Emerging role of long non-coding RNAs in the Rho/ROCK signaling pathway in tumor metastasis (Review)

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Abstract. Metastasis is a critical feature of malignant tumors and a major cause of treatment failure and poor prognosis. This complex process primarily involves the rearrangement of the cytoskeleton. Among several cytoskeleton-associated signaling pathways, the ras homolog family (Rho) and Rho-associated coiled-coil containing protein kinase (ROCK) signaling pathway serves a key role in cytoskeleton regulation as it controls intracellular actin dynamics and cytoskeletal remodeling to mediate cell movement. Long non-coding RNAs (lncRNAs), known to serve important roles in tumorigenesis and metastasis, have been shown to regulate the Rho/ROCK pathway. lncRNAs modulate the Rho/ROCK pathway by sponging microRNAs or directly binding to proteins, thereby mediating tumor metastasis. Additionally, lncRNAs can be encapsulated in exosomes and transferred from donor cells to recipient cells, where they regulate components of the Rho/ROCK signaling pathway and further promote the metastatic potential. Based on their functional significance, Rho/ROCK signaling pathway-associated lncRNAs may serve as novel tumor biomarkers and therapeutic targets. The present review summarizes the role and mechanism of Rho/ROCK signaling pathway-associated lncRNAs in tumor metastasis, which may offer novel avenues for the diagnosis and treatment of metastatic cancer.

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Abbreviations: Rho, ras homolog family; ROCK, Rho-associated coiled-coil containing protein kinase; Rac, Ras-related C3 botulinum toxin substrate; lncRNA, long non-coding RNA; ceRNA, competing endogenous RNA; EMT, epithelial-mesenchymal transformation; Cdc42, cell division cycle 42; mDia, mammalian homolog to *Drosophila*; ARHGAP18, Rho GTPase activating protein 18; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; PTC, papillary thyroid carcinoma; TNBC, triple-negative breast cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; Rnd, Rho family GTPase

Key words: Rho/ROCK signaling pathway, lncRNAs, tumor metastasis, exosomes, biomarkers, therapeutic target

Contents

1. Introduction

Tumor metastasis is a hallmark of tumor development and progression. Tumor metastasis involves the detachment of tumor cells from the primary site through a series of biological processes, including local infiltration, entry into the vascular system, circulation, colonization of secondary tissues or organs, and the formation of secondary tumors (1-4). This complex process of tumor invasion and metastasis involves multiple factors, including changes in the tumor microenvironment, epithelial-mesenchymal transformation (EMT), tumor hypoxia, neovascularization, decreased intercellular adhesion, cytoskeleton remodeling, extracellular matrix degradation, and the formation of cellular pseudopods and protuberances (5,6). Although advances in existing treatments have improved survival rates for some patients with cancer, distant metastasis remains a major challenge (7,8). Once metastasis occurs, long-term survival markedly decreases, and numerous patients succumb to the disease shortly thereafter (9). Tumor metastasis is one of the most important contributors to cancer-related mortality and is a major obstacle in effective

clinical management (10). Therefore, there is an urgent need to identify metastasis-specific biomarkers and to explore the underlying molecular mechanisms.

Among numerous pathways, the ras homolog family (Rho) and Rho-associated coiled-coil containing protein kinase (ROCK) signaling pathway serves a key role in tumor metastasis. This signaling pathway regulates cytoskeletal remodeling by modulating myosin and actin activity, establishing cell polarity, and organizing intermediate filaments. This pathway also contributes to tumor cell proliferation, contraction, migration, adhesion and cell-matrix interactions (11). The most widely studied Rho GTP enzymes include Rho, Ras-related C3 botulinum toxin substrate (Rac) and cell division cycle 42 (Cdc42) (12,13). These receptor proteins initiate cytoskeleton reorganization and regulate downstream effectors that affect tumor cell migration (14). Furthermore, the Rho/ROCK pathway can regulate HIPPO/yes-associated protein (YAP) signaling by modulating the actinomycin skeleton, with YAP acting as a mechanical sensor that alters gene expression in response to cytoskeleton dynamics (15). The cytoskeleton, a dynamic network of protein fibers in eukaryotic cells, serves an important role in cell division, intracellular transport, motility and shape maintenance (16,17). The cytoskeleton comprises three main components: Microfilaments, microtubules and intermediate filaments (18). Microfilaments are primarily involved in cytokinesis, cell motility and the formation of intracellular stress fibers. Microtubules maintain cell morphology, resist compression and facilitate intracellular trafficking. Intermediate filaments provide mechanical stability and coordinate cell migration. Together, these three cytoskeletal components coordinate cellular integrity and ensure the smooth progression of several biological functions, such as maintaining cell morphology (16), material transport (19) and cell movement (20). Microtubules serve a crucial role in cancer progression and metastasis (21,22). Microtubule-targeting agents have emerged as promising tools to disrupt cancer cell activity and inhibit metastasis (23,24).

Some antibody-drug conjugates, especially those combined with microtubule-targeting compounds, have yielded encouraging effectiveness in reducing tumor burden at metastatic sites (25,26). Nestin, an intermediate filament protein, is upregulated in several tumors, including pancreatic and prostate cancer, malignant melanoma, and glioma, and is associated with tumor aggressiveness, metastasis and poor prognosis (27,28).

Long non-coding RNAs (lncRNAs) were first identified in the nucleus and cytoplasm of eukaryotic cells (29). Most lncRNAs lack a fully functional open reading frame; however, previous studies have shown that a few lncRNAs can encode a small number of functional short peptides (30-32). Based on their location in the genome, lncRNAs have been classified into five categories: Sense, antisense, bidirectional, intergenic and intronic lncRNAs (33,34). Functionally, lncRNAs can be classified into four types: Signaling, decoy, guide and scaffold lncRNAs (35). Signaling lncRNAs can be used as marker signals in different temporal spaces, developmental stages and gene expression regulation (36). For example, there are three common signaling lncRNAs: Air, Kcnq1ot1 and Xist. They mediate the transcriptional silencing of multiple genes by interacting with chromatin and recruiting chromatin modification mechanisms (37). Guide lncRNAs can guide the localization of ribonucleoprotein complexes to specific targets. For example, the lncRNA COLDAIR can guide the polycomb repressive complex 2 (PRC2) complex to serve a key biological role in the chromatin of the floral repressor, flowering locus c (38). Traditionally, proteins have been important players in various types of scaffold complexes (39). However, it has been shown that lncRNAs can also serve as central platforms for the assembly of relevant molecular components in several biological signaling processes, and this precisely controlled property is essential for precise control of the specificity and dynamics of intermolecular interactions and signaling events (40). lncRNAs have been confirmed to be associated with various cancer types, including colorectal, gastric, hepatocellular and esophageal cancer (41-44). For example, lncRNA CCAT1 and HOTAIR in the plasma of patients with colorectal cancer (CRC) have been shown to serve as biological markers in CRC screening (41). Aberrant expression of three lncRNAs (POU3F3, SPRY4-IT1 and HNF1A-AS1) has been detected in the sera of patients with oesophageal cancer. Notably, the combined use of the three could effectively detect the early development of esophageal cancer (44). lncRNAs also serve key roles in tumor metastasis. lncRNA HIF1A-AS2 can promote the proliferation and invasion of triple-negative breast cancer (TNBC) cells (45). Compared with those in normal lung tissue, lncRNA MALAT1 expression levels are elevated in lung cancer, and abnormal MALAT1 expression can induce EMT to further promote brain metastasis in lung cancer (46). With the continuous development of high-throughput sequencing, numerous lncRNAs have been identified due to their specific expression in tumor metastasis, and as molecular biomarkers for tumor metastasis and potential therapeutic targets for several tumors (47-49). For instance, Zhang *et al* (50) developed a novel computational framework employing six machine learning algorithms to comprehensively analyze transcriptomic data from purified immune cells, glioblastoma cell lines and bulk glioblastoma tissue. This framework was utilized to screen for tumor-infiltrating immune cell-associated lncRNAs predictive of prognosis and response to immunotherapy in patients with glioblastoma.

In summary, among the multiple complex mechanisms of tumor metastasis, lncRNAs are emerging as important modulators of cytoskeleton dynamics, and likely affect tumor cell metastasis by directly binding to cytoskeleton-related proteins or by indirectly regulating key molecules in the Rho/ROCK signaling pathway. The present review aims to explore the molecular mechanisms through which lncRNAs mediate the Rho/ROCK signaling pathway during tumor metastasis. An improved understanding of these interactions between lncRNAs and the Rho/ROCK signaling pathway may provide novel strategies for the early diagnosis and targeted treatment of metastatic tumors.

2. Definition, mechanism and functions of lncRNAs

Definition and biological characteristics of lncRNAs. The majority of the human genome (76-97%) is transcribed into RNAs that are not translated into proteins, and are referred to as non-coding RNAs (ncRNAs) (51). Taking 200 nt as the threshold, ncRNAs are classified into two categories: Short

ncRNAs (<200 nt) and lncRNAs (>200 nt) (52). According to their genomic proximity to neighboring transcripts, lncRNAs can be classified into four categories: i) Intergenic lncRNAs, which are located between two protein-coding transcripts; ii) intronic lncRNAs, which are present in the introns of coding transcripts; iii) sense/antisense strand lncRNAs, which have overlapping parts with introns and exons of different coding transcripts; and iv) bidirectional lncRNAs, which share a promoter and are transcribed from both sense and antisense directions of transcription start areas (53). lncRNAs are transcribed by polymerase II (54). Similar to mRNA, most lncRNAs undergo 5' end capping, polyadenylation and splicing. They are different in that the number of lncRNAs in exons is lower than that in mRNA; therefore, lncRNAs are evolutionarily conserved to a certain extent. Secondary and advanced structures are the most important features of lncRNAs. lncRNAs form secondary structures, including double helices, hairpin loops, protrusions and pseudoknots, as well as tertiary structures with non-Watson-Crick base pairs and more advanced structures. These structures form the basis for the biological functions of lncRNAs. lncRNAs are unevenly distributed in the nucleus and cytoplasm (55); however, the specific localization of lncRNAs in the cytoplasm or nucleus, and the factors determining such localization have not been fully confirmed (56).

Biological functions of lncRNAs. In the whole genome, 50-70% of genomic DNA can be transcribed; however, <2% of this is ultimately translated into proteins (57), and the vast majority of the remaining transcripts are transcribed into non-coding ncRNAs. Although not translated, previous studies have shown that ncRNAs are widely involved in various biological processes of organisms (34,58-60). Compared with mRNAs, lncRNAs have higher spatial and temporal specificity and lower interspecies conservation, and they serve an essential role in regulating chromatin dynamics (61,62), gene expression (63), cell proliferation (64), cell differentiation (65) and development of organisms (63). One of the most important functions of lncRNAs is the regulator of transcription (66,67). Among the identified action modes, signaling, decoy, scaffolding and guidance are the most frequent modes of action of lncRNAs in the cell (68). The main function of signaling type lncRNAs is to regulate transcription as a molecular signal in response to various stimuli, while the chromatin state of regulatory elements can be further inferred from the expression of related lncRNAs (36). In addition, cellular stimulation can affect the transcriptional expression of lncRNAs, which can perform regulatory functions to affect the biological processes of organisms (69). Therefore, their production and presence can be used as an indicator of transcriptional activity. For example, DNA damage can induce the transcription of lncRNA PANDA in a p53-dependent manner, which acts to limit the expression of pro-apoptotic genes and arrest the cell cycle after interacting with transcription factors (70). In an experiment involving the induction of somatic cell reprogramming in pluripotent stem cells, Loewer *et al* (71) demonstrated that a large number of lncRNAs were aberrantly expressed during this process. Among them, lncRNA RoR could directly regulate the pluripotency factors OCT4, SOX2 and Nanog, and served a role as a signaling molecule in the pluripotency and reprogramming of stem cells. Decoy lncRNAs can directly bind regulatory molecules such as transcription factors or RNA-binding proteins, thereby sequestering them and blocking their activity and downstream signaling pathways (72,73). For example, lncRNA PANDA inhibits the expression of apoptotic genes by directly binding to nuclear transcription factor Y subunit α, thus arresting the cell cycle (74). Scaffold lncRNAs can serve as molecular scaffolds that guide the assembly of protein complexes onto target genes (75). For example, HOTAIR serves as a molecular scaffold that links and targets the PRC2 and the lysine specific demethylase 1 histone-modifying complexes, thereby coordinating H3K27 methylation and H3K4 demethylation to reprogram chromatin states (76). Guide lncRNAs perform a 'guide-like' function, interacting with ribonucleoprotein particles and taking them to specific target genes, and serve the roles of cis-guides and trans-guides (77). In addition, some studies have shown that a small number of lncRNAs can encode short peptides that further function in the organism (78-80). With the widespread application of next-generation sequencing technologies in different tumors, the mystery of lncRNAs has been gradually unraveled. Thousands of lncRNAs are aberrantly expressed in various tumors, suggesting that they may serve an important role in the disease process of tumors (81). The validated mechanisms of lncRNAs in tumors are acting as competing endogenous RNAs (ceRNAs), participating in chromatin remodeling, regulating chromatin interactions and acting as natural antisense transcripts (82). lncRNA HOTAIR is dysregulated in a variety of cancer types (76,83,84), such as oral squamous cell carcinoma (OSCC), hepatocellular carcinoma (HCC) and breast cancer. Wu *et al* (76) found that HOTAIR binds with EZH2 and H3K27me3 to form a complex, which can bind to the promoter region of E-cadherin to regulate its expression, thereby affecting OSCC metastasis. Recent studies have revealed that lncRNAs can be encapsulated in exosomes, and transferred from donor cells to recipient cells in the tumor microenvironment by the fluid circulation, thereby regulating several phenotypes of tumor processes (85,86), including malignant proliferation and invasive metastasis of tumor cells, radiotherapy resistance of tumor cells, formation of the tumor microenvironment and internal angiogenesis. For example, Zhang *et al* (87) reported that exosomal lncRNA MALAT1 was differentially expressed in non-small cell lung cancer (NSCLC), high exosomal MALAT1 expression could promote metastasis in NSCLC and the expression levels of MALAT1 were closely associated with lymph node metastasis in patients with NSCLC. In addition, exosomal lncRNAs released into the tumor microenvironment have the potential to become tumor markers due to their specificity and sensitivity (88-90).

3. Rho/ROCK signaling pathway

Composition of the Rho/ROCK signaling pathway. The Rho/ROCK signaling pathway consists of the Rho-GTPase family and its downstream effector ROCK (91-93) (Fig. 1). Rho GTPases are members of the Ras superfamily of small GTP-binding proteins and contain >20 Rho proteins that can be broadly classified into the following five groups based on their primary sequence and functional type: Rho, Rac, Cdc42, Rho Family GTPase (Rnd) and Rho-related BTB

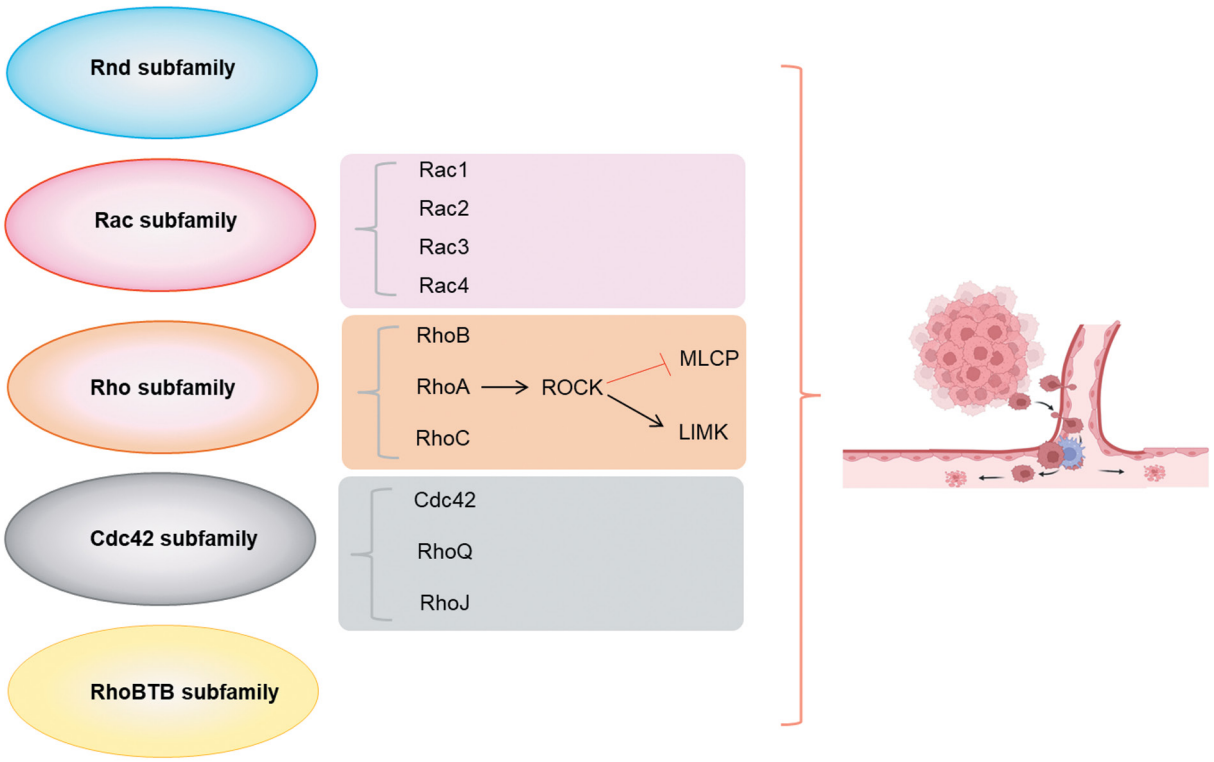

Figure 1. Members of the Rho family. The main members of the Rho family include the Rnd, Rac, Rho, Cdc42 and RhoBTB subfamilies. The members of the Rho subfamily include RhoA, RhoB and RhoC. The members of the Rho subfamily regulate the cytoskeleton by modulating the ROCK/MLCP and ROCK/LIMK pathways. Cdc42, cell division cycle 42; LIMK, LIM domain kinase; MLCP, myosin light chain phosphatase; Rac, Ras-related C3 botulinum toxin substrate; Rho, Rho family GTPases; RhoBTB, Rho-related BTB domain-containing; Rnd, Rho family GTPase; ROCK, Rho-associated coiled-coil containing protein kinase.

domain-containing subfamilies (92). Among these, the Rho, Rac and Cdc42 subfamilies are the most intensively investigated and best characterized functionally. The Rho subfamily includes RhoA, RhoB and RhoC, which are very similar in sequence, and because they share the same set of effectors, the mode of action of the three is presumed to be similar (94). RhoA, RhoB and RhoC have two different states in organisms (inactive GDP-bound and active GTP-bound forms); the molecules cycle between the two states. The transition from the inactive GDP-bound form to the active GTP-bound form is catalyzed by the diffuse B-cell lymphoma family of RhoGTP guanine nucleotide exchange factors (95). By contrast, the transition from the active to the inactive state is mediated by intrinsic GTPase hydrolysis stimulated by Rho GTPase-activating proteins (96). In the active state, Rho proteins act on >60 downstream targets, including ROCK, mammalian homolog of *Drosophila* (mDia), Par6B, p21 (RAC1) activated kinase 4 and Wiskott-Aldrich syndrome proteins (97). Activation of RhoGTPase ultimately leads to the remodeling of the cytoskeleton and changes in other fundamental processes, such as cell division, adhesion and migration (98,99). The ROCK family consists of two structurally similar isoforms, ROCK1 and ROCK2. Both kinases share >30 direct downstream substrates, including myosin phosphatase-targeting subunit 1, myosin light chain (MLC) and LIM domain kinase, in addition to containing an N-terminal catalytic kinase structural domain, a central coiled-coil structural domain and a C-terminal PH structural domain (100). In Rho/ROCK signaling, Rho (RhoA/RhoC) activates Rho-related kinases (ROCK1/ROCK2) by binding to their C-terminal. ROCK regulates key proteins in the cytoskeleton by mediating the phosphorylation of MLC, and activating Lin-11, Isl1 and MEC-3 (LIM) structural domain kinases, which are widely involved in basic cellular functions, including adhesion, migration, contraction, proliferation and apoptosis (101).

The vast majority of cellular activities are directly or indirectly influenced by Rho family proteins. Rho family proteins regulate the actin cytoskeleton to control cell morphology, and serve an important role in cell polarity, endocytosis, vesicle trafficking, adhesion and migration (13). RhoA interacts with effectors at the cell membrane (102). RhoA mediates the formation of myosin bundles and stress fibers (103), and serves an important role in membrane folding and lamellipodia formation (104). RhoB is present on the outer membranes of multivesicular bodies and in the plasma membrane and serves a role in vesicle transport (105). RhoC is mainly located in the plasma membrane or cytoplasmic matrix, and mainly regulates the activity of actin and myosin and limits lamellipodial broadening (106). The Rac subfamily primarily stimulates the formation of lamellar pseudopods, membrane folds and invasive foot types (107). Rac1 is commonly distributed in tissues, and mainly regulates the formation of scaffolding proteins, membrane ruffles and lamellipodia (108). Rac2 is confined to haematopoietic tissues, and regulates cell adhesion and participates in cellular immune synapse formation (109). Rac3 is a neuron-specific protein that is important for regulating autophagy, inducing the formation of invadopodia and

degrading extracellular matrix (110,111) The Cdc42 subfamily mediates the formation of a third actin-based structure, the filopodia, by binding to Wiskott-Aldrich syndrome protein or neural Wiskott-Aldrich syndrome protein (112). Additionally, Cdc42 serves an important role in cell polarization (113). Rho downstream effectors include ROCK and p140mDia (114). The ROCK family belongs to the AGC family of serine/threonine protein kinases. ROCK1 serves a key role in the formation of actin bundles, actin contractility and stress fibers by mediating the cross-linking of myosin, while ROCK2 is required for phagocytosis and cell contraction and is important in stabilizing the cytoskeleton (115). The Rho/ROCK signaling pathway serves a key role in central nervous system disorders, pulmonary hypertension and other diseases (116,117).

Rho/ROCK signaling pathway and tumor metastasis. Metastasis, the spread of malignant cells to distant organs, represents the ultimate stage of cancer progression and remains a leading cause of cancer-related deaths (107). The majority of cancer deaths result not from the primary tumor but from the secondary lesions in vital organs. This complex process includes a series of sequential events: Primary tumor cells gradually acquire invasive abilities, spread through blood or lymphatic vessels (or directly invade adjacent tissues), and finally colonize and proliferate in distant organs (118). Although different cancer types and molecular subtypes exhibit marked differences in metastasis-driving genes, microenvironmental cues and anatomical dissemination routes, several core cellular processes are shared (119). Among these, cell migration is a core process that is universally present across various tumor types (120). Therefore, targeting the signaling networks that regulate cell motility could offer an effective strategy for the management of metastasis in multiple cancer types (121-123).

The Rho GTPase family functions as a core molecular switch regulating cytoskeletal dynamics and cell movement (124). Growing evidence has highlighted the critical role of this family in tumor invasion and metastasis (123,125). For example, Zhang *et al* (126) demonstrated that inhibition of RhoA suppressed proliferation in gastric cancer cells. In breast cancer, altered Rho GTPase signaling disrupts cytoskeleton architecture in cancer cells, and serves a critical role in cell motility, migration and invasion (127). In cholangiocarcinoma, tumor cells recruit cancer-associated fibroblasts by secreting PDGF-D, which stimulates fibroblast migration by upregulating platelet-derived growth factor receptor β and Rho GTPase, and activating the JNK pathway (128). With the emergence of pharmacological agents targeting the Rho/ROCK signaling axis, particularly selective ROCK inhibitors, this pathway has become a promising target for the development of antimetastatic treatments (123).

4. Regulatory mechanisms of Rho/ROCK signaling pathway-associated lncRNAs in tumor metastasis

lncRNAs regulate tumor metastasis by sponging miRNAs. The subcellular localization of lncRNAs is closely related to their biological functions (129). Unlike the relatively discrete cytoplasmic distribution of mRNAs, most lncRNAs are found in both the nucleus and cytoplasm, with the cytoplasm often being their primary site of localization (130,131). Structurally, lncRNAs contain intronic and other non-coding elements that provide potential binding sites for miRNAs. Through sequence complementarity, lncRNAs can bind intracellular miRNAs and weaken or block their ability to suppress target genes (24). This competitive binding between lncRNAs and miRNAs forms ceRNA networks, indirectly affecting components of the Rho/ROCK signaling pathway (132).

Several studies have demonstrated that lncRNAs influence components of the Rho/ROCK signaling pathway via ceRNA networks, ultimately modulating tumor cell proliferation, invasion, migration and apoptosis (38,133-181) (Table I). For example, the expression of lncRNA DAPK1 is reduced in pancreatic cancer tissues, where it modulates invasion and migration by sponging miR-182 to regulate ROCK1 expression (133). Similarly, Liu *et al* (134) demonstrated that lncRNA ZFAS1 promoted pancreatic cancer metastasis by acting as a sponge for miR-3924 and subsequently regulated the RhoA/ROCK2 pathway to serve a pro-metastatic role in pancreatic cancer. Furthermore, lncRNA NORAD facilitates EMT in pancreatic cancer by binding miR-125a-3p, which regulates the expression of the downstream effector molecule RhoA (135). Liu *et al* (136) reported that lncRNA NEAT1 acted as a ceRNA by sponging miR-382-3p and upregulating ROCK1 in ovarian cancer (OC), and thus, enhanced the metastatic potential. NEAT1 also inhibits the progression of lung adenocarcinoma by sponging miR-490-3p, leading to suppression of the RhoA/ROCK pathway (137). Furthermore, Zhang *et al* (138) found that lncRNA LINC01087 promoted lung adenocarcinoma progression by regulating the miR-514a-3p/CEP55/RhoA/ROCK1 axis.

In osteosarcoma, the lncRNA DANCR sponges miR-335-5p and miR-1972, leading to an increase in ROCK1 expression, which promotes metastasis (139). Similarly, Shao *et al* (140) demonstrated that, in osteosarcoma, lncRNA ZNF281 suppressed invasion by upregulating miR-144 expression, thus suppressing ROCK1 expression. Furthermore, in osteosarcoma, lncRNA SNHG1 is overexpressed and promotes cell metastasis by altering apoptosis and the cell cycle; functional experiments have shown that SNHG1 regulated ROCK1 expression by sponging miRNA-101-3p (141). Additionally, Wang *et al* (142) reported that SNHG5 functioned as a ceRNA for miR-26a and activated the ROCK signaling pathway through the miR-26a/ROCK1 axis to promote osteosarcoma cell malignancy. In HCC, lncRNA CDKN2BAS is upregulated in metastatic tissues and sponges miR-153-5p to increase the expression of Rho GTPase activating protein 18 (ARHGAP18), thus enhancing cell migration (143). Furthermore, lncRNA LINC00607 promotes HCC cell proliferation, migration and invasion through the miR-584-3p/ROCK1 axis (144). Thus, cytoplasmic lncRNAs regulate tumor metastasis by forming ceRNA networks with miRNAs that target Rho/ROCK signaling components.

lncRNAs regulate tumor metastasis by directly binding proteins. In addition to sponging miRNAs by acting as ceRNAs, lncRNAs can also directly bind to specific proteins, including those involved in the Rho/ROCK signaling pathway, and regulate tumor metastasis (182) (Fig. 2). In bladder cancer, lncRNA lnc00892 is downregulated and is positively associated with the prognosis of patients with bladder cancer.

Table I. Relationship between Rho/ROCK signaling pathway-associated lncRNAs and miRNAs in tumor metastasis.

Authors, year	Cancer types	lncRNAs	miRNAs	Target genes	Expression alteration	Functions	(Refs.)
Li *et al*, 2020	Papillary thyroid carcinoma	DLEU1	miR-421	ROCK1	↑	Promotes proliferation and invasion	(145)
Lian *et al*, 2018	Nasopharyngeal carcinoma	AFAP1-AS1	miR-423-5p	RAB11B/LASP1	↑	Promotes invasion and metastasis	(146)
Feng *et al*, 2020		EGFR-AS1	miR-145	ROCK1	↑	Promotes invasion and migration	(147)
Zhou *et al*, 2020	Non-small cell lung cancer	ZFAS1	miR-590-3p	Cdc42	↑	Promotes proliferation	(148)
Song *et al*, 2022		BCYRN1	miR-30b-3p	ROCK1	↑	Promotes proliferation, migration and invasion	(149)
Yang *et al*, 2019	Lung adenocarcinoma	LCAT1	miR-4715-5p	RAC1	↑	Promotes proliferation and invasion	(150)
Xiao *et al*, 2019		MALAT1	miR-429	RhoA	↑	Promotes proliferation, metastasis and invasion	(151)
Zhao *et al*, 2023		NEAT1	miR-490-3p	RhoA	↑	Promotes proliferation and migration	(137)
Zhang *et al*, 2024		LINC01087	miR-514a-3p	CEP55/RhoA	↑	Promotes proliferation, migration and invasion	(138)
Chen *et al*, 2018	Hepatocellular carcinoma	CDKN2BAS	miR-153-5p	ARHGAP18	↑	Promotes migration	(143)
Chen and Zhang, 2019		LINC00339	miR-152	ROCK1	↑	Promotes proliferation and migration	(152)
Wang *et al*, 2021		LINC00491	miR-324-5p	ROCK1	↑	Promotes invasion and metastasis	(153)
You *et al*, 2021		LINC00161	miR-590-3p	ROCK2	↑	Promotes angiogenesis and metastasis	(154)
Dong *et al*, 2023		LINC00607	miR-584-3p	ROCK1	↑	Promotes proliferation, migration and invasion	(144)
Zhou *et al*, 2019	Glioma	H19	miR-15b	Cdc42	↑	Promotes proliferation, migration and invasion	(155)
Guo *et al*, 2019		DANCR	miR-27a-3p	ROCK1	↑	Promotes proliferation and metastasis	(156)
Ma *et al*, 2017		SNHG15	miR-153	Cdc42	↑	Promotes vascular endothelial cell proliferation, migration and tube formation	(157)
Li *et al*, 2020	Glioblastoma	XIST	miR-448	ROCK1	↑	Promotes proliferation, migration and invasion	(158)
Chen *et al*, 2020		LINC00346	miR-340-5p	ROCK1	↑	Promotes proliferation, migration and invasion	(159)
Wang *et al*, 2021		DLGAP1-AS1	miR-515-5p	ROCK1	↑	Promotes proliferation	(160)
Liu *et al*, 2019	Acute myeloid leukemia	LINC00662	miR-340-5p	ROCK1	↑	Promotes proliferation and inhibits apoptosis	(161)
Bai *et al*, 2023	Cervical cancer	LOXL1-AS1	miR-21	RHOB	↓	Inhibits proliferation, migration and invasion	(162)
Chen *et al*, 2020		LINC02381	miR-133b	RhoA	↑	Promotes proliferation and migration	(163)
Wang *et al*, 2018	Osteosarcoma	DANCR	miR-335-5p	ROCK1	↑	Promotes proliferation, metastasis, invasion and EMT	(139)
Shao *et al*, 2020		ZNF281	miR-144	ROCK1	↑	Promotes metastasis and invasion	(140)
Deng *et al*, 2019		SNHG1	miR-101-3p	ROCK1	↑	Promotes proliferation, migration and invasion	(141)
Wang *et al*, 2018		SNHG5	miR-26a	ROCK1	↑	Promotes proliferation, metastasis and invasion	(142)
Yao *et al*, 2020		GAS5	miR-663a	RHOB	↓	Inhibits proliferation, migration and invasion	(164)
Wang *et al*, 2017	Colorectal cancer	TUG1	miR-335-5p	ROCK1	↑	Promotes proliferation, migration and invasion	(165)

Table I. Continued.

Authors, year	Cancer types	lncRNAs	miRNAs	Target genes	Expression alteration	Functions	(Refs.)
Cui *et al*, 2017		HOXA11-AS	miR-124-3p	ROCK1	↑	Promotes proliferation, metastasis and invasion	(166)
Yu *et al*, 2019		XIST	miR-133a-3p	RhoA	↑	Promotes EMT and infiltration of macrophages	(167)
Kong *et al*, 2021		MCF2L-AS1	miR-105-5p	RAB22A	↑	Promotes proliferation, metastasis, invasion and EMT	(168)
Horita *et al*, 2019		UCA1	miR-18a/ miR-182	Cdc42	↑	Enhances sensitivity to oncolytic vaccinia virus	(169)
Tian *et al*, 2021	Oral squamous cell carcinoma	LINC00974	miR-122	RhoA	↑	Promotes proliferation, migration and invasion	(170)
Yang *et al*, 2020	Ovarian cancer	LINC00452	miR-501-3p	ROCK1	↑	Promotes proliferation, migration and invasion	(171)
Yang *et al*, 2021		SNHG20	miR-148a	ROCK1	↑	Promotes proliferation, migration and invasion	(172)
Chen *et al*, 2018		TDRG1	miR-93	RhoC	↑	Promotes proliferation, migration and invasion	(173)
Liu *et al*, 2017		PCA3	miR-106b	RhoC	↑	Promotes proliferation, migration and invasion	(174)
Liu *et al*, 2018		NEAT1	miR-382-3p	ROCK1	↑	Promotes metastasis	(136)
Li *et al*, 2022	Breast cancer	PVT1	miR-148a-3p	ROCK1	↑	Promotes migration and invasion	(175)
Chou *et al*, 2016		MALAT1	miR-1	Cdc42	↑	Promotes migration and invasion	(176)
Chen *et al*, 2021	Esophageal carcinoma	SNHG1	miR-195	Cdc42	↑	Promotes proliferation, migration and invasion	(177)
Wang *et al*, 2020		LIN00080	miR-498	Cdc42	↑	Promotes proliferation and invasion	(178)
Zong *et al*, 2020	Gastric cancer	CTC-497E21.4	miR-22	RhoA	↑	Promotes proliferation and invasion	(179)
Chen *et al*, 2021		DSCR8	miR-137	Cdc42	↑	Promotes proliferation and invasion	(180)
Liu *et al*, 2020	Pancreatic adenocarcinoma	ZFAS1	miR-3924	ROCK2	↑	Promotes metastasis	(134)
Li *et al*, 2017		NORAD	miR-125a-3p	RhoA	↑	Promotes EMT	(135)
Xu *et al*, 2017		DAPK1	miR-182	ROCK1/RhoA	↓	Inhibits proliferation, migration and invasion	(133)
Wang *et al*, 2021		LINC00941	miR-335-5p	ROCK1	↑	Promotes proliferation, migration, invasion and EMT	(181)

Cdc42, cell division cycle 42; CEP55, centrosomal protein 55; EMT, epithelial-mesenchymal transformation; LASP1, LIM and SH3 protein 1; lncRNA, long non-coding RNA; miRNA/miR, microRNA; RAB11B, Ras-related protein Rab-11B; RAB22A, Ras-related protein Rab-22A; RAC1, Rac family small GTPase 1; Rho, Rho family GTPases; RHOB, Ras homolog family member B; ROCK, Rho-associated coiled-coil containing protein kinase.

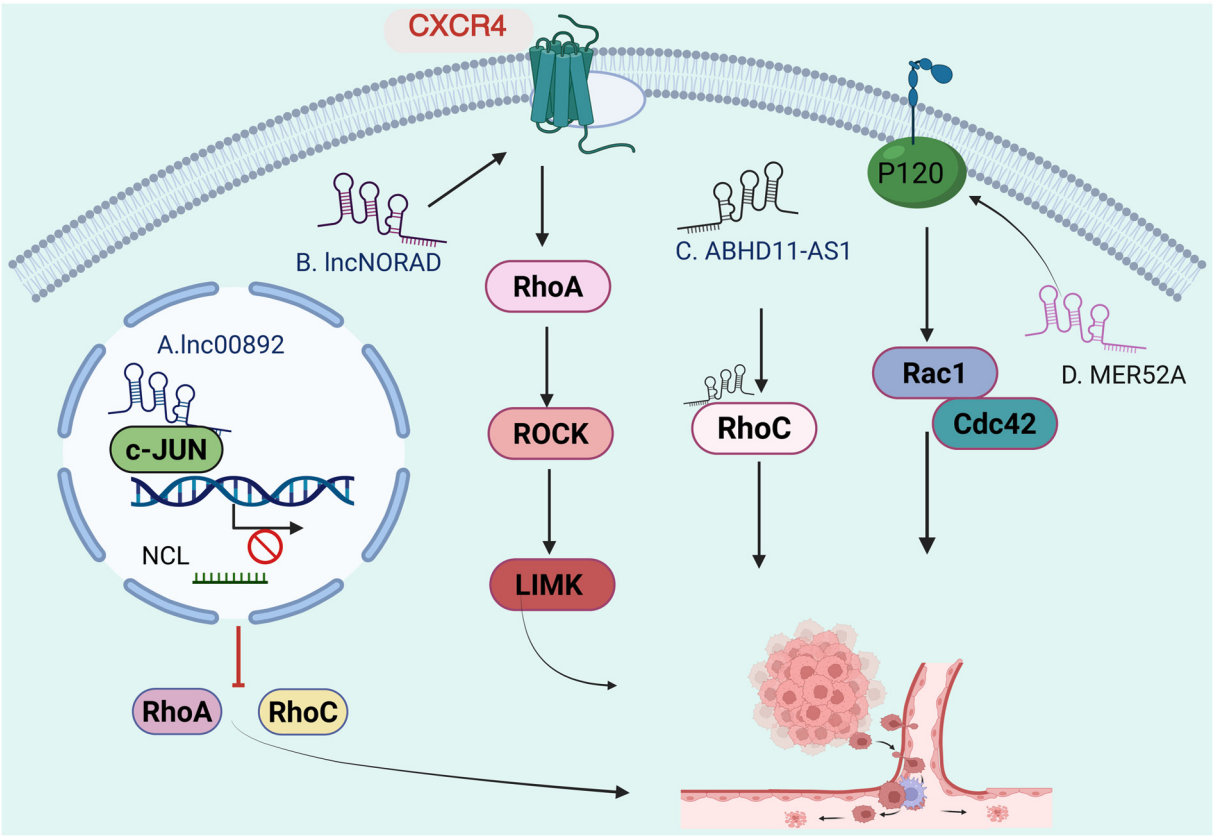

Figure 2. lncRNAs promote tumor invasion and metastasis by regulating the Rho/ROCK signaling pathway. (A) lncRNA lnc00892 inhibits metastasis of bladder cancer by binding to c-Jun, a protein in the activator protein-1 transcription complex, which reduces transcription of the nucleolin gene and the stability of RhoA/RhoC mRNA in the Rho/ROCK signaling pathway. (B) lncRNA NORAD inhibits the RhoA/ROCK signaling pathway by interfering with CXCR4, which inhibits the proliferation, invasion and migration of non-small cell lung cancer cells. (C) lncRNA ABHD11-AS1 binds to RhoC and promotes the proliferation, invasion and migration of ovarian cancer cells. (D) lncRNA MER52A promotes the invasion and metastasis of hepatocellular carcinoma cells by stabilizing P120-catenin and activating the downstream target molecules Rac1 and Cdc42. Cdc42, cell division cycle 42; CXCR, CXC chemokine receptor; LIMK, LIM domain kinase; lncRNA/lnc, long non-coding RNA; NCL, nucleolin; Rac, Ras-related C3 botulinum toxin substrate; Rho, Rho family GTPases; ROCK, Rho-associated coiled-coil containing protein kinase.

Mechanistically, lnc00892 binds to c-JUN, a component of the activating protein-1 transcriptional complex, and reduces nucleolin transcription and affects the stability of RhoA/RhoC mRNAs, which suppresses bladder tumor metastasis (183). In NSCLC, lncRNA NORAD inhibits metastasis by binding to and interfering with CXC chemokine receptor 4, which in turn suppresses the RhoA/ROCK signaling pathway (184). Similarly, in bladder cancer, overexpressed lncRNA KTN1-AS1 recruits EP300, leading to histone H3 lysine 27 acetylation at the KTN1 promoter region. This epigenetic regulation ultimately affects bladder cancer growth and metastasis by mediating the Rho GTPase signaling pathway through Rac1, RhoA and Cdc42 (185). In HCC, overexpression of lncRNA SchLAH (also referred to as BC035072) inhibits distant metastasis. Functional experiments have shown that SchLAH interacts with DNA/RNA-binding protein-fusion sarcoma, regulating the mRNA expression of downstream effector molecules RhoA and Rac1 (186). Dai *et al* (187) used mass spectrometry and reported that a total of 93 upregulated and 352 downregulated lncRNAs were identified in patients with bladder cancer; downregulated lncRNA MUC20-9 bound directly to ROCK1 and inhibited tumor growth, migration and invasion. MUC20-9 was considered to be a potential therapeutic target for bladder cancer. In OC, lncRNA ABHD11-AS1 is upregulated and facilitates metastasis by directly binding to RhoC (188). Similarly, Wu *et al* (189) identified a novel lncRNA, MER52A, which was highly expressed in HCC tissues. Mechanistically, MER52A promoted HCC cell invasion and metastasis by stabilizing P120-catenin, thus activating Rac1 and Cdc42, key downstream Rho-GTPases. Furthermore, high MER52A expression was strongly associated with advanced TNM stage, poor differentiation and reduced overall survival of patients with HCC. In osteosarcoma, AFAP1-AS1 is also highly expressed and directly interacts with RhoC and activates the RhoC/ROCK1/p38MAPK signaling pathway, which in turn exerts oncogenic effects (190).

5. Rho/ROCK signaling pathway-associated lncRNAs as biomarkers and therapeutic targets in tumor metastasis

lncRNAs can serve as novel biomarkers for tumor metastasis. Tumor metastasis remains a major contributor to treatment failure and cancer-related mortality (191). Numerous patients with cancer are diagnosed at intermediate or advanced stages, when clinical symptoms appear; consequently, their prognosis is poorer than that of patients diagnosed earlier (192). Epidemiological data indicate that ~90% of cancer-related deaths are due to tumor metastasis (193). Therefore, identifying

Table II. Rho family GTPases/Rho-associated coiled-coil containing protein kinase signaling pathway-associated lncRNAs as novel tumor biomarkers.

Authors, year	Types of tumor	lncRNAs	Expression	Clinicopathological features	(Refs.)
Li *et al*, 2020	Papillary thyroid carcinoma	DLEU1	↑	TNM stage and lymph node metastasis	(145)
Fan *et al*, 2019	Nasopharyngeal carcinoma	LOC284454	↑	TNM stages and cancer metastasis	(195)
Hu *et al*, 2018		ARHGAP42	↑	Cancer metastasis and metastasis-free survival	(196)
Xiao *et al*, 2019	Lung adeno-carcinoma	MALAT1	↑	TNM stage, tumor size and lymphatic metastasis	(151)
Ma *et al*, 2018		LINC00707	↑	TNM stage, tumor size and lymphatic metastasis	(199)
Fang *et al*, 2020	Hepatocellular carcinoma	MAGI2-AS	↓	Tumor size, differentiation and cancer metastasis	(197)
Zhang *et al*, 2016		AFAP1-AS1	↑	Pathological stage and lymphovascular invasion	(194)
Wang *et al*, 2021		LINC00491	↑	TNM stage and lymph node metastasis	(153)
Wu *et al*, 2020		lncMER52A	↑	TNM stage, differentiation and overall prognosis	(189)
Song *et al*, 2020	Cervical cancer	OIP5-AS1	↑	Tumor size, differentiation, clinical stage and lymph node metastasis	(200)
Shao *et al*, 2020	Osteosarcoma	ZNF281	↑	Clinical stage	(140)
Wang *et al*, 2017		TUG1	↑	TNM stage and distant metastasis	(165)
Cui *et al*, 2017		HOXA11-AS	↑	Clinical stage, distant metastasis and overall prognosis	(166)
Liu *et al*, 2020	Laryngeal squamous cell cancer	CDKN2B-AS1	↑	Overall prognosis, clinical stage and lymph node metastasis	(198)
Chen *et al*, 2020	Glioma	LINC00346	↑	Disease-free survival and overall prognosis	(159)
Pan *et al*, 2019	Ovarian cancer	LINC00339	↑	FIGO stage and differentiation	(201)
Chen *et al*, 2018		PCGEM1	↑	Differentiation	(202)
Chen *et al*, 2018		TDRG1	↑	Differentiation	(173)
Wu *et al*, 2017		ABHD11-AS 1	↑	Tumor stage	(188)
Liu *et al*, 2018		NEAT1	↑	FIGO stage, tumor size, peritoneal metastasis and differentiation	(136)
Yang *et al*, 2020		LINC00452	↑	Recurrence-free survival	(171)
Yuan *et al*, 2020	Bladder cancer	EGFR-AS1	↑	Overall prognosis	(203)
Shang *et al*, 2018	Retinoblastoma	BDNF-AS	↓	Clinical stage and differentiation	(204)
Zong *et al*, 2020	Gastric cancer	CTC-497E21.4	↑	T stage, lymph node metastasis and perineural invasion	(179)
Chen *et al*, 2021		DSCR8	↑	Tumor size, cancer metastasis and tumor stage	(180)
Li *et al*, 2017	Pancreatic cancer	NORAD	↑	Overall prognosis	(135)
Xu *et al*, 2017		DAPK1	↓	Pathological stage and lymph node metastasis	(133)

When the lncRNA was upregulated in the tumor tissue, high expression of the lncRNA was positively associated with adverse clinicopathological features in patients with cancer. When the lncRNA was downregulated in the tumor tissue, low expression of the lncRNA was positively associated with adverse clinicopathological features in patients with cancer. FIGO, International Federation of Gynecology and Obstetrics; lncRNA, long non-coding RNA.

novel and reliable biomarkers and therapeutic targets associated with the metastatic potential is critical to improve early detection and intervention strategies.

Rho/ROCK signaling pathway-associated lncRNAs have increasingly been explored and defined. These lncRNAs not only serve an important role in tumor metastasis but also have a close relationship with the clinical characteristics of patients with tumors (133,135,136,140,145,151,153,159,165, 166,171,173,179,180,188,189,194-204) (Table II). A previous study has demonstrated that lncRNA AFAP1-AS1 was upregulated in patients with HCC, and was associated with pathological stage and lymphovascular interstitial infiltration (194). Multifactorial analysis revealed that AFAP1-AS1 was an independent predictor for overall survival, supporting the hypothesis that AFAP1-AS1 is a potential therapeutic target for HCC. Similarly, lncRNA LOC284454, upregulated in nasopharyngeal carcinoma (NPC), promotes migration and invasion by regulating the cytoskeleton-related Rho/Rac

signaling pathway, and is strongly associated with poor prognosis in patients with NPC (195). Hu *et al* (196) demonstrated that ARHGAP42, another pro-metastatic lncRNA in NPC, was associated with shorter metastasis-free survival. *In vitro* experiments demonstrated that ARHGAP42 promoted the metastasis and invasion of NPC cells, suggesting that it may serve as a tumor migration marker, a prognostic factor or a therapeutic target for patients with NPC. In gliomas, lncRNA LINC00346 is upregulated and is strongly associated with both disease-free and overall survival, suggesting its usage as a potential therapeutic target and therapeutic candidate (159). lncRNA MAGI2-AS3 expression is downregulated in serum samples from patients with HCC with distant metastases compared with in those from non-metastatic patients. Overexpression of MAGI2-AS3 suppresses cell invasion and migration by modulating ROCK2, while its downregulation is associated with distant recurrence following surgical resection (197). In papillary thyroid carcinoma (PTC), lncRNA DLEU1 expression is elevated and associated with lymph node metastasis and clinical stage (145). Follow-up bioinformatics and dual luciferase reporter gene analysis revealed that DLEU1 affects PTC proliferation, survival and metastasis by regulating miR-421 binding to the 3' untranslated region of ROCK1 in TPC-1 cells. Furthermore, lncRNA CDKN2B-AS1 expression is elevated in laryngeal squamous cell carcinoma (LSCC) tissues, and its high expression is positively associated with overall survival, lymph node metastasis and the clinical stage of patients with LSCC (198).

Rho/ROCK signaling pathway-associated lncRNAs may also serve as liquid biopsy biomarkers. Liquid biopsy, an innovative technology, has opened novel pathways for the early diagnosis and prognostic evaluation of cancer. Compared with traditional tissue biopsies, liquid biopsy enables real-time monitoring of disease progression and therapeutic responses (205). Liquid biopsy platforms can simultaneously detect multiple circulating biomarkers, including circulating tumor cells (CTCs), circulating tumor DNA, exosomes, tumor-educated platelets and circulating free RNA. Among these, exosomes, nanosized extracellular vesicles (30-150 nm), serve crucial roles in intercellular communication and carry active molecules such as proteins and nucleic acids (DNA and RNA, including lncRNAs) (206,207). Previous studies have shown that several lncRNAs can be encapsulated in exosomes and transferred from donor cells to recipient cells, where they regulate components of the Rho/ROCK signaling pathway, thereby regulating cancer progression and metastasis (154,208,209). For example, You *et al* (154) demonstrated that exosome-derived lncRNA LINC00161 sponged miR-590-3p to promote HCC metastasis by activating the ROCK signaling pathway, suggesting that LINC00161 may serve as a novel prognostic marker for HCC. Furthermore, Ding *et al* (209) reported that CRC cell-derived exosomal lncRNA BANCR promoted M2 macrophage polarization and enhanced CRC cell proliferation and invasion via the RhoA/ROCK pathway, with insulin like growth factor 2 mRNA binding protein 2 acting as a mediator. Together, these findings suggest that Rho/ROCK pathway-associated lncRNAs, particularly those in exosomes, are emerging as valuable molecular biomarkers with potential applications in liquid biopsy-based diagnostics.

lncRNAs can serve as potential therapeutic targets for tumor metastasis. In addition to their diagnostic utility, Rho/ROCK signaling pathway-associated lncRNAs represent potential therapeutic targets for metastatic cancer (154,210) (Fig. 3). As shown in Fig. 3, You *et al* (154) established a xenograft model in which tail-vein inoculation of HCC cells produced widespread metastases; notably, tail-vein injection of HCC cells with stable LINC00161 knockdown markedly attenuated both tumor initiation and metastatic dissemination *in vivo*, indicating that LINC00161 silencing suppressed HCC tumorigenesis and metastasis. Horita *et al* (210) reported that lncRNA UCA1 is upregulated in OC and enhances oncolytic poxvirus dissemination by modulating the Cdc42 signaling pathway, a key regulator of cytoskeletal reorganization (210). Similarly, UCA1 sponges miR-18a/miR-182 to regulate Cdc42/filopodia, thereby increasing sensitivity to poxvirus-based virotherapy in CRC (169). Clinically, glucocorticoids, such as dexamethasone and prednisolone, can be used in combination with other chemotherapeutic agents for the treatment of hematologic malignancies. In acute myeloid leukemia, lncRNA HOTAIRM1 promotes glucocorticoid resistance by binding to the transcriptional repressor region of ARHGAP18, which in turn activates the RhoA/ROCK1 signaling pathway. This finding has implications for the optimization of glucocorticoid-based leukemia treatment strategies (211). In oral squamous cell cancer, low expression levels of lncRNA LOC441178 are associated with longer postoperative survival, suggesting a potential role as a tumor suppressor and prognostic marker (212). In osteosarcoma, lncRNA CCHE1 expression is higher in patients with distant recurrence after surgery and associated with ROCK1 expression, suggesting that CCHE1 may help guide subsequent chemotherapy or radiotherapy (213). Rho-GTPases and their downstream signaling molecules have been shown to serve a key role in regulating tumor angiogenesis, invasion, metastasis and EMT (214-216). Targeting EMT is considered a relatively promising strategy to inhibit metastasis and improve the survival rate of patients with cancer (191). lncRNA AFAP1-AS1 expression is upregulated in osteosarcoma, and is involved in the growth and metastasis of osteosarcoma by interacting with RhoC and regulating EMT. Therefore, AFAP1-AS1 inhibitors may serve as therapeutic agents in osteosarcoma (190). Furthermore, targeting lncRNAs involved in drug resistance has also shown promise. In cholangiocarcinoma, lncRNA CCAT1 modulates EMT via ROCK2. CCAT1 knockdown increased the susceptibility of an erlotinib-resistant cholangiocarcinoma cell line xenograft to erlotinib *in vivo*, suggesting that targeting the miR-181a-5p/ROCK2 signaling axis could overcome resistance (217). Using a small-molecule microarray, Abulwerdi *et al* (218) identified several chemotypes that bind the MALAT1 element for nuclear expression triplex-binding chemotypes (referred to as MALAT1-IN-1). Notably, compounds 5 and 16 lowered MALAT1 RNA levels and suppressed branching morphogenesis in mammary tumor organoids, establishing triplex-targeting scaffolds as preclinical leads for anticancer therapeutics and molecular probes.

Inhibitors targeting the Rho/ROCK signaling pathway have gained attention in drug research for tumor-targeted therapy (91). These inhibitors of the Rho/ROCK pathway are divided into three categories: Inhibitors of ROCK, geranylgeranyltransferase-1 and 3-hydroxy-3-methyl-glutaryl-CoA

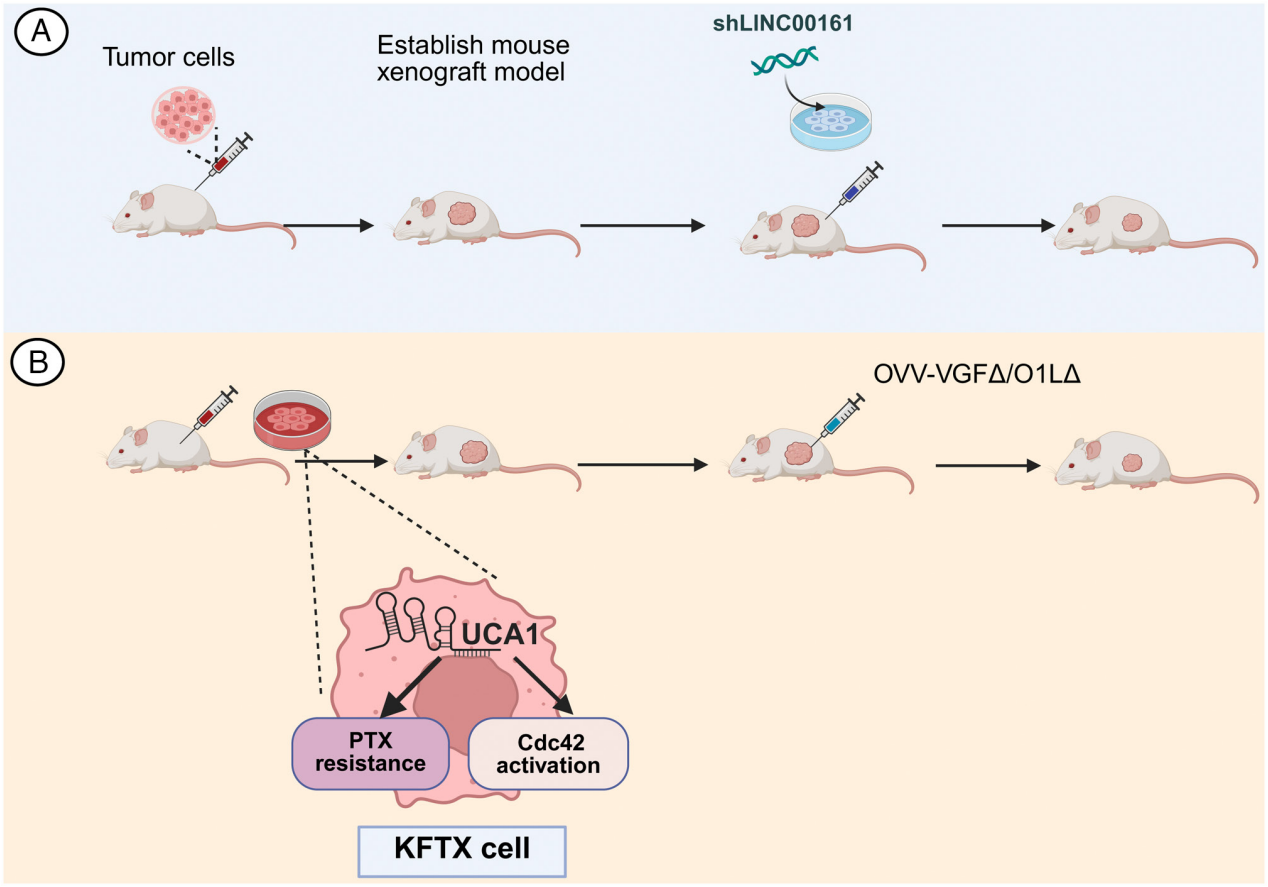

Figure 3. Effect of long non-coding RNAs on tumor metastasis *in vivo*. (A) A mouse xenograft model was established. HCC cells with stable expression of shLINC00161 were injected into the tail vein, and tumor growth and metastasis in mice were observed (154). The study aimed to demonstrate the effect of lncRNAs on HCC metastasis in an *in vivo* model. (B) KFTX OC cells with high expression of UCA1 were intraperitoneally injected into mice, then OVV-VGFΔ/O1LΔ was intraperitoneally injected into mice, and the tumor growth was observed (210). The study aimed to demonstrate the effect of lncRNAs on OC metastasis in an *in vivo* model. Cdc42, cell division cycle 42; HCC, hepatocellular carcinoma; lncRNA, long non-coding RNA; OC, ovarian cancer; OVV-VGFΔ/O1LΔ, oncolytic vaccinia virus-VGF deleted/O1L deletion; PTX, paclitaxel; sh, short hairpin RNA; UCA1, urothelial carcinoma-associated 1.

reductase (219-222). MBQ-167, a newly developed Rac and Cdc42 inhibitor, has been shown to inhibit p21 activated protein kinase signaling, metastatic cell migration and mammosphere growth in TNBC. Its short half-life and low toxicity make this inhibitor a promising candidate for future TNBC therapy (219). NecroX-5 has demonstrated anti-metastatic effects in lung cancer, breast cancer and melanoma models by suppressing the expression of Cdc42, Rac1 and RhoA (220). NSC23766, the first Rac1-specific inhibitor, blocks Rac1 activation by targeting the guanine nucleotide exchange factors. NSC23766 inhibits the invasion and migration of human HCC by interfering with the Rac1/JNK or LIM and cysteine-rich domains 1-Rac1 pathways (221). Inhibition of Rac1 by NSC23766 affects the proliferation and migration of NSCLC (222). Overall, Rho/ROCK pathway inhibitors represent a promising strategy to overcome drug resistance and prevent tumor metastasis. Therefore, the development of Rho/ROCK pathway inhibitors remains a key clinical strategy in cancer therapy.

6. Conclusions and future perspectives

Tumorigenesis is a complex process that involves multiple malignant phenotypes, among which metastasis is a leading contributor to cancer-related mortality. Tumor metastasis involves a series of complex pathophysiological changes, with cytoskeletal reorganization serving a critical role in cancer cell invasion and migration. Among the classical signaling pathways implicated in cytoskeletal reorganization, the Rho/ROCK signaling pathway has attracted considerable attention. Accumulating evidence has also demonstrated that lncRNAs regulate tumorigenic processes, including proliferation, migration, metastasis and resistance to radiotherapy (198,223). With the development of high-throughput sequencing and related technologies, an increasing number of lncRNAs have been identified that interact, either directly or indirectly, with key cytoskeletal regulators such as ROCK1 and ROCK2, mediating tumor metastasis by altering the three-dimensional structure of cancer cells and regulating the reconstruction of the cytoskeleton. As research continues to uncover the specific mechanisms and clinical implications of Rho/ROCK signaling pathway-associated lncRNAs, several promising applications have emerged. First, Rho/ROCK signaling pathway-associated lncRNAs may serve as pathological and liquid biopsy markers for patients with tumors. Unlike protein-based pathological tissue biomarkers, which often reflect downstream changes, the aberrant expression of lncRNAs often occurs earlier than changes at the protein level,

providing greater tissue specificity and expression sensitivity for early cancer diagnosis (224,225). Their tissue specificity, dynamic expression and distinct subcellular localization make them particularly suitable for precise classification and prognosis (226). While tissue biopsy remains the gold standard for diagnosing tumor subtypes and grades, its invasiveness limits its applications for dynamic monitoring of disease progression. Liquid biopsy, on the other hand, offers a minimally invasive monitoring strategy by analyzing circulating tumor components in bodily fluids such as blood and urine (227). In addition, circulating lncRNAs exhibit high stability and resistance to nuclease degradation, offering advantages over other biomarkers such as cell-free DNA (including circulating tumor DNA), CTCs and exosomal RNA (228). Several lncRNAs, including those detectable in liver, colorectal, gastric and prostate cancer, have already shown promise as reliable diagnostic and prognostic markers (229-231). Second, next-generation sequencing, combined with artificial intelligence (AI) and machine learning, has accelerated the collaborative development of basic cancer research and clinical oncology (232-234). Tumor genomic databases constructed from high-throughput sequencing systematically analyze disease-specific expression profiles and tumor microenvironment characteristics. Researchers can leverage advanced machine learning algorithms to deeply mine sequencing data, successfully identifying functional lncRNAs that can serve as biomarkers for personalized treatment decisions or prognostic predictions. Deep learning algorithms enable the precise identification of Rho/ROCK signaling pathway-associated lncRNAs, as well as the prediction of their interacting proteins and binding miRNAs, providing a novel strategy for the development of cancer-specific diagnostic and prognostic biomarkers. Third, despite the potential of RNA-based therapeutics, clinical translation is challenged by issues such as target specificity, low delivery efficiency and *in vivo* stability (235). Notably, while a few miRNA drugs have entered phase II/III clinical trials, the development of inhibitors targeting lncRNAs remains in the preclinical stage (236-238). However, nanotechnology provides a promising strategy to overcome these limitations. Nanomaterials can enable precise targeting at the tissue and even subcellular levels, delivering complex therapeutic molecules to key metastatic sites (such as lymph nodes, liver and lungs) and specific subcellular regions (239). Advances in translational medicine have focused on co-delivering lncRNA inhibitors with small molecule drugs or immune checkpoint inhibitors via nanoparticle systems, synergistically enhancing antitumor efficacy (240-243). Based on this research, the future development of nanoparticle carriers encapsulating Rho/ROCK signaling pathway-associated lncRNA inhibitors may improve the prognosis of patients with metastatic cancer.

Nevertheless, existing research on Rho/ROCK signaling pathway-associated lncRNAs still has several limitations. First, although high-throughput studies have identified numerous dysregulated lncRNAs in tumor tissues (244,245), the specific molecular mechanisms by which Rho/ROCK signaling pathway-associated lncRNAs influence metastasis require further elucidation. Second, Rho/ROCK signaling pathway-associated lncRNAs may regulate gene expression through multiple miRNA sponging interactions or binding proteins, but the specific target axis may not be limited to one or two axes. Third, some lncRNAs implicated in the Rho/ROCK signaling pathway may also regulate other signaling cascades. In addition, the Rho/ROCK signaling pathway mainly promotes tumor metastasis; however, a study has reported that the Rho/ROCK signaling pathway may induce apoptosis (246). Street *et al* (247) demonstrated that the ROCK inhibitor Y27632 could enhance the survival of neuroblastoma cells. Therefore, future studies must validate pathway specificity when proposing drug targets. Fourth, whether Rho/ROCK signaling pathway-associated lncRNAs can be used as therapeutic targets still requires further research at present. Existing studies are only at the stage of animal experiments (135,146,150,153,154), and there is still a long way to go from basic research to clinical application. Therefore, the relationship between Rho/ROCK signaling pathway-associated lncRNAs and tumor metastasis needs to be further clarified. Fifth, although the drug delivery systems of nanoparticle-based lncRNA inhibitors show potential (239-241), further clinical validation is needed to ensure their efficacy, safety and long-term effects of the delivery of nucleic acids in humans.

In summary, lncRNAs associated with the Rho/ROCK signaling pathway are emerging as key regulators of cytoskeletal remodeling and tumor metastasis. Through interactions with miRNAs, proteins and exosomal transport mechanisms, these lncRNAs regulate key processes involved in cancer cell migration, invasion and metastasis. They hold promise not only as novel biomarkers for early cancer diagnosis but also as therapeutic targets to prevent metastasis. Advances in high-throughput sequencing, AI-driven bioinformatics and nanomedicine provide novel opportunities to leverage lncRNAs in personalized treatment strategies and improve prognostic predictions. However, further research is needed to fully elucidate the mechanisms by which lncRNAs regulate the Rho/ROCK pathway and to confirm their clinical applicability. The present review highlights the growing potential of Rho/ROCK signaling pathway-associated lncRNAs as promising diagnostic and therapeutic targets, with the potential to improve the management and prognosis of metastatic cancer.

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Availability of data and materials

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Authors' contributions

HN and XY performed the literature search. HN and XY prepared the first draft of the manuscript. QC, XH and YH wrote and edited the manuscript. HN and YH drew the figures. QH

and CO prepared the tables and were responsible for revising the manuscript. CO obtained funding support. Data authentication is not applicable. All authors reviewed the manuscript, and have read and approved of the final version of the manuscript.

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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