

# Regulation of ROCK1/2 by long non-coding RNAs and circular RNAs in different cancer types (Review)

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**Abstract.** Recent breakthroughs in high-throughput technologies have enabled the development of a better understanding of the functionalities of rho-associated protein kinases (ROCKs) under various physiological and pathological conditions. Since their discovery in the late 1990s, ROCKs have attracted the attention of interdisciplinary researchers due to their ability to pleiotropically modulate a myriad of cellular mechanisms. A rapidly growing number of published studies have started to shed light on the mechanisms underlying the regulation of ROCK1 and ROCK2 via long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in different types of cancer. Detailed analyses have suggested that lncRNAs may be characteristically divided into oncogenic and tumor suppressor lncRNAs. Several exciting recent discoveries have also indicated how different lncRNAs and circRNAs modulate ROCK1/2 and mediate multistep cancer onset and progression. The present review chronicles the major advances that have been made in our understanding of the regulatory role of ROCK1/2 in different types of cancer, and how wide-ranging lncRNAs and circRNAs potentiate ROCK-driven signaling by blocking the targeting activities of tumor suppressor microRNAs.

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## 1. Introduction

Landmark discoveries in molecular oncology have started to shed light both on the underlying causes of cancer onset and progression, and on unmet clinical needs that have hastened re-interpretation of the recently emerging landscape of deregulated signaling pathways. Overexpression of oncogenes, loss of tumor suppressors, intra- and inter-tumor heterogeneity, and drug resistance are among the most extensively studied mechanisms (1-8).

Groundbreaking discoveries from the past decades have paradigmatically shifted the conceptual understanding of non-coding (nc)RNAs from being merely 'junk' transcriptional products to being considered as multifunctional regulators that contextually modulate a number of cellular processes, including transcription, post-transcriptional processing, chromatin remodeling and the regulation of cell signaling cascades. Together with an expansion of knowledge regarding the transcriptome space, it has become evident that a wide variety of RNA transcripts contain different microRNA (miRNA/miR)-binding sites (9-11).

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Rapidly accumulating scientific evidence has enabled a transition to be made from a purely phenomenological to a more detailed mechanistic understanding that all RNA transcripts that contain miRNA-binding sites are able to regulate and communicate with each other by specifically competing for shared miRNAs, and they thereby serve as competing endogenous RNAs (ceRNAs). The diversity and complexity of known ceRNA interactions have increased exponentially with the discovery of an ever-increasing number of oncogenic and tumor suppressor long ncRNAs (lncRNAs) (12-15) and circular RNAs (16-18).

Rho-associated protein kinase (ROCK) is a serine/threonine protein kinase that was identified as a RhoGTP-binding protein, having a molecular mass of ~160 kDa (19,20). To date, two isoforms encoded by two different genes of ROCK (ROCK1 and ROCK2) have been investigated. ROCK1 and ROCK2 have been shown to fulfill major roles in carcinogenesis. These two proteins share an overall sequence similarity in their kinase domains of 92%, and at the amino-acid level, a similarity of 65% (21). Myosin light chain (MLC) is an important downstream substrate of ROCK1 that is phosphorylated by ROCK1 at Ser-19.

The present review exclusively focuses on cancer-related roles of lncRNAs, circular RNAs and ROCK1/2. PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) was independently searched using the keywords 'lncRNA', 'ROCK1' and 'ROCK2'. All the articles were carefully screened and short-listed for inclusion in the manuscript. Only those articles were selected which provided the findings about ncRNAs and ROCK1/ROCK2 exclusively in cancers.

The present review aims to summarize the interplay between ncRNAs and ROCK proteins in different types of cancer. First, a mechanistic overview of the ROCK proteins, and their key role in carcinogenesis, is provided. Subsequently, the review features an exclusive focus on how ncRNAs, particularly lncRNAs and circular RNAs (circRNAs), have been shown to interact with ROCK1 and ROCK2 in a wide variety of different types of cancer.

## 2. Overview of the role of ROCKs in different types of cancer

Transcription factor AP2- $\gamma$  (TFAP2C) has been shown to enhance chemoresistance in colorectal cancer cells by stimulating the expression of ROCK1 and ROCK2 (22). Treatment with 5-fluorouracil induced regression of tumors in mice inoculated subcutaneously with TFAP2C-silenced HCT116 cells. TFAP2C also transcriptionally upregulates ROCK1 and ROCK2 in colorectal cancer cells (Fig. 1). Administration of Y-27632, a ROCK1/ROCK2 inhibitor, caused a considerable decrease in chemoresistance and stemness in TFAP2C-overexpressing cells (22).

FERM domain-containing protein 5 (FRMD5) has been shown to serve as a tumor suppressor, markedly restricting the motility of cancer cells (23). FRMD5 also physically interacts with ROCK1 and inhibits its activity (Fig. 1). The FERM-associated domain of FRMD5 was shown to be critical for interaction with the N-terminal domain of ROCK1. FRMD5 knockdown induced an increase in the phosphorylated levels of MLC, whereas FRMD5 overexpression inhibited the

phosphorylation of MLC (23). Collectively, these findings suggested that FRMD5 is able to structurally interact with ROCK1, interfering with the ROCK1-mediated phosphorylation of MLC. Therefore, FRMD5 may inhibit the migration of lung cancer cells through the inhibition of ROCK1 kinase activity.

6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) has been shown to play a critical role in the metastasis of osteosarcoma (24). In a previous study, ROCK2 downregulation led to an obvious decrease in the migratory and invasive abilities of 143B and U2-OS cells, whereas PFKFB3 upregulation rescued the ROCK2 knockdown-induced effects. Furthermore, ROCK2 inhibition caused a marked decrease in the proliferative capabilities of 143B and U2-OS cells, whereas PFKFB3 upregulation restored the proliferative abilities of the osteosarcoma cells. ROCK2 prevented ubiquitin-mediated degradation of PFKFB3; moreover, ROCK2 inhibition enhanced the process of PFKFB3 ubiquitination, whereas, conversely, overexpression of ROCK2 led to a decrease in the levels of ubiquitinated PFKFB3. ROCK2 inhibition reduced the levels of PFKFB3 in osteosarcoma cells, and finally, lung metastasis was not observed in mice inoculated with ROCK2-silenced osteosarcoma cells (24).

Matrix metalloproteinase 2 (MMP2) is another widely studied protein that is reportedly involved in the positive regulation of metastasis (25). ROCK2 was shown to both prevent degradation of MMP2 and to induce an increase in MMP2 levels in hepatic cellular carcinoma (HCC) cells (25).

Forkhead box M1 (FOXM1) has been shown to modulate ROCK-driven signaling (26). ROCK2 has been reported to be an important FOXM1-binding protein (FOXM1D being a novel isoform of FOXM1). In a previous study, ROCK inhibitors (fasudil and Y-27632) induced actin depolymerization, markedly decrease the levels of phosphorylated MLC and altered the shape of FOXM1D-overexpressing colorectal cancer LoVo and SW-480 cells. FOXM1D-induced activation of ROCK also contributed to the destruction of cell junctions and enhanced cell motility. Downregulation of E-cadherin could also potentially be a contributory factor towards the destruction of cell junctions (26).

The RNA-binding protein Lin28A, which contains a CCHC-zinc finger RNA-binding domain and cold shock domain (27), has also been shown to physically interact with ROCK2 and promote metastasis. The growth rates of tumors in mice injected with ROCK2-silenced ovarian cancer cells were found to be markedly lowered. There was also a marked decrease in the number of metastatic nodules present on lung surfaces of the mice injected with ROCK2-silenced ovarian cancer cells (27).

## 3. Introduction of ncRNAs

Evidence from genome-wide analyses and preclinical studies, supported by recently identified molecular insights, has improved our understanding of the fundamental role of ncRNAs in different types of cancer. miRNAs are small (ranging from 18-24 nucleotides), single-stranded ncRNAs. Ever since their discovery in 1993, it has been generally understood that these small molecules fulfill important roles in gene regulation; their mechanism of action is based on their binding to the

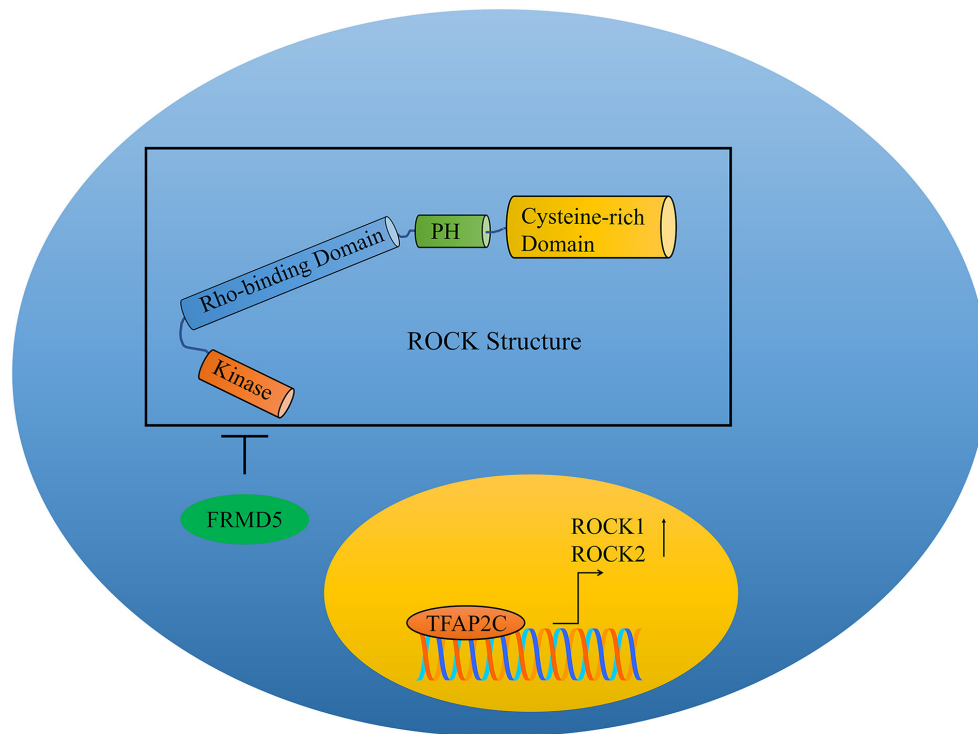


Figure 1. TFAP2C is a transcriptional factor and upregulates the expression of ROCK1 and ROCK2. ROCK is negatively regulated by FRMD5. PH, pleckstrin homology domain; TFAP2C, transcription factor AP2- $\gamma$ ; ROCK, rho-associated protein kinase; FRMD5, FERM domain-containing protein 5. Arrow indicates activation;  $\perp$  indicates inhibition.

3'-untranslated region of mRNA transcripts (28). lncRNAs also regulate gene transcription, although they consist of >200 nucleotides and are transcribed predominantly by RNA polymerase II. Similar to mRNAs, lncRNAs are also characterized by the presence of a 3' polyadenine tail (29). Regarding their role in cancer, both miRNAs and lncRNAs are considered to fulfill key roles in tumorigenesis and in tumor progression. Downregulation of certain tumor suppressor miRNAs is a common finding in breast, gynecological, prostate and lung cancer and brain tumors (30). The term 'oncomiR', which is used for several miRNAs, is indicative of the role of those miRNAs that have oncogenic functions. lncRNAs are also important in cancer, and a greatly expanding list of them has been noted to be correlated with particular types of cancer. A number of reviews have been recently published that provide a comprehensive overview of landmark discoveries in the field of ncRNAs (31-35).

#### 4. Gaze through a 'molecular lens': ROCK-driven signaling

ROCK1-driven downstream signaling has been reported to occupy a central role in enhancing the invasive potential of cancer cells. The upcoming section focuses exclusively on lncRNAs and circRNAs reportedly involved in positive and negative regulation of ROCK in different cancer types.

##### *Positive regulation of ROCK1 by lncRNAs: Tumorigenic role of lncRNAs*

*Cyclin-dependent kinase inhibitor 2B antisense RNA 1 (CDKN2B-AS1).* CDKN2B-AS1 (also known as ANRIL) is an lncRNA that is frequently overexpressed in laryngeal squamous

cell cancer (36). In a study by Liu *et al* (36) CDKN2B-AS1 knockdown was shown to cause the arrest cells in the G<sub>1</sub> phase and to decrease the number of cells in the S phase. Furthermore, the levels of proliferating cell nuclear antigen, an indicator of cell proliferation, were shown to be markedly decreased in cells where CDKN2B-AS1 had been knocked down. However, the levels of apoptosis-associated markers, in particular cleaved caspase-3 and cleaved poly (ADP-ribose) polymerase, were found to be markedly increased. Further experiments revealed that CDKN2B-AS1 knockdown induced apoptosis in AMC-HN-8 cells. Mechanistically, CDKN2B-AS1 regulated ROCK1 by blocking the activity of miRNA-324-5p in AMC-HN-8 cells. Taken together, the molecular analyses clearly suggested that miRNA-324-5p directly targeted ROCK1, whereas CDKN2B-AS1 sequestered miRNA-324-5p away from ROCK1, thereby relieving its inhibitory effects on ROCK1 (36).

*Epidermal growth factor receptor-antisense RNA 1 (EGFR-AS1).* EGFR-AS1 overexpression was shown to enhance the migratory and invasive capabilities of esophageal squamous cell carcinoma (ESCC) cells (37). miR-145 negatively regulated ROCK1 and decreased the invasive potential of ESCC cells. However, EGFR-AS1 sponged away miR-145 and promoted ROCK1 expression. Therefore, EGFR-AS1 was demonstrated to act as an oncogenic lncRNA that effectively potentiated ROCK1 expression (37).

*Opa-interacting protein 5 antisense RNA 1 (OIP5-AS1).* OIP5-AS1 is a cytoplasmic lncRNA (38). OIP5-AS1 inhibition was revealed to exert repressive effects on cell proliferation,

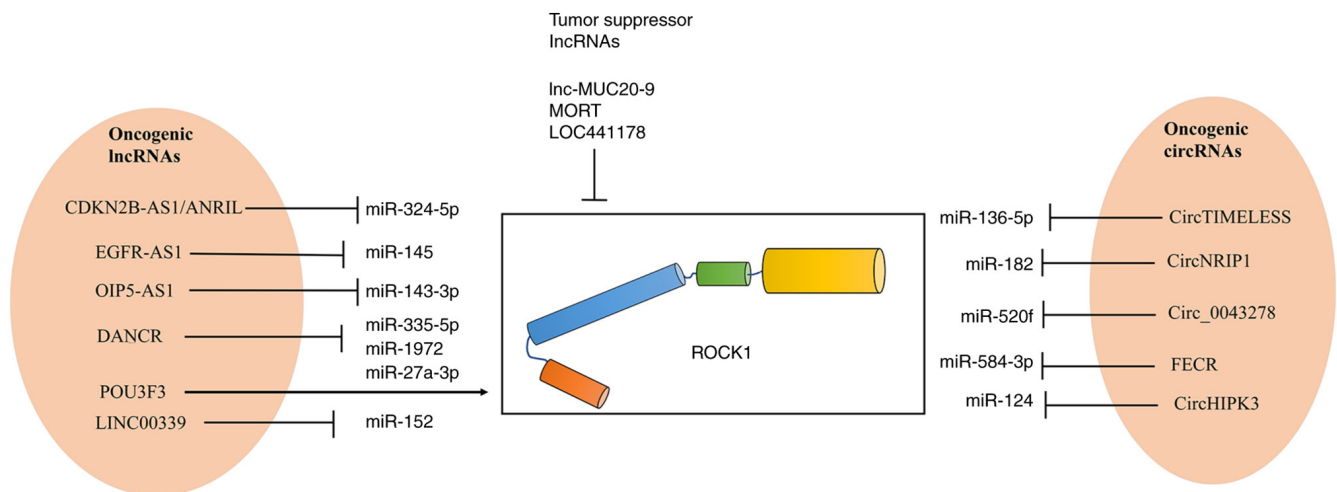


Figure 2. Oncogenic lncRNA- and circRNA-mediated inhibition of the ROCK1-targeting activity of tumor suppressor miRNAs. lncRNA, long non-coding RNA; circRNA, circular RNA; ROCK, rho-associated protein kinase; miR, microRNA; CDKN2B AS1, cyclin dependent kinase inhibitor 2B antisense RNA 1; EGFR AS1, epidermal growth factor receptor antisense RNA 1; OIP5 AS1, opa interacting protein 5 antisense RNA 1; DANCER, differentiation antagonizing non-protein coding RNA; POU3F3, POU domain class 3 transcription factor 2; NEAT1, nuclear paraspeckle assembly transcript 1; MORT, mortal obligate RNA transcript; FEER, FLI1 exonic circRNA. Arrow indicates activation;  $\perp$  indicates inhibition.

and OIP5-AS1 also acted as an inducer of apoptotic cell death in cervical cancer cells. Accordingly, ROCK1 was quantitatively controlled by miR-143-3p; however, OIP5-AS1 could interfere with the miR-143-3p-driven targeting of ROCK1 and potentiate its expression (38).

**Differentiation antagonizing non-protein-coding RNA (DANCER).** DANCER, a novel lncRNA, was found to be overexpressed in cervical cancer cells. Notably, DANCER stimulated the expression of ROCK1 mainly by interfering with the miR-335-5p-induced inhibition of ROCK1 (Fig. 2). Transfection of cervical cancer cells with miRNA-335-5p mimics or targeted inhibition of ROCK1 reversed the effects of upregulated DANCER (39).

Higher expression levels of DANCER were previously reported to be associated with a poor prognosis in clinical patients with osteosarcoma (40). miR-335-5p and miR-1972 both directly targeted ROCK1 mRNA expression. Transfection of cells with mimics of miR-1972 and miR-335-5p led to abrogation of DANCER-induced ROCK1 upregulation. DANCER overexpression also served a vital role in the metastasis of osteosarcoma cells to the lungs in xenografted mice (40).

In addition, DANCER was shown to stimulate both the proliferation and the metastasizing potential of HCC cells, whereas knockdown of DANCER exerted the opposite effects (41). Metastatic nodules on the surface of lungs were found to be considerably decreased in size in a xenograft mouse model established using DANCER-silenced cancer cells. Collectively, these experiments revealed that DANCER could act as a ceRNA, sequestering away miR-27a-3p to potentiate the expression of LIM domain kinase 1 (LIMK1) in HCC cells. DANCER activated the ROCK1/LIMK1/COFILIN1 signaling axis via inhibition of miR-27a-3p (41).

**POU domain class 3 transcription factor 2 (POU3F3).** POU3F3 acts as an oncogenic lncRNA, promoting an increase in the expression level of ROCK1 in prostate cancer cells (42).

POU3F3 overexpression has also been shown to induce an increase in ROCK1 expression in prostate cancer cells (42).

**Nuclear paraspeckle assembly transcript 1 (NEAT1).** High-grade endometrioid and serous endometrial cancer are therapeutically resistant (43). NEAT1, an oncogenic lncRNA, was observed to be overexpressed in this cancer type; it acted as a molecular sponge and sequestered miR-361 away from STAT3. The orchestrated interaction of a myriad of oncogenic proteins was shown to induce drug resistance in endometrial cancer. The addition of miR-361 mimics significantly decreased paclitaxel resistance, whereas STAT3 overexpression enhanced paclitaxel resistance in SPAC-1-L and HI cells. Furthermore, NEAT1 inhibition resulted in decreases in the levels of ROCK1, STAT3, VEGF-A and WNT7A in SPAC-1-L cells (43).

**LINC00339.** LINC00339 has been shown to potentiate ROCK1 expression (44). miR-152 directly targeted ROCK1, although LINC00339 was shown to protect ROCK1 from being targeted by miR-152 in HCC cells. The metastatic spread of LINC00339-overexpressing HCC cells was also observed to be notably higher. However, LINC00339-silenced HCC cells did not metastasize to the lungs (44).

**Small nucleolar RNA host gene 1 (SNHG1).** SNHG1 was shown to interact with a tumor suppressor miRNA-101-3p, blocking its activity and potentiating ROCK1 expression (45). Levels of ROCK1, phosphorylated (p)-phosphoinositide 3-kinase (PI3K) and p-AKT were also found to be lowered in osteosarcoma cells transfected with miR-101-3p mimics; however, miR-101-3p knockdown by miR-101-3p inhibitor led to a robust increase in the levels of ROCK1, p-PI3K and p-AKT (45).

**Taurine-upregulated gene 1 (TUG1).** TUG1 has been shown to effectively sequester miR-145-5p away from ROCK1,

also stimulating ROCK1 expression (46). TUG1 suppression resulted in suppression of RhoA, ROCK1, MMP2 and MMP9 in laryngeal carcinoma cells (46).

*E2F-mediated cell proliferation enhancing lncRNA (EPEL).* EPEL has also been shown to promote ROCK1 expression (47). EPEL overexpression promoted both the migratory and invasive capabilities of osteosarcoma cells, and induced ROCK1 overexpression (47).

*Terminal differentiation-induced non-coding RNA (TINCR).* TINCR was also found to promote the migration and invasion of HCC cells (48). ROCK1 is a target of miR-214-5p. miR-214-5p targeted ROCK1 and markedly decreased the invasive potential of HCC cells; however, TINCR protected ROCK1 from miR-214-5p-mediated targeting (48).

*LINC00452.* LINC00452 was shown to promote ovarian carcinogenesis by antagonizing the miR-501-3p-mediated targeting of ROCK1. Additionally, LINC00452 physically interacted with ROCK1, thereby protecting it from ubiquitination. LINC00452 overexpression significantly promoted tumor growth in a xenograft model, although the simultaneous inhibition of ROCK1 markedly decreased the growth of the tumors in spite of the overexpression of LINC00452. Tumors developed from CaOV3 cells with overexpression of LINC00452, but where ROCK1 had been knocked down, were observed to be smaller in size (49).

*LINC01087.* LINC01087 has also been shown to act as an oncogenic lncRNA, as it effectively enhanced ROCK1 expression by blockade of miR-335-5p-mediated targeting of ROCK1 (50).

*KCNMB2 antisense RNA 1 (KCNMB2-AS1).* Ectopically expressed miR-374a-3p was shown to effect a significant reduction in the luciferase activity of ROCK1 in SK-MES-1 and H460 cells. However, KCNMB2-AS1 induced an increase in the expression of ROCK1 by sponging away miR-374a-3p. A marked decrease in the growth of the tumors developed from KCNMB2-AS1-silenced H460 cells was also observed. The level of KCNMB2-AS1 was notably decreased, whereas the expression of miR-374a-3p was elevated, in the tumor tissues of mice inoculated with KCNMB2-AS1-silenced H460 cells (51).

*LINC00346.* LINC00346 is capable of sponging miR-340-5p away from ROCK1 in glioma cells. In one study, tumor growth rates were found to be markedly decreased in mice subcutaneously injected with LINC00346-silenced U251 cells (52).

*LINC00941.* LINC00941 was found to enhance the metastatic potential of pancreatic cancer cells. miR-335-5p was shown to target ROCK1 and inhibit the metastatic spread. However, LINC00941 caused blockade of the miR-335-5p-mediated targeting of ROCK1. Tumors derived from LINC00941-silenced PANC-1 cells were also observed to be smaller in size. LINC00941 inhibition resulted in a marked decrease in the number of metastatic lesions on the surface of the liver and lungs of tumor-bearing mice (53).

## 5. Negative regulation of ROCK1 by lncRNAs

Lnc-MUC20-9 has been demonstrated to act as a tumor suppressor lncRNA, inhibiting the migratory potential of bladder cancer cells (54). Lnc-MUC20-9 has been reported to bind to ROCK1, thereby inhibiting its expression. Tumor growth was shown to be markedly decreased in mice transplanted with Lnc-MUC20-9-overexpressing bladder cancer cells (54).

Mortal obligate RNA transcript (MORT) is a tumor suppressor lncRNA (55). Overexpression of MORT markedly decreased the proliferative ability of oral squamous cell carcinoma (OSCC) cells, and led to the downregulation of ROCK1. However, ROCK1 overexpression led to a significant increase in the proliferative ability of the OSCC cells. Furthermore, ROCK1 overexpression interfered with the inhibitory effects of MORT on the proliferation of OSCC cells (55).

LOC441178 also negatively regulated ROCK1 in OSCC cells (56). LOC441178 knockdown was shown to induce an increase in the ROCK1 levels (56).

## 6. Regulation of ROCK2 by lncRNAs: Oncogenic role

miR-4435-2HG, an oncogenic lncRNA, was shown to promote the expression of ROCK2, and inhibited the apoptotic death of ovarian cancer cells (57). miR4435-2HG overexpression induced the upregulation of ROCK2 in ovarian cancer UWB1.289 cells (57). Similarly, other lncRNAs that promote carcinogenesis have also been identified in ovarian cancer. TTN-AS1 blocked the ROCK2-targeting activity of miR-139-5p in SKOV3 cells, and the sizes and masses of subcutaneous tumors were observed to be significantly decreased in mice subcutaneously injected with TTN-AS1-silenced SKOV3 cells (58).

ZNFX1 antisense RNA 1 (ZFAS1) was also shown to promote the expression of ROCK2 by interfering with miR-3924-mediated targeting of ROCK2 in pancreatic cancer cells (59). Significant inhibition of liver metastasis was observed, although the extent of lung metastasis was not shown to be decreased in mice transplanted with ZFAS1-depleted SW1990 cells (59). These findings are of note, and future studies should concentrate on the identification of the underlying mechanisms.

EGFR-AS1 has also been found to be frequently overexpressed in bladder cancer cells (60). In bladder cancer HT-1197 cells, miR-381 directly targeted ROCK2 and decreased the invasive capability of the cells. miR-381-mediated targeting of ROCK2 was inhibited by EGFR-AS1 (60). LINC01638 overexpression induced ROCK2 upregulation in bladder cancer cells, although overexpression of ROCK2 did not exert a significant influence on LINC01638 expression (61). Overexpression of LINC01638 and ROCK2, however, led to an increase in both the migratory and invasive potentials of the bladder cancer cells. More importantly, ROCK2 inhibition abrogated the LINC01638-induced increase in the invasive potential of the cancer cells (61).

## 7. Tumor suppressor lncRNAs

HCC is a multifaceted disease, and lncRNAs have been shown to fulfill fundamental roles in the onset and progression of



cancer. Tumor suppressor lncRNAs have major roles with respect to inhibiting tumor invasion and spread. Overexpression of MAGI1 antisense RNA 3 (MAGI2-AS3) has been shown to induce the downregulation of ROCK2 (62). MAGI2-AS3 overexpression decreased the cell migratory and invasion rates, whereas ROCK2 abolished the effects of overexpression of MAGI2-AS3 (62). Taken together, these findings clearly suggested that the MAGI2-AS3-induced decrease in the cell migration and invasion rates was reversed by overexpression of ROCK2. Similarly, HAND2 antisense RNA 1 (HAND2-AS1) was found to induce downregulation of ROCK2 in HCC cells. HAND2-AS1 overexpression inhibited, whereas overexpression of ROCK2 potentially enhanced, the migratory and invasive abilities of HCC cells (63).

### 8. circRNA-mediated regulation of ROCK1: Cancer-promoting roles of circRNAs and ROCK1

Recent advancements in circRNA-specific computational tools and high-throughput RNA sequencing have greatly helped in the development of state-of-the-art techniques for identification of circRNAs. circTIMELESS (hsa\_circ\_0000408) has been shown to serve as an oncogenic circRNA in lung squamous cell carcinoma (64). miR-136-5p negatively regulated ROCK1, although circTIMELESS antagonized the miR-136-5p-mediated targeting of ROCK1 and stimulated its expression (Fig. 2). Tumor growth was also markedly decreased in experimental mice injected with circTIMELESS-silenced cancer cells (64).

circNRIP1 has also been demonstrated to promote the expression of ROCK1, thereby enhancing carcinogenesis. The luciferase activity of ROCK1-expressing MGC-803 and AGS cells was significantly inhibited by overexpression of miR-182 (65). circNRIP1 sequestered miR-182 away from ROCK1, and promoted the expression of ROCK1 in gastric cancer cells. A marked decrease in Bcl-2 levels, with a concomitant increase in Bax levels, was also identified in circNRIP1-silenced gastric cancer cells (65).

circ\_0043278 is another oncogenic circRNA that has been reported to be involved in enhancing the proliferative and migratory capabilities of non-small cell lung cancer (NSCLC) cells (66). miR-520f acted as a tumor suppressor and inhibited the growth and migration of NSCLC cells; however, miR-520f-mediated targeting of ROCK1 was impaired by circ\_0043278 (66).

FLI1 exonic circRNA (FEER) has been shown to have critical roles in the migration and metastasis of cancer cells (67). FEER relieved the inhibitory effects of miR-584-3p on ROCK1 by sponging the miRNA away from its target. ROCK1 was found to be upregulated in miR-584-3p inhibitor-transfected SCLC cells. FEER silencing induced a decrease in the levels of ROCK1 in NCI-H446 and NCI-H1688 SCLC cells, whereas ectopic expression of FEER caused a marked upregulation of ROCK1 in NCI-H446 cells. Development of the tumors was observed to be markedly decreased in mice injected with FEER-silenced NCI-H446 cells. In addition, metastatic spread to the lungs and liver was significantly suppressed in mice inoculated with FEER-silenced NCI-H446 cells (67).

circHIPK3 has been shown to promote the proliferation of gallbladder cancer cells (68). Ectopic overexpression of circHIPK3 promoted the proliferative ability of gallbladder

cancer cells, whereas an enforced expression of circHIPK3 exerted inhibitory effects on the levels of miR-124. ROCK1 was directly targeted by miR-124, although circHIPK3 was able to impair the tumor-suppressive effects exerted by miR-124 (68).

circ0001591 has also been shown to enhance the metastasizing potential of melanoma cells. Overexpression of circ0001591 caused an increase in the levels of PI3K and p-AKT. ROCK1 was directly targeted by miR-431-5p in melanoma cells. Furthermore, circ0001591 antagonized the miR-431-5p-mediated targeting of ROCK1 in melanoma cells (69). circ\_101141 has also been shown to serve as an oncogenic circRNA, blocking miR-1297-mediated inhibition of ROCK1. The sizes of tumors were markedly decreased in mice injected with circ\_101141-silenced Hep3B cells (70).

### 9. circRNAs and ROCK2 as tumor suppressors

Cisplatin-resistant gastric cancer cell lines have been demonstrated to have significantly lower ROCK2 and circCUL2 levels, and significantly higher miR-142-3p levels. In a previous study, circCUL2 acted as a tumor suppressor circRNA, sequestering away miR-142-3p. miR-142-3p was shown to act as an oncogenic miRNA, directly targeting ROCK2 and promoting carcinogenesis. Extensive tumor shrinkage was observed in mice injected with circCUL2-overexpressing SGC-7901 cells (71).

### 10. Cancer-promoting roles of circRNAs and ROCK2

circ\_HN1 has been demonstrated to promote cancer progression by blocking the targeting of ROCK2 by miR-302b-3p. Tumors derived from circ\_HN1-silenced HGC-27 cells were found to be smaller in size. The levels of circ\_HN1 and ROCK2 were also shown to be decreased in the tumor tissues of xenograft model mice established with circ\_HN1-silenced HGC-27 cells (72).

### 11. Concluding remarks

The present review has critically discussed recent information associated with the regulation of ROCK1/2 by lncRNAs and circRNAs, providing an updated translational perspective that may be useful in terms of guiding the selection of optimal targets and disease-tailored interventions. ROCK-driven signaling has been shown to serve as a linchpin during various steps of cancer. Pharmacological and pharmaceutical researchers have started to focus their attention on the design and development of chemical inhibitors for ROCK1 and ROCK2. Nevertheless, much further research needs to be done, since sufficient experimental evidence associated with epigenetic regulation of ROCK1/2 in different types of cancer remains lacking. However, a series of cutting-edge studies have started to shed light on the post-transcriptional regulation of ROCK1/2 by lncRNAs and circRNAs in different types of cancer. These aspects are of note and allow researchers to analyze various lncRNAs that are involved in the positive regulation of ROCK1/2 in different cancer types. lncRNAs regulate the expression of ROCK1/2 by interfering with the miRNA-mediated targeting of ROCK, and this knowledge has already been carried forward to tests conducted in preclinical

models. Therefore, there is a need to pursue the interplay between ncRNAs and ROCK1/2 more comprehensively in order for scientists to critically evaluate the efficacy of ROCK inhibitors in different types of cancer.

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### Availability of data and materials

Not applicable.

### Authors' contributions

RZ and HN collected raw data after extensive browsing through Scopus and PubMed. JS, RM and EP shortlisted the most relevant and English language based research articles for inclusion in this review. AAF, RA, MG and RB wrote the manuscript. RZ and HN constructed the figures. JS, RM and EP carefully edited the manuscript for technical errors and accurate scientific presentation. All authors have read and approved the final 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 do not have any competing interests.

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