Implication of non-coding RNA-mediated ROCK1 regulation in various diseases

Soudeh Ghafouri-Fard1, Yadollah Poornajaf2, Bashdar Mahmud Hussen3,4, Atefe Abak5, Hamed Shoorei6,7, Mohammad Taheri8,9* and Guive Sharifi10*

1Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 2Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran, 3Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil, Iraq, 4Center of Research and Strategic Studies, Lebanese French University, Erbil, Iraq, 5Men’s Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 6Clinical Research Development Unit of Tabriz Valiasr Hospital, Tabriz University of Medical Sciences, Tabriz, Iran, 7Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran, 8Institute of Human Genetics, Jena University Hospital, Jena, Germany, 9Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 10Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Rho Associated Coiled-Coil Containing Protein Kinase 1 (ROCK1) is a protein serine/threonine kinase which is activated upon binding with the GTP-bound form of Rho. This protein can modulate actin-myosin contraction and stability. Moreover, it has a crucial role in the regulation of cell polarity. Therefore, it participates in modulation of cell morphology, regulation of expression of genes, cell proliferation and differentiation, apoptotic processes as well as oncogenic processes. Recent studies have highlighted interactions between ROCK1 and several non-coding RNAs, namely microRNAs, circular RNAs and long non-coding RNAs. Such interactions can be a target of medications. In fact, it seems that the interactions are implicated in therapeutic response to several medications. In the current review, we aimed to explain the impact of these interactions in the pathoetiology of cancers as well as non-malignant disorders.

KEYWORDS
miRNA, lncRNA, ROCK1, expression, biomarker

Introduction

Rho Associated Coiled-Coil Containing Protein Kinase 1 (ROCK1) human gene is located on 18q11.1. The protein serine/threonine kinase encoded by this gene is activated upon binding with the GTP-bound form of Rho. Functioning as a small GTPase, Rho can regulate construction of focal adhesion molecules and stress fibers in fibroblasts, establishment of adhesion molecules that induce platelet aggregation and lymphocyte adhesion. Activity of Rho is regulated through binding with GDP or GTP. ROCK1 is regarded as an important modulator of actin-myosin contraction and stability. Moreover, it has a crucial role in the regulation of cell polarity. Therefore, it participates in...
modulation of cell morphology, regulation of expression of genes, cell proliferation and differentiation, apoptotic processes as well as stemness and oncogenic processes (Rath and Olson, 2012).

In fact, members of the Rho family such as RhoA and RhoC can enhance production of actomyosin contractile force via ROCK1- and ROCK2-mediated phosphorylation of several downstream targets, such as LIMK1/2 and MLC (Riento and Ridley, 2003). ROCK proteins have catalytic kinase domain responsible for the substrate promiscuity, a coiled-coil region, and a split PH domain that is intersected by the protein kinase C conserved region 1 (Rath and Olson, 2012). A single Rho-binding domain (RBD) exists inside the coiled-coil region of both ROCK proteins (Fujisawa et al., 1996), in addition to several Rho GTPases-interacting regions which have been identified within the coiled-coil region of ROCK1, which contributes to its localization (Blumenstein and Ahmadian, 2004).

Recent studies have highlighted interactions between ROCK1 and several non-coding RNAs, namely microRNAs (miRNAs), circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs). In the current review, we aimed to explain the impact of these interactions in the pathoetiology of cancers as well as non-malignant disorders. Figure 1 illustrates that aberrant expression of various ncRNAs could contribute in adversely modulating the ROCK1 signaling pathway, with consequent triggering several kinds of cancers as well as a number of non-malignant conditions.

**ROCK1-interacting microRNAs in non-malignant conditions**

Interactions between miRNAs and ROCK1 have been assessed in different disorders, including metabolic...
syndrome, diabetes, acute lung injury, endometriosis, LPS-induced lung endothelial hyperpermeability and pneumonia. These miRNAs mainly bind to 3′ UTR of ROCK and suppress its expression. Thus, the underlying mechanisms of such interactions are shared between these disorders. For instance, Guo et al. showed up-regulation of levels of a ROCK1-targeting miRNA, namely miR-324-5p, in the circulation of patients with hyperglycemia or hyperlipidemia. Investigations in an animal model of diabetes type II and obesity also verified over-expression of miR-324-5p both in the peripheral blood and hepatic tissue. Up-regulation of this miRNA results in reduction of activity of the AKT/GSK pathway and enhancement of lipid buildup. Moreover, ROCK1 silencing has resulted in deterioration of lipid and glucose metabolism. Notably, ROCK1 silencing has overturned the effect of miR-324-5p inhibition on amelioration of glucose and lipid metabolism. Taken together, miR-324-5p was shown to regulate metabolism of glucose and lipid through influencing expression of ROCK1 (Guo et al., 2020). Another miRNA, miR-217, was shown to affect immune responses and proliferative and migratory potential of vascular smooth muscle cells (VSMCs) in high-glucose condition through modulation of ROCK1. Expression of miR-217 was increased in high glucose-exposed VSMCs as well as aorta VSMCs obtained from diabetic animals. Mechanistically, miR-217 can induce cell cycle arrest, inhibit of proliferation, reduce migration, and enhance apoptosis of VSMCs in high glucose conditions through regulation of expression of ROCK1 (Zhou et al., 2021).

Another experiment in an animal model of sepsis-induced acute lung injury demonstrated the effect of miR-539-5p in alleviation of lung injury through modulation of expression of ROCK1. miR-539-5p could also decrease apoptotic potential and inflammatory responses in LPS-treated pulmonary microvascular endothelial cells of mice. The effects of miR-539-5p in inhibition of caspase-3 activity and inhibition of release of inflammatory cytokines have been reversed by up-regulation of ROCK1 (Meng et al., 2019).

Another study revealed the down-regulation of miR-202-3p expression in primary endometrial stromal cells obtained

| Type of diseases | miRNA/ expression pattern | Sample | Cell line | Target/ Pathway | Molecular mechanism | References |
|------------------|---------------------------|--------|-----------|----------------|---------------------|------------|
| Metabolic Syndrome | miR-324-5p (Up) | Peripheral blood samples: hyperglycemia (n = 102), hyperlipidemia (n = 106), healthy control (n = 110), db/db and C57BL/6 J mice | HepG2 | ROCK1, AKT, GSK, PEPCK, FAS, ACC | Enhancing peripheral blood miR-324-5p by suppressing ROCK1 could promote the risk of metabolic syndrome | Guo et al. (2020) |
| Diabetes | miR-217 (Down) | SD rats | VSMCs | ROCK1, TNF-α, IL-6, IL-1β | Up-regulation of miR-217 could alleviate high-glucose-induced VSMCs dysfunction via targeting ROCK1 | Zhou et al. (2021) |
| ALI | miR-539-5p (Down) | male C57BL/6 mice | MPVECs | ROCK1 | miR-539-5p could alleviate sepsis-induced ALI by targeting ROCK1 | Meng et al. (2019) |
| Endometriosis | miR-202-3p (Down) | Endometriosis patients (n = 27), health control (n = 31) | ESCs | ROCK1 | Dysregulation of miR-202-3p could affect migration and invasion of ESCs in endometriosis via targeting ROCK1 | Zhang et al. (2020a) |
| LEHP | miR-144 (-) | C57BL/6 J male mice | CC-3156, CC-4147 | ROCK1, TNF-α, IL-1β | miR-144 could protect against LPS-induced LEHP via regulating ROCK1 | Siddiqui et al. (2019) |
| Pneumonia | miR-495 (Down) | Pneumonia patients (n = 28), health control (n = 20) | 293T, WI-38 | ROCK1, Caspase-3, Be-2, Bax, IL-1β, IL-6, TNF-α | miR-495 could inhibit LPS-induced WI-38 cells apoptosis and inflammation by targeting ROCK1 | Zhang et al. (2020b) |
| — | miR-599 (-) | — | HUVECs, 293T | ROCK1, JAK2, STAT3, TNF-α, Caspase-3, p53 | miR-599 could regulate LPS-mediated apoptosis and inflammatory responses of HUVECs by targeting ROCK1 | Wang et al. (2020a) |
| — | miR-135a (Down) | SD rats | TSPCs, 293T | ROCK1, p16 | miR-135a could modulate tendon/stem/progenitor cell senescence via suppressing ROCK1 | Chen et al. (2015) |
| Type of cancer | miRNA/ expression pattern | Sample | Cell line | Target/Pathway | Molecular mechanism | References |
|---------------|--------------------------|--------|-----------|----------------|---------------------|------------|
| NSCLC         | miR-135a (Down)          | NSCLC patients (n = 60) | HCC366, HCC27, NCI-H224, MRC-5, NCI-H1770 | ROCK1, Bax, Bcl-2, Caspase-3, Vimentin, E/N-cadherin | miR-135a could inhibit malignant proliferation and diffusion of NSCLC by down-regulation of ROCK1 protein | Zhao et al. (2020) |
| NSCLC         | miR-148b (Down)          | 16 pairs of NSCLC and ANTs | HBE1, H1299, H1650, H460, A549 | ROCK1 | miR-148b by regulating ROCK1 could inhibit proliferation and increase radiosensitivity of NSCLC. | Luo and Liang, (2018) |
| NSCLC         | miR-335-5p (Down)        | NSCLC tissue samples (n = 60) | 16HBE, A549, HCC27, H1299, H1975, SPC-A1, H226, H1650, H460 | ROCK1, TGF-β1, N-cadherin, Snail, Vimentin, MMP2 | miR-335-5p via targeting ROCK1 can inhibit TGF-β1-induced EMT in NSCLC. | Du et al. (2019) |
| OS            | miR-101 (Down)           | 20 pairs of OS and ANTs | MG63, U2OS, OSM321, SFOB1.19 | ROCK1, PTEN, JAK1, STAT3, PI3K/AKT | miR-101 can inhibit proliferation, invasion, and migration in OS cells by targeting ROCK1 | Jiang et al. (2017) |
| OS            | miR-139 (Down)           | OS (n = 25), non-tumor tissue samples (n = 19) | HOS, SAOS2, MG-63, U2OS, OSM321, SFOB1.19 | ROCK1, β-catenin, E-Cadherin, p53 | miR-139 by targeting ROCK1 could inhibit OS cell proliferation and invasion | Fan et al. (2019) |
| OS            | miR-144 (Down)           | 51 pairs of OS and ANTs | SFOB1.19 | ROCK1, RhoA | miR-144 could inhibit tumor growth and metastasis in OS via dual-suppressing the RhoA/ROCK1 axis | Liu et al. (2019) |
| OS            | miR-202-5p (Down)        | 36 pairs of OS and ANTs | U2OS, MG-63, HOS, SFOB1.19 | ROCK1 | miR-202-5p could inhibit the migration and invasion of OS cells by targeting ROCK1 | Li et al. (2018) |
| OS            | miR-150 (Down)           | 40 pairs of OS and ANTs | cSaO2, U2OS, MG63, SFOB1.19 | ROCK1 | miR-150 could suppress cell proliferation, migration, and invasion of OS by targeting ROCK1 | Li et al. (2017a) |
| OS            | miR-335 (Down)           | OS (n = 91), non-tumor tissue samples (n = 47) | - | ROCK1 | miR-335 could influence tumor progression and prognosis of this cancer by targeting ROCK1 | Wang et al. (2017) |
| OS            | miR-214-5p (Down)        | 48 pairs of OS and ANTs | SFOB, HOS, MG63, G293, SAOS2, U2OS | ROCK1 | miR-214-5p can suppress proliferation and invasion of OS cells by targeting ROCK1 | Zhang et al. (2017) |
| EWS           | miR-1246-3p, miR139-5p, miR-584-5p, (Down) | 19 pairs of melanoma and adjacent normal tissues | SK-ES-1, RD-ES | ROCK1 | Dysregulation of microRNAs could contribute to tumor progression of EWS by targeting ROCK1 | Roberto et al. (2020) |
| AML           | miR-592 (Down)           | 94 pairs of AML and ANTs | H5-5, HL-60, THP-1, NB4 | ROCK1, MTHFD2 | miR-592 could function as a tumor suppressor in AML by targeting ROCK1 | Xia et al. (2019) |
| CML           | miR-497-5p (Down)        | Peripheral blood samples of CML patients (n = 37) and normal control group (n = 30) | K562, NHL | ROCK1 | miR-497-5p could induce apoptosis in K562 cells by down-regulation of ROCK1 | Chen et al. (2021a) |
| CRC           | miR-199a-5p (Down)       | 40 pairs of CRC and ANTs, nude mice | SW480, HT29, LoVo, LS174T, SW620, HCT116, NCM460 | ROCK1, STAT3, PI3K/AKT | miR-199a-5p could inhibit the growth and metastasis of CRC by targeting ROCK1 | Zhu et al. (2018) |
| HCC           | miR-145 (Down)           | 9 pairs of HCC and ANTs | HepG2 | ROCK1, NF-κB, CCNE1 | miR-145 could inhibit proliferation and increase apoptosis of HepG2 cells by targeting ROCK1 | Pan et al. (2019) |

(Continued on following page)
TABLE 2 (Continued) ROCK1-interacting miRNAs in cancers (ANTs: adjacent non-cancerous tissues, NSCLC: non-small cell lung cancer, OS: osteosarcoma, EWS: Ewing sarcoma, AML/CML: acute/chronic myeloid leukemia, HCC: hepatocellular carcinoma, CRC: colorectal cancer).

| Type of cancer | miRNA/ expression pattern | Sample | Cell line | Target/Pathway | Molecular mechanism | References |
|----------------|---------------------------|--------|-----------|----------------|---------------------|------------|
| HCC            | miR-199a/b-5p (Down)      | TCGA datasets, 35 pairs of HCC and ANTs; BALB/c nude mice | SMMC-7721, HepG2, Bel-7404, 97L, QSG-7701, 293T | ROCK1, MLC, ERK, PI3K/AKT | miR-199a/b-5p could inhibit hepatocellular carcinoma progression by post-transcriptionally suppressing ROCK1 | Zhan et al. (2017) |
| HCC            | miR-145 (Down)            | 96 pairs of HCC and ANTs | THLE-3, HepG2, Hep3B, PLC/PRF/5, MRC98H | ROCK1 | miR-145 could suppress cell proliferation and motility of HCC by inhibiting ROCK1 | Ding et al. (2016) |
| Liver Cancer   | miR-31 (Down)             | - | HepG2, L02 | ROCK1, Bax, Cyt-c, Caspase-3/9 | miR-31 could modulate apoptosis and invasion of HepG2 cells via ROCK1/F-Actin axis | Zhang et al. (2020c) |
| Renal cell carcinoma | miR-199a (Down)        | 150 pairs of RCC and ANTs | ACHN, A498 | ROCK1 | miR-199a could affect the kidney cell invasion, proliferation, and apoptosis by targeting ROCK1 | Qin et al. (2018) |
| Bladder cancer | miR-199a (Down)           | 98 pairs of RCC and ANTs; nude mice | A498 | ROCK1 | miR-199a, regulated by Snail, could modulate clear cell aggressiveness via repressing ROCK1 | Zhang et al. (2018) |
| Bladder cancer | miR-335 (Down)            | 27 pairs of RLC and ANTs | T24, EJ | ROCK1 | Down-regulation of miR-335 could enhance the invasion and migration of BLC cells via targeting ROCK1 | Wu et al. (2016) |
| Breast cancer  | miR-145 (Down)            | 88 pairs of BCa and adjacent normal tissues | MCF-7, BT-474, MDA-MB-435, BT-549, SK-BR-3, MDA-MB-231 | ROCK1 | miR-145 could inhibit the growth and migration of breast cancer cells via targeting oncoprotein ROCK1 | Zhong et al. (2016) |
| Breast cancer  | miR-10b-5p (Down)         | GEO database, 20 pairs of BCa and adjacent normal tissues | MCF-10A, MCF-7, MDA-MB-231, 293T, CAMA-1, T47D | ROCK1, Rho, CNN1, STAT1 | miR-10b-5p could contribute to the lung metastasis of BCa via targeting CNN1 and regulating Rho/ROCK1 axis | Wang et al. (2020a) |
| Thyroid cancer | miR-26a (Down)            | 51 pairs of PTC and adjacent normal | BCPAP, TPIC-1, K1, HT588 | ROCK1, PI3K/AKT | miR-26a could suppress the malignant biological behaviors of PTC by targeting ROCK1 and regulating the PI3K/AKT pathway | Wu et al. (2019) |
| Thyroid cancer | miR-506-3p (Down)         | - | K1, TCP-1, W3 | ROCK1 | miR-506-3p could suppress invasion and cell migration of thyroid carcinoma by regulating ROCK1 | Xiang et al. (2015) |
| GBM            | miR-300 (Down)            | Nude mice | U87, U373, U251, A172, NHAs | ROCK1 | miR-300 by ROCK1 could inhibit GBM cell progression | Zhou et al. (2016) |
| Neuroblastoma  | miR-306 (Down)            | 28 pairs of NB and ANTs | IMR-32, N2A, SK-N-SH, SH-SY5Y | ROCK1 | miR-306 could suppress NB metastasis by targeting ROCK1 | Li et al. (2017b) |
| Laryngeal squamous cell carcinoma | miR-195 (Down)     | 51 pairs of LSCC tissues and adjacent normal epithelial tissues | AMC-HN-8, Ta-177, Hep-2, HaCat, 293T | ROCK1 | miR-195 could inhibit cell proliferation, migration, and invasion of laryngeal squamous cell carcinoma by targeting ROCK1 | Liu et al. (2017) |
| Melanoma       | miR-335 (Down)            | 30 pairs of melanoma and adjacent normal tissues | A375, COLO829, HMBCB PMW-8, B16 | ROCK1, Cyclin-D1, Caspase-3 | miR-335 could act as a tumor suppressor and enhance ionizing radiation-induced tumor regression by targeting ROCK1 | Cheng and Shen, (2020) |
from eutopic or ectopic endometriosis compared to endometrial stromal cells from normal endometrium. Functional studies have shown that up-regulation of miR-202-3p impairs viability, migratory potential, and invasion of these cells, while it is silencing has the opposite impact. miR-202-3p mimics could decrease expression of ROCK1 in...
endometrial stromal cells. Taken together, dysregulation of miR-202-3p can participate in the pathogenesis of endometriosis through influencing expression of ROCK1 (Zhang et al., 2020a). Table 1 indicates the role of ROCK1-interacting miRNAs in non-malignant disorders.

**ROCK1-interacting microRNAs in cancers**

Similarly, cancer-related miRNAs can bind to 3′ UTR of ROCK1 to regulate its expression. A number of ROCK1-interacting miRNAs have been found to reduce tumor burden. For instance, experiments in non-small cell lung carcinoma cells showed that the tumor suppressor roles of miR-135a (Zhao et al., 2020), miR-148b (Luo and Liang, 2018) and miR-335-5p (Du et al., 2019) are exerted through modulation of expression of ROCK1. The interactions between miRNAs and ROCK1 have been mostly assessed in osteosarcoma cells among other cancers. miR-101 (Jiang et al., 2017), miR-139 (Fan et al., 2019), miR-144 (Liu et al., 2019), miR-202-5p (Li et al., 2018), miR-150 (Li et al., 2017a), miR-335 (Wang et al., 2017) and miR-214-5p (Zhang et al., 2017) are examples of down-regulated miRNAs in this type of cancer that were shown to directly regulate expression of ROCK1.

Roberto et al. measured expression of a number of ROCK1/ROCK2-targeting miRNAs, namely miR-124-3p, miR-138-5p, miR-139-5p, miR-335-5p and miR-584-5p in samples obtained from patients with Ewing sarcoma. They reported down-regulation of ROCK1 in these tissues; however its expression has not been associated with pathological factors. Expression levels of miR-124-3p, miR-139-5p and miR-335-3p were also shown to be reduced in these samples in correlation with ROCK1 levels. Down-regulation of miR-139-5p and miR-584-5p has been associated with disease progression. Moreover, down-regulation of miR-139-5p and miR-124-5p has been linked with poor clinical outcome. However, the results of in vitro studies on function of miR-139-5p were inconsistent. While its overexpression has led to a significant decrease in invasive abilities of cells, their clonogenic capability was enhanced (Roberto et al., 2020).

Expression levels of ROCK1-targeting miR-592 were reported to be decreased in clinical samples from patients with acute myeloid leukemia (AML) as well as AML cell lines. Down-regulation of miR-592 was associated with advanced French-American-British classification and adverse clinical outcomes. Functional studies also showed that up-regulation of miR-592 inhibits cell growth and metastatic capacity of cells, and enhances apoptosis (Xu et al., 2019). Table 2 shows the role of ROCK1-interacting miRNAs in cancers.

**ROCK1-interacting circular RNAs in non-malignant conditions**

CircRNAs mainly affect expression of ROCK1 through sponging ROCK1-interacting miRNAs. These interactions have been assessed in the context of non-alcoholic fatty liver disease and atherosclerosis. Expression of circ_0057558 was shown to be increased in nonalcoholic fatty liver disease, parallel with down-regulation of miR-206. Circ_0057558 silencing and up-regulation of miR-206 could decrease accumulation of lipids and secretion of

| Type of diseases | IncRNA/ expression pattern | Sample | Cell line | Interacting miRNAs | Target/ Pathway | Molecular mechanism | References |
|-----------------|---------------------------|--------|-----------|-------------------|----------------|---------------------|-----------|
| AD              | TUG1 (Down)               | BALB/c mice | Hippocampal Neurons (HN) | miR-15a | ROCK1, Bax, Caspase-3 | Knockdown of TUG1 could depress apoptosis of hippocampal neurons by elevating miR-15a and repressing ROCK1 | Li et al. (2020) |
| Cerebral I/R injury | SNHG14 (Up) | SD rats | PC-12 | miR-136-5p | ROCK1, Caspase-3, IL-1β, IL-6, TNF-α | SNHG14 promotes inflammatory responses induced by cerebral I/R injury via regulating miR-136-5p/ROCK1 axis | Zhang et al. (2019) |
| CF              | SNHG7 (Up)                | C57BL/6 mice | - | miR-34-5p | ROCK1, TGF-β1 | SNHG7 could promote cardiac remodeling via sponging miR-34-5p and up-regulation of ROCK1 | Wang et al. (2020c) |
| NAFLD           | NEAT1 (Up)                | C57BL/6 J mice | HepG2 | miR-146a-5p | ROCK1, SREBP1c, FAS, ACC, CPT1 | NEAT1 could promote hepatic lipid accumulation in NAFLD via regulating miR-146a-5p/ROCK1 axis | Chen et al. (2019) |
| OP              | ROR (Down)                | Affected persons (n = 82), healthy controls (n = 79) | MC3T3-E1 | miR-145-5p | ROCK1 | IncRNA ROR could modulate the osteoblasts proliferation and apoptosis by regulating miR-145-5p/ROCK1 axis | Fu et al. (2021) |
| Type of cancer | lncRNA/ expression pattern | Sample | Cell line | Interacting miRNAs | Target/ Pathway | Molecular mechanism | References |
|----------------|---------------------------|--------|-----------|-------------------|-----------------|---------------------|------------|
| NSCLC          | PSMG3-AS1 (Up)            | 60 pairs of NSCLC and ANTs | H1993    | miR-340           | ROCK1           | PSMG3-AS1 could promote cell migration and invasion via down-regulation of miR-340 and up-regulation of ROCK1 | Wang et al. (2021a) |
| NSCLC          | KCNMB2-AS1 (Up)           | 61 pairs of NSCLC and ANTs | A549, SK-MES-1, BEAS-2B, H522, H460 | miR-374a-3p     | ROCK1           | KCNMB2-AS1 via sponging miR-374a-3p and regulating ROCK1 could facilitate the progression of NSCLC. | Yang et al. (2020) |
| SCLC           | MCM3AP-AS1 (Up)           | 60 pairs SCLC of and ANTs | SHP-77   | miR-148a          | ROCK1           | MCM3AP-AS1 could enhance cell invasion and migration of small cell lung carcinoma via sponging miR-148a and elevating ROCK1 | Luo et al. (2021) |
| NSCLC          | KCNMB2-AS1 (Up)           | 61 pairs of SCLC and ANTs | A549, SK-MES-1, H460, BEAS-2B | miR-374a-3p     | ROCK1           | KCNMB2-AS1 could facilitate the progression of NSCLC via sponging miR-374a-3p and increasing ROCK1 expression | Yang et al. (2020) |
| OS             | HAGLROS (Up)              | 10 pairs of OS and ANTs; MG-63, hFOB 1.19, SW1353, U2OS | miR-152   | ROCK1           | HAGLROS could promote cell invasion and metastasis of osteosarcoma via sponging miR-152 and up-regulation of ROCK1 | Zhou et al. (2020) |
| OS             | DANCR (Up)                | 95 pairs of OS and ANTs; Female nude mice | MG-63, U2OS, MNNG/HOS, 143B, hFOB 1.19 | miR-335-5p, miR-1972 | ROCK1           | DANCR could promote proliferation and metastasis of OS cells via sequestering miR-335-5p and miR-1972 | Wang et al. (2018) |
| OS             | HOXA11-AS (Up)            | 51 pairs of OS and ANTs; nude mice | U2OS, MG-63, KHOS, NHost | miR-124-3p      | ROCK1           | HOXA11-AS could enhance the invasion and migration of OS cells via sponging miR-124-3p | Cui et al. (2017) |
| HCC            | DANCR (Up)                | Databases; BALB/C nude mice | L02, Hep3B, Huh7, HepG2, MHCC-97H, HCC-LM3 | miR-27a-3p      | ROCK1, LIMK1, Cofilin-1, E-cadherin, N-cadherin, Vimentin | DANCR could promote hepatocellular carcinoma progression via sponging miR-27a-3p and regulating the ROCK1/LIMK1/Cofilin-1 axis | Guo et al. (2019) |
| HCC            | LINC00339 (Up)            | 60 pairs of HCC tissues and ANTs; BALB/c nude mice | L02, JHUH7, Hep2G2, HUH-6, SK-Hep-1, 293T | miR-152         | ROCK1, E-cadherin, N-cadherin, Vimentin | LINC00339 could enhance proliferation and migration of HCC via regulating miR-152 | Chen and Zhang (2019) |
| HCC            | PITPNA-AS1 (Up)           | 93 pairs of HCC tissues and ANTs; BALB/c female nude mice | L02, Hep3B, HepG2, HCCLCM3, SMMC-7721 | miR-448         | ROCK1, E-cadherin, N-cadherin, Vimentin | PITPNA-AS1 could facilitate invasion and migration of HCC via the miR-448/ROCK1 axis | Wang et al. (2021b) |

(Continued on following page)
| Type of cancer | IncRNA/ expression pattern | Sample | Cell line | Interacting miRNAs | Target/ Pathway | Molecular mechanism | References |
|----------------|-----------------------------|--------|-----------|-------------------|-----------------|---------------------|-----------|
| ESCC           | EGFR-AS1 (Up)               | 56 pairs of ESCC tissues and ANTs | KYSE-30, EC109 | miR-324-5p | ROCK1 | EGFR-AS1 could promote Invasion and Migration of ESCC via sponging miR-145 and up-regulation of ROCK1 | Feng et al. (2020) |
| Liver Cancer   | LINC00491 (Up)              | TCGA, GEO databases | HUH-7, HepG2, HUH-6, SK-Hep-1 | ROCK1 | LINC00491 could promote cell growth and metastasis via miR-324-5p/ROCK1 axis | Wang et al. (2021c) |
| Pancreatic cancer | LINC00941 (Up)         | 54 pairs of PC and ANTs | AsPC-1, BaPC-3, Panc-1, Capan-2, HPDR | miR-335-5p | ROCK1, LIMK1, Cofilin-1, ZEB2, E/N-cadherin, Vimentin | LINC00941 promotes the progression of pancreatic cancer through binding with miR-335-5p and regulating the ROCK1-mediated LIMK1/Cofilin-1 axis | Wang et al. (2021d) |
| Leukemia       | HOTAIRM1 (Up)               | -      | K562, U937, THP1, Jurkat, 293T, Kasumi-1, SKNO-1 | ROCK1 | HOTAIRM1 could enhance glucocorticoid resistance in leukemia by activating the RHOA/ROCK1 axis via suppressing ARHGAP18 | Liang et al. (2021) |
| Glioma         | LINC00346 (Up)              | 20 pairs of G and ANTs, BALB/c nude mice | NHAs, U87, H4, U251, LN229 | miR-340-5p | ROCK1 | LINC00346 could promote cell migration, invasion and proliferation of glioma cells by up-regulation of ROCK1 | Qiu et al. (2020a) |
| CC             | OIP5-AS1 (Up)               | 306 pairs of CC and ANTs | C33A | miR-143-3p | ROCK1, Bax, Caspase-3, Cyclin-A/B1 | OIP5-AS1 in cervical cancer could affect expression of ROCK1 via sponging miR-143-3p | Song et al. (2020) |
| CC             | DANCR (Up)                  | 65 pairs of CV tissues and ANTs | Caski, SW756, SiHa, C33A, HeLa, ME-180, End1/E6E7 | miR-335-5p | ROCK1, E-cadherin, Vimentin | DANCR could promote CC progression via sponging miR-335-5p and up-regulation of ROCK1 | Liang et al. (2019) |
| OC             | SNHG20 (Up)                 | -      | SKOV3, A2780, OVCAR-3, CAOV-3 | miR-148a | ROCK1 | SNHG20 could promote migration and invasion of ovarian cancer via modulating the miR-148a/ROCK1 axis | Yang and Dong. (2021) |
| BCa            | PVT1 (Up)                   | BCa tissue samples (n = 30) | MCF-10, MCF7, MDA-MB-468, MDA-MB-231 | miR-148a-3p | ROCK1 | PVT1 could facilitate invasion and migration of breast cancer by regulating miR-148a-3p and ROCK1 | Liu et al. (2021) |
| LSCC           | CDKN2B-AS1 (Up)             | 60 pairs of LSCC tissues and ANTs | NP69, TU177, BNCC388439, BNCC341383, AMC-HN-8 | miR-324-5p | ROCK1, PCNA, P21, Caspase-3, PARP | CDKN2B-AS1 could enhance invasion, migration, and proliferation of laryngeal squamous cell carcinoma via regulating miR-324-5p | Liu et al. (2020) |
triglycerides. Functionally, miR-206 could directly target ROCK1 and activate AMPK pathway through this route. In fact, circ_0057558 serves as a miR-206 sponge to suppress AMPK signals. Cumulatively, circ_0057558/miR-206/ROCK1/AMPK was found to be a functional axis in the etiology of nonalcoholic fatty liver disease (Chen et al., 2021b).

Another study reported the up-regulation of circ_UBR4 in an in vitro model of atherosclerosis. Moreover, expression levels of circ_UBR4 and ROCK1 have been found to be increased in sera of patients with atherosclerosis, parallel with down-regulation of miR-107. Circ_UBR4 silencing has led to induction of cell cycle arrest, suppression of cell viability, colony-forming capability, migration aptitude, and depression of proliferating cell nuclear antigen and MMP2. miR-107 was found to act as a mediator of circ_UBR4 effects on ROCK1 expression. Taken together, circ_UBR4/miR-107/ROCK1 pathway has a possible role in the development of atherosclerosis through modulation of proliferative ability, migration, and cell cycle transition of human VSMCs (Zhang et al., 2021). Table 3 shows the role of ROCK1-interacting circRNAs in non-malignant conditions.

| Type of diseases | Non-coding RNAs/ expression pattern | Sample | Drug and dose | Cell line | Target/ Pathway | Molecular mechanism | References |
|------------------|-------------------------------------|--------|---------------|-----------|-----------------|---------------------|------------|
| NSCLC            | Circ_PIP5K1A (Up)                   | Tumor-sensitive (n = 33), tumor-resistant (n = 23), BALB/c male nude mice | Cisplatin, 0–30 µM; I.P, 6 mg/kg DDP once 2 days | A549, H460, AS49/DDP, H460/DDP | ROCK1, miR-493-5p | Circ_PIP5K1A could regulate cisplatin resistance in NSCLC via regulation of miR-493-5p/ROCK1 axis | Feng et al. (2021) |
| HNC              | miR-136-5p (-)                      |        | Cisplatin, 2.6 µM | FaDu, FD-LSC-1 | ROCK1, E-N-cadherin, LCHII/L, Caspase-3, AKT/mTOR | miR-136-5p could enhance cisplatin sensitivity and suppress invasion and migration in head and neck cancer cells via targeting the ROCK1 | Yang et al. (2021) |
| Cerebral I/R injury | miR-214 (-)                        | SD rats| Dexmedetomidine (DEX), intravenously, 1 µg/kg at the beginning of the surgery and 0.05 µg/kg/min for the next 2 h | L02, Huh7, HCCLM3 | ROCK1, NF-κB | DEX could ameliorate cerebral I/R injury via the miR-214/ROCK1/NF-κB axis | Liu et al. (2021) |
| HCC              | miR-148a-3p (-)                     | ALB/c nude mice | Sevoflurane (SEVO), 1–4% SEVO mixed with 95% air and 5% CO2 at 6 L/min for 6 h, mice intravenously injected with 4% SEVO for 30 days | L92, Huh7, HCCLM3 | ROCK1, p53, p21 | miR-148a-3p could enhance the effect of SEVO on HCC progression via ROCK1 repression | Sun et al. (2021) |
| Glioma           | Circ_0079593 (-)                    | Glioma patients (n = 34), normal brain tissues (n = 19), BALB/c nude mice | Cells treated with 0–5.1% SEVO for 6 h, mice subcutaneously injected with 5.1% SEVO for 7 days | T98G, LN-229, NHA | ROCK1, miR-633, E-cadherin, Vimentin | SEVO could suppress glioma tumorigenesis via regulating circ_0079593/miR-633/ROCK1 axis | Cheng and Cheng, (2021) |
| Osteoarthritis   | miR-143, miR-124 (Down)            | Mice   | Curcumin, 1–5 μmol/L | BMSCs, primary chondrocytes | ROCK1, NF-κB, TLR9 | Curcumin could reinforce BMSC-derived exosomes and attenuate osteoarthritis via modulating the miR-143/ROCK1/TLR9 and miR-124/NF-κB pathways | Qiu et al. (2020b) |
| Ischemia         | miR-494-3p (Down)                  | SD rats| Ginsenoside Rgl1; 100 µg/ml | rBMSCs | ROCK1, MLC-2, Bax, Bcl-2 | Ginsenoside can protect rBMSCs against ischemia-associated apoptosis Rgl1 via the miR-494-3p and ROCK1 | Zheng et al. (2018) |
ROCK1-interacting circular RNAs in cancers

A number of ROCK1-interacting circRNAs have been reported to be up-regulated in tissue or serum samples of patients with malignant conditions. For instance, circ-TIMELESS via the miR-136-5p/ROCK1 axis could regulate proliferation of lung squamous cell carcinoma cells (Zhang et al., 2020d). Moreover, hsa_circ_0001591 could promote metastasis and cell proliferation of human melanoma via modulation of ROCK1 through targeting miR-431-5p (Yin et al., 2021). hsa_circ_0043278 could promote cell proliferation and migration of NSCLC via sponging miR-520f and regulating ROCK1 expression (Cui et al., 2019). Finally, circ-ABCB10 could promote growth and metastasis of NPC by up-regulation of ROCK1 (Duan et al., 2020). Table 4 shows the role of ROCK1-interacting circRNAs in cancers.

ROCK1-interacting long non-coding RNAs in non-malignant conditions

Similar to circRNAs, IncRNAs can act as sponges for ROCK1-interacting miRNAs. Experiments in an animal model...
ROCK1-interacting long non-coding RNAs in cancers

The impact of ROCK1-interacting IncRNAs on carcinogenesis has been evaluated in different cancers such as lung cancer, osteosarcoma, hepatocellular carcinoma and cervical cancer. For instance, PSMG3-AS1 via down-regulation of miR-340 and subsequent up-regulation of ROCK1 could promote cell migration and invasion of non-small cell lung carcinoma (Wang et al., 2021a). Moreover, KCNMB2-AS1 via sponging miR-374a-3p and regulating ROCK1 could assist in the progression of lung cancer (Yang et al., 2020).

In osteosarcoma, HAGLROS could promote cell invasion and metastasis via sponging miR-152 and up-regulation of ROCK1 (Zhou et al., 2020). Moreover, DANC5 could promote proliferation and metastasis of these cells via sponging ROCK1-targeting miRNAs miR-335-5p and miR-1972 (Wang et al., 2018). Finally, HOXA11-AS could enhance the invasion and migration of osteosarcoma via sponging miR-124-3p and up-regulation of ROCK1 (Cui et al., 2017).

In cervical cancer, OIP5-AS1 (Song et al., 2020) and DANC5 (Liang et al., 2019) were found to up-regulate ROCK1 via sponging miR-143-3p and miR-335-5p, respectively. Table 6 shows the role of ROCK1-interacting IncRNAs in cancers.

The impact of interactions between non-coding RNAs and ROCK1 on therapeutic responses

A number of therapeutic agents have been found to act through regulation of ROCK1-interacting non-coding RNAs. For instance, sevoflurane through regulation of circ_0079593/miR-633/ROCK1 axis could suppress tumorigenesis process in glioma (Cheng and Cheng, 2021). In addition, dexamethasone (DEX) could ameliorate cerebral I/R injury via the miR-214/ROCK1/NF-kB axis (Liu et al., 2021). Besides, the therapeutic effects of curcumin in osteoarthritis are possibly exerted via modulating the miR-143/ROCK1/TLR9 and miR-124/NF-kB pathways (Qiu et al., 2020b).

Furthermore, some ROCK1-interacting non-coding RNAs can affect response to therapeutic agents. For example, circ_PIP5K1A via regulation of miR-493-5p/ROCK1 axis could regulate cisplatin resistance in lung cancer (Feng et al., 2021). Moreover, miR-136-5p could enhance cisplatin sensitivity and suppress invasion and migration in head and neck cancer cells via targeting the ROCK1 (Yang et al., 2021). Table 7 shows the mutual interactions between drug and ROCK1-interacting non-coding RNAs. Figure 2 represents the role of several miRNAs in various human disorders via regulating the ROCK1/NF-kB signaling pathway.

Discussion

Several non-coding RNAs have been shown to interact with ROCK1. The interaction between ROCK1 and these transcripts can affect development of different types of cancers as well as a number of non-malignant conditions such as metabolic syndrome, diabetes, acute lung injury, pneumonia, endometriosis, non-alcoholic fatty liver disease, cerebral ischemia/reperfusion injury, myocardial Infarction, osteoporosis and atherosclerosis.

CircRNAs and IncRNAs that influence expression of ROCK1 mainly act through sponging ROCK1-targeting miRNAs. Circ_0057558/miR-206, circ_UBR4/miR-107, circ-TIMELESS/miR-136-5p, has_circ_0001591/miR-431-5p, hsa_circ_0043278/miR-520f, hsa_Circ_101141/miR-1297, Circ_0009910/miR-335-3p, circ_NRIP1/miR-182, circ_E2F3/miR-204-5p, TUG1/miR-15a, SNHG14/miR-136-5p, SNHG7/miR-34-5p, NEAT1/miR-146a-5p, Inc-ROR/miR-145-5p, PSMG3-AS1/miR-340, KCNMB2-AS1/miR-374aa-3p, MCM3AP-AS1/miR-148a, HAGLROS/miR-152, DANC5/miR-335-5p, DANC5/miR-1972, DANC5/miR-27a-3p, HOXA11-AS/miR-124-3p, LINCO0339/miR-152, PITPN1A-AS/miR-448 and EGRF-AS1/miR-145 are examples of ROCK1-regulating axes which contribute in the development of human disorders.
In addition, interactions between non-coding RNAs and ROCK1 have important role in determination of response to a number of drugs such as cisplatin, dexmedetomidine, sevoflurane, curcumin and ginsenoside Rg1. In fact, alterations in the expression levels of ROCK1-interacting non-coding RNAs can affect expression of ROCK1 and induce sensitivity or resistance to these drugs through modulation of cell apoptosis or other fundamental aspects of cell biology. Thus, through modulation of expression of these non-coding RNAs, it is possible to enhance therapeutic effects of these substances.

Based on the above-mentioned evidence, it is clear that ROCK1 has direct or indirect interactions with numerous types of non-coding RNAs constructing a complex network. Identification of elements of this network is an important step for unraveling the molecular pathology of human disorders.

**Author contributions**

SG-F wrote the manuscript and revised it. MT and GS supervised and designed the study. YP, AA, HS, and BMH collected the data and designed the figures and tables. All authors read and approved the submitted version.

**References**

Blumenstein, L., and Ahmadian, M. R. (2004). Models of the cooperative mechanism for Rho effector recognition: implications for RhoA-mediated effector activation. *J. Biol. Chem.* 279 (51), 53419–53426. doi:10.1074/jbc.M409551200

Chen, K., and Zhang, L. (2019). LINC00339 regulates ROCK1 by miR-152 to promote cell proliferation and migration in hepatocellular carcinoma. *J. Cell. Biochem.* 120 (9), 14431–14443. doi:10.1002/jcb.28701

Chen, L., Wang, G.-D., Liu, J.-P., Wang, H.-S., Liu, X.-M., Wang, Q., et al. (2015). miR-153a modulates tendon stem/progenitor cell senescence via suppressing ROCK1. *Bone* 51, 210–216. doi:10.1016/j.bone.2014.11.001

Chen, X., Tan, X.-R., Li, S.-J., and Zhang, X.-X. (2019). lncRNA NEAT1 promotes hepatic lipid accumulation via regulating miR-146a-5p/ROCK1 in nonalcoholic fatty liver disease. *Life Sci.* 235, 116829. doi:10.1016/j.lfs.2019.116829

Chen, N., Meng, Z., Song, J., Kong, L., Zhang, Y., Guo, S., et al. (2021). miR-497-5p induces apoptosis in K562 cells by downregulating ROCK1. *J. Transl. Med.* 13 (8), 9278–9284.

Chen, X., Tan, Q.-Q., Tan, X.-R., Li, S.-J., and Zhang, X.-X. (2021). Circ_0057558 promotes nonalcoholic fatty liver disease by regulating ROCK1/AMPK signaling through targeting miR-206. *Cell Death Dis.* 12 (9), 809–812. doi:10.1038/s41419-021-04090-z

Cheng, S., and Cheng, J. (2021). Sevoflurane suppresses glioma tumorigenesis via regulating circ_0079593/miR-633/ROCK1 axis. *Brain Res.* 1767, 147543. doi:10.1016/j.brainres.2021.147543

Cheng, Y., and Shen, P. (2020). miR-335 acts as a tumor suppressor and enhances effector activation. *J. Biol. Chem.* 279 (51), 53419–53426. doi:10.1074/jbc.M409551200

Cui, M., Wang, J., Li, Q., Zhang, J., Jia, I., and Zhan, X. (2017). Long non-coding RNA HOXA11-AS functions as a competing endogenous RNA to regulate ROCK1 expression by sponging miR-124-3p in osteosarcoma. *Biomed. Pharmacother.* 92, 437–444. doi:10.1016/j.biopha.2017.05.081

Cui, J., Li, W., Liu, G., Chen, X., Gao, X., Lu, H., et al. (2019). A novel circular RNA hsa_circ_0043278 acts as a potential biomarker and promotes non-small cell lung cancer cell proliferation and migration by regulating miR-520f. *Artif. Cells Nanomed. Biotechnol.* 47 (1), 810–821. doi:10.1080/21691401.2019.1575847

Ding, W., Tan, H., Zhao, C., Li, X., Li, Z., Jang, C., et al. (2016). MiR-145 suppresses cell proliferation and motility by inhibiting ROCK1 in hepatocellular carcinoma. *Tumour Biol.* 37 (5), 6255–6260. doi:10.1007/s13277-015-4462-3

Du, W., Tang, H., Lei, Z., Zhu, J., Zeng, Y., Liu, Z., et al. (2019). miR-335-5p inhibits TGF-β1-induced epithelial-mesenchymal transition in non-small cell lung cancer via ROCK1. *Respir. Rev.* 20 (1), 225–311. doi:10.1016/j.surfrev.2019.01.1184-x

Duan, Z., Dong, C., and Liu, J. (2020). Circ-ABC11t promotes growth and metastasis of nasopharyngeal carcinoma by upregulating ROCK1. *Eur. Rev. Med. Pharmacol. Sci.* 24 (3), 12208–12215. doi:10.26355/eurrev_202012_24011

Fan, G., He, Z., Gao, L., Shi, X., Wu, S., and Zhou, G. (2019). miR-139 inhibits osteosarcoma cell proliferation and invasion by targeting ROCK1. *Front. Biosci. 24*, 1167–1177. doi:10.2741/4773

Feng, Z., Li, X., Qiu, M., Luo, R., Lin, J., and Liu, B. (2020). lncRNA EGFR-ASI upregulates ROCK1 by sponging miR-143-5p to promote Esophageal squamous cell carcinoma cell invasion and migration. *Cancer Biother. Radiopharm.* 35 (1), 66–71. doi:10.1089/cbr.2019.2926

Feng, N., Guo, Z., Wu, X., Tian, Y., Li, Y., Geng, Y., et al. (2021). Circ_PIPSK1A regulates cisplatin resistance and malignant progression in non-small cell lung cancer cells and xenograft murine model via depending on miR-493-5p/ROCK1 axis. *Cell Death Dis.* 12 (9), 809–812. doi:10.1038/s41419-021-04090-z

Fu, Y., Hu, X., Gao, Y., Li, K., Fu, Q., Liu, Q., et al. (2021). lncRNA BOR/miR-145-5p axis modulates the osteoblasts proliferation and apoptosis in osteoporosis. *Biomed. Eng. 12* (1), 7714–7723. doi:10.21655979.2021.1982323

Fujisawa, K., Fujita, A., Ishizaki, T., Saito, Y., and Narumiya, S. (1996). Identification of the Rho-binding domain of p160ROCK, a Rho-associated coiled-coil containing protein kinase. *J. Biol. Chem.* 271 (38), 23028–23033. doi:10.1074/jbc.271.38.23022

Guo, D., Li, Y., Chen, Y., Zhang, D., Wang, X., Lu, G., et al. (2019). DANCR promotes HCC progression and regulates EMT by sponging miR-27a-3p via ROCK1/LIMK1/COFILIN1 pathway. *Cell Physiol. 52* (4), e12628. doi:10.1111/cpc.12628

Guo, J., Yang, C., Lin, Y., Hu, G., Wei, J., Zhang, X., et al. (2020). Enhanced peripheral blood miR-324-5p is associated with the risk of metabolic syndrome by

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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targeting ROCK1 to affect kidney cell proliferation, invasion and apoptosis. doi:10.5414/NP301233

Cancer Biol. Ther.
tachykinin-1 receptor axis via inactivating extracellular signal-regulated kinases. doi:10.1016/j.yexmp.2021.104637

Cells Nanomed. Biotechnol.168

case microRNA polymorphisms and development of coronary artery disease: A

Ghafouri-Fard et al. 10.3389/fmolb.2022.986722

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ROCK1-mediated proliferation and metastasis via decoying of miR-335-5p and ROCK1 repression.

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Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences

Frontiers in Molecular Biosciences
prognosis. Eur. Rev. Med. Pharmacol. Sci. 23 (4), 1610–1619. doi:10.26355/eurrev_201902_17120

Yang, Q., and Dong, Y. J. (2021). LncRNA SNHG20 promotes migration and invasion of ovarian cancer via modulating the microRNA-148a/ROCK1 axis. J. Ovarian Res. 14 (1), 168–213. doi:10.1186/s13058-021-00889-8

Yang, H., Wang, Z., and Wang, W. (2020). Long noncoding RNA KCNMB2-AS1 increases ROCK1 expression by sponging microRNA-374a-3p to facilitate the progression of non-small-cell lung cancer. Cancer Manag. Res. 12, 12679–12695. doi:10.2147/CMAR.S270646

Yang, B., Zhang, J., Yuan, W., Jiang, X., and Zhang, F. (2021). The miR-136-5p/ROCK1 axis suppresses invasion and migration, and enhances cisplatin sensitivity in head and neck cancer cells. Exp. Ther. Med. 21 (4), 317. doi:10.3892/ettm.2021.9748

Yin, D., Wei, G., Yang, F., and Sun, X. (2021). Circular RNA has circ001591 promoted cell proliferation and metastasis of human melanoma via ROCK1/PI3K/AKT by targeting miR-431-5p. Hum. Exp. Toxicol. 40 (2), 310–324. doi:10.1177/0960327120950014

Zhan, Y., Zheng, N., Teng, F., Bao, L., Liu, F., Zhang, M., et al. (2017). MiR-199a/b-5p inhibits hepatocellular carcinoma progression by post-transcriptionally suppressing ROCK1. Oncotarget 8 (40), 67169–67180. doi:10.18632/oncotarget.18052

Zhang, M., Wang, D., Zhu, T., and Yin, R. (2017). miR-214-5p targets ROCK1 and suppresses proliferation and invasion of human osteosarcoma cells. Oncol. Res. 25 (1), 75–81. doi:10.3272/ojor.147087134001

Zhang, X., Li, P., Ding, Z., Wang, H., Wang, J., Han, L., et al. (2018). The putative tumor suppressor, miR-199a, regulated by Snail, modulates clear cell renal cell carcinoma aggressiveness by repressing ROCK1. Oncol. Targets. Ther. 11, 103–112. doi:10.2147/OTT.S147184

Zhang, M., Zhang, Y., Li, L., Ma, L., and Zhou, C. (2020). Dysregulation of miR-202-3p affects migration and invasion of endometrial stromal cells in endometriosis via targeting ROCK1. Reprod. Sci. 27 (2), 731–742. doi:10.1111/902-019-00079-4

Zhang, J., Xiang, J., Liu, T., Wang, X., Tang, Y., and Liang, Y. (2020). MiR-495 targets ROCK1 to inhibit lipopolysaccharides-induced WI-38 cells apoptosis and inflammation. Kaohsiung J. Med. Sci. 36 (8), 607–614. doi:10.1002/kjm.21210

Zhang, X., Xu, L., and Yang, T. (2020). miR-31 modulates liver cancer HepG2 cell apoptosis and invasion via ROCK1/F-Actin Pathways. Onco. Targets. Ther. 13, 877–888. doi:10.2147/OTT.S227467

Zhang, W., Shi, J., Cheng, C., and Wang, H. (2020). CircTIMELESS regulates the proliferation and invasion of lung squamous cell carcinoma cells via the miR-136-5p/ROCK1 axis. J. Cell. Physiol. 235 (9), 5962–5971. doi:10.1002/jcp.25421

Zhang, T., Zhang, L., Han, D., Tursun, K., and Lu, X. (2020). Circular RNA hsa_Circ_101141 as a competing endogenous RNA facilitates tumorigenesis of hepatocellular carcinoma by regulating miR-1297/ROCK1 pathway. Cell Transpl. 29, 0963689720948016. doi:10.1177/0963689720948016

Zhang, Y., Zhang, C., Chen, Z., and Wang, M. (2021). Blocking circ_UBR4 suppressed proliferation, migration, and cell cycle progression of human vascular smooth muscle cells in atherosclerosis. Open Life Sci. 16 (1), 419–430. doi:10.1515/ols-2021-0044

Zhao, Y., Sun, X., Zhu, K., and Cheng, M. (2020). miR-135a inhibits malignant proliferation and diffusion of non-small cell lung cancer cells by down-regulating ROCK1 protein. Biosci. Rep. 40 (6), BSR20201276. doi:10.1042/BSR20201276

Zheng, M., Sun, X., Li, Y., and Zuo, W. (2016). MicroRNA-145 inhibits growth and migration of breast cancer cells through targeting oncoprotein ROCK1. Tumour Biol. 37 (6), 8189–8196. doi:10.1007/s13277-015-4722-2

Zheng, H.-z., Fu, X.-k., Zhang, J.-l., Lu, R.-x., Ou, Y.-f., and Chen, C.-l. (2018). Ginsenoside Rg1 protects rat bone marrow mesenchymal stem cells against ischemia induced apoptosis through miR-494-3p and ROCK1. Eur. J. Pharmacol. 822, 154–167. doi:10.1016/j.ejphar.2018.01.001

Zhou, W., Ye, S., and Wang, W. (2021). LncRNA SNHG14 promotes inflammatory response induced by cerebral ischemia/reperfusion injury through regulating miR-136-5p/ROCK1. Cancer Gene Ther. 27 (2), 234–247. doi:10.1038/s41417-018-0067-5

Zhou, F., Li, Y., Hao, Z., Liu, X., Chen, L., Cao, Y., et al. (2016). MicroRNA-300 inhibited glioblastoma progression through ROCK1. Oncotarget 7 (24), 36529–36538. doi:10.18632/oncotarget.9068

Zhou, K., Xu, J., Yin, X., and Xia, J. (2020). Long noncoding RNA HAGILROS promotes cell invasion and metastasis by sponging miR-152 and upregulating ROCK1 expression in osteosarcoma. Comput. Math. Methods Med. 2020, 7236245. doi:10.1155/2020/7236245

Zhou, W., Ye, S., and Wang, W. (2021). miR-217 alleviates high-glucose-induced vascular smooth muscle cell dysfunction via regulating ROCK1. J. Biochem. Mol. Toxicol. 35 (3), e22668. doi:10.1002/jbt.22668

Zhu, Q. D., Zhou, Q. Q., Dong, L., Huang, Z., Wu, F., and Deng, X. (2018). MiR-199a-5p inhibits the growth and metastasis of colorectal cancer cells by targeting ROCK1. Technol. Cancer Res. Treat. 17, 1533034618775509. doi:10.1177/1533034618775509