Rab27 mediate the role of exosome in tumors.

Authors, year	Cancer type	Rab27 subtype	Exosome secretion	Rab27 expression	Downstream molecules	Phenotype	(Refs.)
Horodecka *et al*, 2025	Melanoma	Rab27a/b	-		HER/AKT, HER/ERK	Proliferation, metastasis, angiogenesis, EMT	(124)
Adnani *et al*, 2022	Brain tumor	Rab27a/b	-	Up	TJ/Claudin5	Angiogenesis, vascular permeability, immunotherapy	(125)
Li *et al*, 2022	CRC	Rab27a	-	Up		Proliferation, metastasis	(126)
Huang *et al*, 2023	OSCC	Rab27a	-	Up	ZDHHC13/EGFR	Proliferation, metastasis	(127)
Liu *et al*, 2017	Bladder cancer	Rab27a	-	Up	p-κB/p-p65/NF-κB	Proliferation, metastasis, chemoresistance	(128)
Ren *et al*, 2023	ML	Rab27b	No	Up	ZDHHC9/NRAS, c-RAF/MEK/ERK	Proliferation	(129)
Nambara *et al*, 2023	GC	Rab27b	-	Up		Metastasis	(130)
Wang *et al*, 2023	TNBC	Rab27a	Yes	Up		Proliferation, metastasis	(131)
Alt *et al*, 2020	TNBC	Rab27a	Yes	Up		Proliferation, metastasis	(132)
Meneses *et al*, 2023	NSCLC	Rab27b	Yes	Up		Proliferation, metastasis, angiogenesis	(133)
Huang *et al*, 2021	HCC	Rab27a	Yes	Up		Regorafenib resistance	(134)
Binenbaum *et al*, 2021	PDAC	Rab27a/b	Yes		miR-365	Gemcitabine resistance	(135)
Song *et al*, 2024	RCC	Rab27a	Yes	Up	miR-127-3p	Metastasis	(136)
Ostenfeld *et al*, 2014	Bladder cancer	Rab27a/b	Yes	Up	miR-23b, miR-921	Metastasis	(137)
Rabas *et al*, 2021	Breast cancer	Rab27a/b	Yes	-	TLR 9	Metastasis	(138)
Zeng *et al*, 2024	NSCLC	Rab27a	Yes	Up	IFNα, TYK2/STAT/HSPA5	Proliferation, metastasis	(139)
Huang *et al*, 2023	LUAD	Rab27a	Yes		Rab27a/SYTL1/CD81	Metastasis	(121)
Zhang *et al*, 2022	HCC	Rab27a	Yes	Up	VEGF, TGF-β	Proliferation, metastasis, EMT	(140)
Bastos *et al*, 2023	PDAC	Rab27a		Down		Metastasis	(141)

CRC, colorectal cancer; OSCC, oral squamous cell carcinoma; GC, gastric cancer; TNBC, triple-negative breast cancer; ML, myeloid leukemia; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; LUAD, lung adenocarcinoma.

Table III. The potential of Rab27 as a tumor biomarker.

Authors, year	Cancer	Rab27 subtype	Rab27 expression	Type of biomarker	Correlation	(Refs.)
Nambara *et al*, 2023	GC	Rab27b	Up	Survival rate	Negative correlation	(130)
Koh and Song, 2019	SQCC	Rab27b	Up	Survival rate	Negative correlation	(142)
Pecqueux *et al*, 2023	Pancreatic cancer	Rab27b	Up Up	Survival rate Chemotherapy sensitivity	Negative correlation Positive correlation	(143)
An *et al*, 2022	GC (Well-differentiated/ moderately differentiated adenocarcinoma) (Poorly differentiated adenocarcinoma)	Rab27a Rab27b Rab27b	Up Up Down	Lymphatic metastasis Survival rate Survival rate	Positive correlation Negative correlation Positive correlation	(144)
Kottorou *et al*, 2023	Colorectal cancer	Rab27a/b	Down	Survival rate	Positive correlation	(145)

GC, gastric cancer.

combination with other agents has synergistic effects. Depletion of Rab27a diminishes tumor-derived exosome secretion, reverses hepatic metabolic reprogramming, alleviates chemoresistance, and reduces adverse effects of chemotherapy (147). In BC cells, silencing Rab27a decreases 6J1-induced PD-L1 secretion in exosomes, potentiates antitumor immune responses, and improves therapeutic efficacy (87). Nevertheless, RNA interference-based strategies generally suffer from insufficient target specificity and poor *in vivo* stability, restricting their clinical application to local administration or reliance on highly efficient delivery carriers (148). In addition, inhibition of a single target may trigger compensatory signaling pathways, resulting in suboptimal therapeutic outcomes (28,149).

Given the limitations associated with single-targeted inhibition of Rab27, the development of multitarget, multi-pathway small-molecule strategies has distinct advantages. Tipifarnib, an inhibitor of exosome biogenesis, simultaneously targets Rab27a, nSMase2 and ALIX. By suppressing the PTM of Rab27 and acting cooperatively on multiple core proteins involved in exosome biogenesis, it overcomes acquired resistance resulting from single-target interventions (150). However, the pharmacokinetic properties and toxicological profiles of such synthetic small molecules still require comprehensive evaluation. Natural small-molecule products have shown promising translational potential in targeting Rab27 because of their multitarget characteristics and favorable cost effectiveness (151). *Acorus calamus* effectively suppresses exosome secretion in TNBC cells through dual targeting of Rab27a and nSMase2 (152). Resveratrol reduces exosome secretion by suppressing Rab27a expression, thereby inhibiting proliferation, migration and EMT in Huh7 cells and blocking HCC progression. Furthermore, resveratrol-induced exosomes further suppress the malignant phenotypes of tumor cells by inhibiting β-catenin nuclear translocation and autophagy activation (153). In the future, identifying and structurally optimizing the core pharmacophores that target Rab27 from natural products is expected to emerge as an important direction for the development of drugs targeting Rab27.

In addition to directly targeting Rab27, disrupting its interaction with downstream effector molecules or blocking downstream signaling pathways represents an effective intervention strategy. The novel compound BHMPS [(E)-N-benzyl-6-(2-(3,4-dihydroxy-benzylidene)hydrazinyl)-N-methylpyridine-3-sulfonamide] has been identified as an effective inhibitor of the Rab27a-Slp4 interaction. The inhibition of Rab27a-mediated exosome secretion represents a promising therapeutic strategy for suppressing BC metastasis and invasion (154). Molecular studies have revealed that MUC1-C interacts with the Rab27a protein and that targeted inhibition of MUC1-C expression significantly suppresses the secretion of MICA/B-containing exosomes (155). Notably, both aforementioned strategies remain at the basic research stage. Camptothecin, a widely used chemotherapeutic agent, targets Topo I to block DNA replication and repair and induce apoptosis in cancer cells (156). Moreover, it has been shown that camptothecin can also inhibit proliferation and migration in head and neck squamous cell carcinoma by blocking the Rab27a-mediated activity of the PI3K/AKT pathway (157). These findings support the feasibility of drug repurposing for cancer therapy.

As inhibitors of exosome biogenesis and secretion, Nexinhib20 and GW4869 exhibit considerable potential in antitumor therapy. Nexinhib20 suppresses exosome secretion by specifically blocking the interaction between Rab27a and JFC1, whereas GW4869 effectively inhibits the expression of nSMase2 and thereby reduces exosome biogenesis (158-160). It has been demonstrated that combining Nexinhib20 or GW4869 with cisplatin/etoposide enhances the inhibitory effects of first-line chemotherapy against small cell lung cancer cells (161). Moreover, Nexinhib20 selectively inhibits granule and exosome release without compromising critical neutrophil functions such as phagocytosis and neutrophil extracellular traps formation, theoretically conferring a lower risk of immunosuppression (162). However, both agents remain at the preclinical stage of cellular and animal models, and their safety profiles and pharmacokinetic properties require further

Table IV. Antitumor approach targeting Rab27.

Authors, year	Cancer	Molecular target	Medication/Method	Function	Current stage	(Refs.)
Zhang *et al*, 2023	Colon cancer, GC, lymphoma	Rab27a	iEBV-Rab27a siRNA	Chemotherapy sensitivity	Preclinical stage	(146)
Wang *et al*, 2023	Melanoma, osteosarcoma	Rab27a	lentiCRISPR	Metabolic reprogramming of the liver and chemotherapy sensitivity	Preclinical stage	(147)
Gupta *et al*, 2025	Triple-negative BC	Rab27a	Acorus calamus	Exosome secretion	Clinical stage	(152)
Tong *et al*, 2024	Hepatocellular carcinoma	Rab27a	Resveratrol	Cell proliferation, migration, EMT	Preclinical stage	(153)
Ye *et al*, 2023	BC	Rab27a	Triazine compound 6J1	Antitumor immune response	Preclinical stage	(87)
Park *et al*, 2022	BC	Rab27a-Slp4 complex	BHMPS	Migration and invasion	Preclinical stage	(154)
Morimoto *et al*, 2023	Colorectal cancer	MUC1-C-Rab27a complex	GO-203 inhibitor	Exosome secretion	Preclinical stage	(155)
Zhao *et al*, 2024	Head and neck squamous cell carcinoma	Rab27a	Camptothecin	Proliferation and migration	Clinical stage	(157)
Irep *et al*, 2024	Small cell lung cancer	Rab27a	Nexinhib20	Exosome secretion	Preclinical stage	(161)

BC, breast cancer.

Figure 4. Potential applications of Rab27. Therapeutic prospects in clinical practice via molecular targets, biomarkers, combined medications and engineered exosome preparation.

validation. Additionally, strategies to achieve selective inhibition of tumor-derived exosomes rather than those from normal cells remain to be addressed.

While several Rab27-targeted strategies have been developed, their safety profiles require critical evaluation. Rab27 is widely involved in physiological vesicle secretion in normal cells and regulates key processes, including immune cytokine release, insulin secretion and neurotransmission. Non-specific targeting may readily lead to multisystem side effects such as immune dysregulation and metabolic disorders (122,163). Therefore, a balance must be maintained between therapeutic efficacy and target selectivity in the development of Rab27-targeted antitumor agents. Although existing studies have indicated that resveratrol at effective doses does not significantly affect Rab27 expression in normal cells, its selectivity and potential toxic side effects in complex human physiological environments still require careful evaluation (153,164). Furthermore, the regulation of Rab27 by camptothecin, resveratrol, and *Acorus calamus* is concentration-dependent. How to maintain potent antitumor activity while avoiding interference with insulin secretion and neurotransmission represents an urgent clinical translation challenge (152,153,157) (Fig. 4 and Table IV).

6. Conclusions

Typically, Rab27a and Rab27b can regulate the malignant progression of tumors by promoting the secretion of exosomes (149,163). Interestingly, the two play different roles in the process of exosome secretion. Rab27a is localized to peripheral CD63-positive MVBs and is essential for mediating the fusion of MVBs with the PM (30). By contrast, Rab27b is predominantly located in the perinuclear region, where it regulates the transfer of MVBs from microtubules to the actin-rich cortex, facilitating membrane turnover from the TGN to MVBs (30). While the majority of studies have identified Rab27 as an oncogene and a molecular switch for exosome release, alternative perspectives have emerged. For instance, recent research has indicated that the impact

of Rab27a on the migration and invasion of melanoma cell lines may be contingent upon the unique characteristics of the cell line and appears to be independent of exosome secretion (165). These findings not only reveal the complex roles of Rab27 in tumors and exosomes but also provided a direction for further exploration of its underlying mechanisms and application value.

The Rab27 protein plays a pivotal role in tumor biology, primarily through its regulation of exosome secretion, which significantly influences tumor cell proliferation, invasion and metastatic potential. Its expression levels are strongly correlated with tumor initiation, progression and clinical outcomes. The scientific community has reached a consensus that the modulation of Rab27 expression directly impacts exosome secretion dynamics. However, the precise molecular mechanisms underlying Rab27-mediated exosome biogenesis and secretion warrant further comprehensive investigation. Considering the critical role of exosomal genetic cargo in tumor regulation, exploring whether Rab27 facilitates the selective enrichment of specific genetic materials within exosomes, thereby influencing tumor progression, is imperative. Beyond its established potential as a diagnostic biomarker and therapeutic target in oncology, the upregulation of Rab27 expression may offer a novel approach for the efficient production of engineered exosomes, presenting innovative strategies for the large-scale preparation of artificial exosomes for therapeutic applications.

Acknowledgements

Not applicable.

Funding

The present study was supported in part by the National Natural Science Foundation of China (grant nos. 82472882, 82302987 and 82303534), the Natural Science Foundation of Hunan (grant nos. 2025JJ30047, 2024JJ4025, 2023ZJ1122, 2023JJ60469, 2023JJ40413, 2023JJ30372 and 2023JJ30375), the Science and Technology Innovation Program of Hunan (grant nos. 2023RC3199, 2023SK4034 and 2023RC1073), the National Key Clinical Specialty Scientific Research Project (grant nos. Z2023086 and Z2023017), the Hunan Provincial Health High-Level Talent Scientific Research Project (R2023040 and R2023093), and the Research Project of the Health Commission of Hunan (grant nos. 20255845 and 20255433).

Availability of data and materials

Not applicable.

Authors' contributions

MT and ZZ drafted the manuscript and prepared the figures. HD, ST, MS, XJ, QP, LO and ZR helped collect the related studies and participated in discussions. YZ and QL designed the review and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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