Abstract: Actin filaments are a major component of the cytoskeleton in eukaryotic cells and play an important role in cancer metastasis. Dynamics and reorganization of actin filaments are regulated by numerous regulators, including Rho GTPases, PAKs (p21-activated kinases), ROCKs (Rho-associated coiled-coil containing kinases), LIMKs (LIM domain kinases), and SSH1 (slingshot family protein phosphate 1). Ubiquitination, as a ubiquitous post-transcriptional modification, decreases protein levels of actin cytoskeleton regulatory factors and thereby modulates the actin cytoskeleton. There is increasing evidence showing cytoskeleton regulation by long noncoding RNAs (lncRNAs) in cancer metastasis. However, which E3 ligases are activated for the ubiquitination of actin-cytoskeleton regulators involved in tumor metastasis remains to be fully elucidated. Moreover, it is not clear how lncRNAs influence the expression of actin cytoskeleton regulators. Here, we summarize physiological and pathological mechanisms of lncRNAs and ubiquitination control mediators of actin cytoskeleton regulators which are involved in tumorigenesis and tumor progression. Finally, we briefly discuss crosstalk between ubiquitination and lncRNA control mediators of actin-cytoskeleton regulators in cancer.

Keywords: ubiquitination; lncRNA; actin; Rho GTPase; cytoskeleton

1. Introduction

The actin cytoskeleton participates in several basic cellular processes, including cell division, cytokinesis, and motility [1–3]. It also plays a prominent role in migration and tumor morphogenesis in cancer cells [4]. Cellular actin exists in two forms: G-actin and F-actin polymers (also referred to as actin filament). All G-actin subunits of F-actin in the same direction; hence, actin filaments are polar. The barbed end of F-actin is more dynamic; polymerization of actin filaments mainly depends on the addition of ATP-bound G-actin to the barbed end, while dissociation is more rapid at the pointed end [5]. The ADF/cofilin family (hereinafter referred to as cofilin) severs and depolymerizes actin filaments and therefore regulates actin filament dynamics and reorganization [5–7].

Cofilin is inhibited by its phosphorylation and reactivated by its dephosphorylation [8,9]. Phosphorylation at Ser3 of cofilin is the major intersection of actin dynamics and extracellular signals [10,11]. In mammals, kinases of cofilin include LIMKs (LIMK1 and LIMK2), testicular protein kinase 1 (TESK1), TESK2, and Nck-interacting kinase (NIK)-related kinase (NRK)/NIK-like embryo-specific kinase (NESK) [9,12–16]; phosphatases of cofilin include slingshot family protein phosphates (SSHs), including SSH1, SSH2, and SSH3, chronophin, protein phosphate 1, and protein phosphate 2A [7,17–21]. Moreover, cofilin activity is inhibited by binding of phosphatidylinositol 4,5-bisphosphate and cortactin [22–24], while it is facilitated by binding of cyclase-associated protein-1.
and actin-interacting protein-1 [25,26]. In humans, the Rho GTPase family comprises 20 members, which can be divided into eight subfamilies [27]. The three most important members of the Rho GTPase family, Rac, Rho, and Cdc42, are well-studied upstream regulators of cofilin [4,28]. The p21-activated kinases (PAKs) and Rho-associated coiled-coil containing kinases (ROCKs) are downstream regulators of Rho GTPases and regulate the activity of LIMKs [29,30]. The Rho GTPase protein family and their downstream effectors are under precise control to maintain actin stability. We summarized these regulators of actin cytoskeleton in Table 1.

Table 1. Cellular structures regulated by actin cytoskeleton regulatory factors.

|                      | Rho GTPases | PAKs | ROCKs | LIMKs | SSH1 |
|----------------------|-------------|------|-------|-------|------|
|                      | RhoA | Rac1 | Cdc42 | PAK1 | PAK4 |       |       |
| podosomes            | -    | [+33,34] | [+35,36] | +    | [+37,38] | +    | [39] | -    | [40,41] | \  | \  |
| invadopodia          | -    | [+44–46] | [+42,49] | +    | [+46,49–51] | -    | [+48] | +    | [+52] | [+53–55] | +    | [53–57] | \  |
| filopodia            | -    | [+58,59] | [+60–63] | +    | [+64–66] | [+28,67–69] | +    | [66,70] | \  | [+59,71] | +    | [61,63] | +    | [63] | \  |
| lamellipodia         | +    | [+62,72] | [+28,73] | +    | [+28,73,74] | +    | [75,76] | \  | +    | [+72] | [+76–78] | +    | [77,79] | \  |

Numbers refer to references; -: inhibition; +: promotion; \: unknown.

Post-translational modification (PTM) like ubiquitination is crucial for activities of actin cytoskeleton-related regulators (Figure 1). Ubiquitin is a highly conserved protein in eukaryotes consisting of 76 amino acid residues. Ubiquitin attaches through its C-terminal glycine to a lysine residue in the target protein as a tag post-translationally and forms an isopeptide bond [80–82]. The process of ubiquitin-proteasome system (UPS) degradation begins with activation of ubiquitin by E1 enzymes (or ubiquitin-activating enzymes). The second step involves the transfer of the activated ubiquitin to an E2 enzyme (or ubiquitin-conjugating enzyme). Activated ubiquitin can be transferred to the target protein by three kinds of E3s (also known as ubiquitin ligase): HECT (homologous to E6-AP C-terminus) domain-containing E3s, RBR (RING-between-RING) family E3s and RING (really interesting new gene) finger domain-containing E3s. The former two receive the activated ubiquitin from E2 and subsequently transfers it to the target protein; the latter one catalyzes the transfer of activated ubiquitin from E2 enzyme to the target protein directly [81,83–85]. E3 ligase then transfers activated ubiquitin to its substrate, sometimes repeatedly to form polyubiquitin chains. In polyubiquitin chains, monomers may conjugate via several lysine residues or N-terminal methionine residue, producing different ubiquitin signals [86]. Polyubiquitin chains linked via residues such as Lys48 and Lys63 may lead to the proteasome-dependent degradation of the substrate [87].

Long non-coding RNAs (lncRNAs) are RNA molecules without protein coding function that are longer than 200 nucleotides in length. LncRNAs regulate various cellular functions, including actin filament dynamics and reorganization [88]. However, the underlying mechanisms related to the regulation of the actin cytoskeleton and ubiquitination of actin cytoskeleton-related regulators are largely unknown. In this review, we summarize the recent evidence on the ubiquitination of actin cytoskeleton-related regulators (Figure 1), and how lncRNAs regulate ubiquitination of these regulators in cancer progression.
was found in primary human pancreatic cancers, and overexpression of Smurf1 leads to loss of contact pathw...

Ubiquitination can influence the actin cytoskeleton by regulating actin cytoskeleton regulators by different mechanisms. Cofilin phosphorylation can induce its degradation through the ubiquitination pathway. Besides the phosphorylation on Ser3 of cofilin, Tyr68 is phosphorylated by an Src counterpart virus. It is commonly activated in colorectal and breast cancers [90]. Phosphorylation on Tyr68 of cofilin increases cofilin ubiquitination thus reducing its activity in stimulating actin depolymerization [89].

2. Ubiquitination of Actin Cytoskeleton Regulators

Ubiquitination can influence the actin cytoskeleton by regulating actin cytoskeleton regulators by different mechanisms. Cofilin phosphorylation can induce its degradation through the ubiquitination pathway. Besides the phosphorylation on Ser3 of cofilin, Tyr68 is phosphorylated by an Src counterpart from a family of tyrosine kinases, v-Src [89]. As a known oncogene, v-Src was found in Rous sarcoma virus. It is commonly activated in colorectal and breast cancers [90]. Phosphorylation on Tyr68 of cofilin increases cofilin ubiquitination thus reducing its activity in stimulating actin depolymerization [89].

2.1. Ubiquitination and Rho GTPases

As a part of the Ras superfamily, Rho GTPases are best known for their regulatory functions of cytoskeleton dynamics and many cellular processes including migration, cell polarity, the cell cycle, and cytokinesis [91,92]. Three of all 20 members of Rho GTPase family, RhoA, Rac1, and Cdc42, are the best studied regulators of cofilin.

2.1.1. Ubiquitination of RhoA

Higher levels of active RhoA promote the formation of long unbranched actin filaments in the rear of a migrating cell [93]. RhoA is reported to be ubiquitinated at Lys6, Lys7 and Lys135 by a HECT domain containing E3, Smurf1 (Smad ubiquitination regulatory factor 1) [94–96]. Then degradation of RhoA is achieved by Smurf1-mediated proteasome degradation [96]. Smurf1 was first discovered to be recruited by atypical protein kinase C zeta (PKCzeta) in filopodia and lamellipodia, which leads to a rapid membrane extension in response to activation of Cdc42 and Rac1 [94]. Because of its specificity for RhoA, Smurf1 also plays a role in tumor migration and invasion. Smurf1 amplification was found in primary human pancreatic cancers, and overexpression of Smurf1 leads to loss of contact pathw...
inhibition of NIH-3T3 mouse embryo fibroblast cells [97]. Smurf1 induced degradation of RhoA promotes EGF (epidermal growth factor) induced breast cancer cell migration and invasion [98]. During EMT (epithelial-to-mesenchymal transition), Smurf1-mediated proteasome degradation controls the dissolution of cellular tight junctions under the control of Par6 (partitioning-defective 6), an adapter protein that regulates cellular polarity [95,99]. Smurf1 interacts with a tumor suppressor, RASSF1A (Ras association domain family member 1), to enhance the ubiquitination of RhoA; therefore, RhoA levels are decreased and tumorigenesis is suppressed [100]. The affinities of Smurf1 for RhoA is enhanced by phosphorylation of Smurf1, contributing to increased degradation of RhoA in axon development [101]. RhoA is also ubiquitinated by two members of the F-box protein family, SCF<sub>FBXL19</sub> (Skp1-Cul1-F-box FBXL19) and SCF<sub>Fbxw7</sub> (F-box and WD repeat domain-containing7).

SCF<sub>FBXL19</sub> targets RhoA for ubiquitination and proteasome-dependent degradation in lung epithelial cells [102]. The SCF<sub>FBXL19</sub>-mediated ubiquitination of RhoA is only achieved with phosphorylation of ERK2 (extracellular signal regulated kinase 2). The degradation of RhoA by SCF<sub>FBXL19</sub> and ERK2 inhibits cell proliferation and stress fiber formation in lung epithelial cells. In gastric cancer cells, SCF<sub>Fbxw7</sub>-mediated downregulation of RhoA induces apoptosis and inhibits EMT [103]. Cul3, a member of the Cullin scaffold protein family, promotes ubiquitination of RhoA through BTB domain-containing adapters via mediating the assembly of SCF-like ubiquitin ligase complexes [104,105]. One of these complexes, Cul3/BACURD, mediates the polyubiquitination and degradation of RhoA. HeLa cells lacking Cul3/BACURD show less migration potential [106].

In addition to proteasome-dependent degradation, autophagy also participates in the degradation of ubiquitinated RhoA. SQSTM1 (sequestosome 1, also known as p62) targets ubiquinated RhoA to the autophagosome [107,108]. Moreover, autophagy selectively degrades GTP-bound RhoA so that the active RhoA maintains an appropriate level at the midbody during cytokinesis [107]. Together with the proteasome, autophagy degradation of ubiquitinated RhoA controls cell motility and genome stability [108]. Interestingly, Smurf1 also participates in the delivery of ubiquitinated RhoA to nascent autophagosomes via its C2 domain [109]. Recently, ubiquitination of the less-understood cytoskeleton regulator RhoB has also been found, as shown in Table 2 [110–112].

### Table 2. E3s and ubiquitination sites of actin cytoskeleton regulators.

| Regulator | Ubiquitination Site | E3 Ligase       | Reference |
|-----------|---------------------|-----------------|-----------|
| Rho A     | Lys6, 7 and 135     | Smurf1          | [94–96]   |
|           |                     | SCF<sub>FBXL19</sub> | [102] |
|           |                     | SCF<sub>Fbxw7</sub> | [103] |
|           |                     | Cul3/BACURD     | [106] |
| Rho GTPases | Lys162 and Lys181   | CUL3/KCTD10     | [110,111] |
|           | Lys6 and Lys7       | Smurf1          | [112] |
| Rac1      | Lys147              | HACE1, IAPs     | [113,114] |
|           | Lys166              | SCF<sub>FBXL19</sub> | [115] |
| Cdc42     | Lys166              | XIAP            | [116] |
| LIMK1     | Lys48               | Rnf6            | [118] |
| ROCK      |                     | APC/CCdh1       | [117] |

#### 2.1.2. Ubiquitination of Rac1

So far, several E3s have been reported to target Rac1 for ubiquitination, including HACE1 (HECT domain and ankyrin repeat Containing E3 ubiquitin protein kinase 1), IAPs (Inhibitor of apoptosis proteins), and SCF<sup>FBXL19</sup>. HACE1 preferentially catalyzes polyubiquitination of GTP-bound Rac1 at Lys147 and decreases Rac1 protein levels in breast cancer cells [113]. HACE1 is considered as a tumor
suppressor for degradation of Rac1 since HACE1 inhibits reactive oxygen species (ROS) generation by Rac1-dependent NADPH oxidases [119–121]. Loss of HACE1 promotes migratory and invasive capabilities of normal mammary epithelial cells MCF12A due to the increased level of activated Rac1 [122]. Under the stimulation of HGF (hepatocyte growth factor), HACE1 increases proteasome degradation of Rac1 and reduces cell migration during epithelial cell scattering [123]. In addition, loss of HACE1 results in excessive levels of activated Rac1 in Xenopus laevis during early embryonic development [124].

IAPs are characterized by the fact they contain at least one Baculovirus IAP Repeat (BIR) domain. IAP proteins are known for their role in the regulation of cell signaling, affecting apoptosis, innate immunity, and tumor shape and migration [114,125,126]. X-linked IAP (XIAP) and cellular IAP1 (cIAP1), which contain a RING domain, function as E3s through binding Rac1 with the RING domains, which leads to the polyubiquitination at Lys147 of Rac1 [114]. Loss of XIAP and cIAP1 leads to stabilization of Rac1 and promotes tumor migration [127]. Interestingly, XIAP has been found to increase endothelial permeability via activation of RhoA, not through its E3 function but through an unknown mechanism [128].

Intriguingly, SCF
FBXL19
also has ability to target Rac1 for ubiquitination at Lys166 and proteasome-dependent degradation [115]. Unlike its regulation of RhoA, the ubiquitination of Rac1 by SCF
FBXL19
is accompanied by the phosphorylation of Rac1 by AKT. Induced ubiquitination of Rac1 by SCF
FBXL19
leads to a reduction in Rac1 levels and decreased cell motility.

2.1.3. Ubiquitination of Cdc42

Unlike RhoA or Rac1, little is known about the ubiquitination of Cdc42. Recently, XIAP was proven to be an E3 ubiquitin ligase of Cdc42 [116]. XIAP directly conjugates ubiquitin chains to the Lys166 residue of the C-terminus of Cdc42 and targets Cdc42 for proteasome-dependent degradation. Mice injected with XIAP-depleted tumor cells have more metastasis nodules in the lung, whereas co-depletion of Cdc42 and XIAP strongly inhibits lung metastasis.

2.2. Ubiquitination of PAK1

PAKs are important effectors of Rho GTPase such as Rac1, Cdc42, and Cdc42 homologous protein (Chp, or RhoV) [29,129]. Overexpression of Cdc42 or Chp may paradoxically downregulate PAK1 [130]. Overexpression of Chp reduces PAK1 protein levels via proteasome-dependent degradation, thereby inhibiting T cell chemotaxis, while the related E3 of PAK1 remains unidentified. Ivermectin is a broad-spectrum anti-parasitic drug and a potential anticancer agent. Ivermectin blocks AKT/mTOR signaling and promotes ubiquitination-dependent degradation of PAK1, thereby promoting cytostatic autophagy which inhibits breast cancer [131,132].

2.3. Ubiquitination of ROCK

ROCKs are effectors of Rho GTPases, such as RhoA [30]. Downstream effectors of activated ROCKs are involved in processes including actin organization, apoptosis, and development [133]. Little is known about the ubiquitination of ROCKs. ROCK2 can be ubiquitinated by APC/C (anaphase-promoting complex/cyclosome) and induced to degradation to maintain dendritic stability and integrity of neuron cells [117]. APC/C
Cdh1
is an E3 analog of ROCK2 and works together with its cofactor Cdh1. Thus, APC/C
Cdh1
might be a potential target against neurodegenerative diseases.

2.4. Ubiquitination of LIMKs

LIMKs include LIMK1 and LIMK2; both phosphorylate and inactivate cofilin [134]. The Ring finger protein Rnf6 can ubiquitinate LIMK1 during neuron development leading to its degradation [135]. Rnf6 serves as a ubiquitin ligase and binds to LIMK1, contributing to Lys48-linked polyubiquitination of LIMK1 in the presence of UbCH5, which functions as an E2 enzyme. CRABP2 (cellular retinoic acid binding protein 2) participates in osteogenic differentiation via interacting with LIMK1 in a
ubiquitin-proteasome pathway and compromises LIMK1 activity [118]. However, the exact domain of CRABP2 that interacts with LIMK1 and which ubiquitin ligase is involved in this process remain unclear. Parkin is an E3 of LIMK1 and influences activity of LIMK1. In an in vitro experiment, parkin specifically reduces the activity of LIMK1 via ubiquitination in human neuroblastoma-derived BE(2)-M17 cells [136]. No LIMK2 ubiquitination has been found yet.

2.5. Ubiquitination of SSH

A relationship between ubiquitin-proteasome dependent degradation and SSHs has rarely been reported. Infection and replication of herpes simplex virus 1 (HSV-1) lead to inactivation of cofilin through ubiquitin-proteasome dependent downregulation of SSH1, which benefits HSV-1 replication in neuronal cells [137].

The known E3s and the ubiquitination sites of actin cytoskeleton regulators are summarized in Table 2.

3. LncRNA and the Actin Cytoskeleton

LncRNAs can influence actin directly. For example, the lncRNA CRYBG3 binds G-actin directly, which inhibits F-actin polymerization and blocks cytokinesis of lung cancer cells. The binding also enables lncRNA CRYBG3 to block MAL nuclear localization, thereby inhibiting several immediate early genes which are important in cell proliferation and cancer metastasis [138]. Another lncRNA, TUG1 (taurine up-regulated gene 1), is necessary for EZH2 (enhancer of zeste homolog 2)-mediated methylation of α-actin in rat vascular smooth muscle cells. The formation of the cytoplasmic TUG/EZH2/α-actin complex promotes cortex actin polymerization in synthetic vascular smooth muscle cells [139]. Though lncRNAs exert influence on the actin cytoskeleton of cancer cells in many ways, they mostly act as competitive endogenous RNAs (ceRNAs) for miRNAs by inhibiting miRNAs, thereby increasing expression levels of mRNAs targeted by these miRNAs. Here, we summarized how lncRNAs regulate actin cytoskeleton by interacting with the above-mentioned regulators. Some of these regulators, such as regulators of LIMK, have so far not been found to be controlled by lncRNAs.

3.1. LncRNA and Cofilin

The LncRNA GAS5 (growth arrest-specific 5) is currently under intense investigation because of its dysregulation in various diseases, including several types of cancer [140–144], childhood pneumonia [145], and traumatic brain injury [146]. GAS5 is a tumor suppressor that acts by downregulating miR-222 in human glioma cells. In two glioma cell lines, miR-222 knockdown induces upregulation of Plexin C1, which induces cofilin inactivation and thereby promotes cell migration and invasion [147].

3.2. LncRNA and Rho GTPases

The regulation of Rho GTPases by lncRNAs has drawn much attention, especially in cancer research. Previously, Zou et al. summarized how lncRNAs influence the cytoskeleton by actin regulatory factors during the process of cancer metastasis [88]. Nevertheless, regulation of the cytoskeleton by lncRNAs also occurs in other pathological processes. For instance, the lncRNA NONMMUGO14387 activates the Wnt/PCP pathway after injury during regeneration of peripheral nerve in Schwann cells [148]. Rho family members, such as RhoA and Rac1, are significantly upregulated to promote proliferation and nerve regeneration in Schwann cells. Moreover, the lncRNA LERFS (lowly expressed in rheumatoid fibroblast-like synoviocytes) binds RhoA, Rac1, and Cdc42 mRNA to downregulate their levels under healthy conditions in fibroblast-like synoviocytes. Downregulation of LERFS promotes invasion and migration of fibroblast-like synoviocytes in patients with rheumatoid arthritis [149].
3.2.1. LncRNA and RhoA

Studies have showed that RhoA expression levels are regulated by lncRNAs. Some lncRNAs regulate RhoA expression by acting as ceRNA of specific miRNA, such as the lncRNA XIST (X-inactive-specific transcript) binding to miR-133a-3p under the regulation of CXCR4 (chemokine receptor 4) in an in vitro model of colorectal cancer cells [150]. Other examples are the lncRNA LOC554202, which binds to miR-31 in laryngeal squamous cell carcinoma [151], and lncRNA NORAD (non-coding RNA activated by DNA damage), which binds to miR-125a-3p in pancreatic cancer [152].

There are other mechanisms by which lncRNA regulates on RhoA. Overexpression of the lncRNA PCGEM1 (prostate cancer gene expression marker 1) promotes cancer growth by upregulating protein expression of RhoA and its downstream factors YAP (Yes-associated protein), MMP2 (matrix metalloproteinase 2), Bcl-xL, and P70S6K in ovarian cancer [153]. The lncRNA TBILA (TGFβ-induced lncRNA) is upregulated in human germinal center-associated lymphoma and enhances RhoA activation by forming the Smad transcription factor complex [154]. The lncRNA SchLAH (a seven-chromosome locus associated with hepatocellular carcinoma) is lowly expressed in HCC (hepatocellular carcinoma) and downregulates mRNA levels of RhoA and Rac1 in HCC cells [155]. The miRNA miR-31 suppresses breast cancer cell metastasis by targeting genes such as RhoA. Its host gene lncRNA LOC554202 as well as itself are lowly expressed in triple negative breast cancer, due to promoter hypermethylation [156]. The lncRNA AFAP1-AS1 is involved in many types of malignant tumors [157] and upregulates RhoA expression to promote proliferation and metastasis of HCC [158]. MALAT1 (Metastasis associated in lung adenocarcinoma transcript 1) increases protein levels of RhoA and the downstream ROCK in osteosarcoma [159]. Self-assembled TDNs (tetrahedral DNA nanostructures) are degradation-resistant small DNA nanostructures. TDNs promote expression of RhoA, Rac1, and ROCK2 by suppressing the transcription of the lncRNA XLOC010623 and thereby stimulate adipose-derived stem cell migration when internalized by adipose-derived stem cells. TDNs are regarded to have high potential for future applications in regenerative medicine [160].

3.2.2. LncRNA and Rac1

LncRNAs often serve as ceRNAs of Rac1 and promote its expression to promote proliferation and metastasis in various types of cancer, such as MALAT1 binding to miR-509 in osteosarcoma cells [161], the lncRNA TP73-AS1 (TP73 antisense RNA 1) to miR-142 in osteosarcoma cells [162], the lncRNA UCA1 (urothelial cancer associated 1) to miR-126 in myelogenous leukemia cells [163], the lncRNA FTH1P3 (ferritin heavy chain 1 pseudogene 3) to miR-224-5p in uveal melanoma cells [164], and XIST to miR-137 in glioma cells [165].

MALAT1, as mentioned above, promotes the progression of osteosarcoma via upregulation of RhoA, ROCK and Rac1 [161]. Moreover, MALAT1 promotes Rac1 expression as a ceRNA of miR-101b and contributes to liver fibrogenesis in activated hepatic stellate cells [166].

However, several lncRNAs act as tumor-suppressing genes, which are generally lowly expressed in tumor tissue and suppress tumor proliferation or metastasis via repressing Rac1 by unknown mechanisms. Among the reported lncRNAs, we find SchLAH and linc-cdh4-2 in HCC cells [155,167], NBAT-1 in lung cancer cells [168], and MEG3 in primary thyroid cancer [169]. In addition, TUNAR (neural differentiation-associated RNA) represses migration, and invasion of glioma cells by positively regulating miR-200a which suppresses the expression of Rac1 [170].

3.2.3. LncRNA and Cdc42

The lncRNA H19, MALAT1, and SNHG15 (small nucleolar RNA host gene 15) upregulate Cdc42 expression by acting as ceRNAs. H19 targets miR-15b in HCC [171], MALAT1 targets miR-1 in breast cancer cells [172], and SNHG15 binds to miR-153 in glioma vascular endothelial cells [173].

The expression levels of Cdc42 are also regulated by lncRNAs. For example, Cdc42 is upregulated upon downregulation of the lncRNA LINC00707 and thereby promotes cell proliferation and migration
in lung adenocarcinoma [174]. Overexpression of the lncRNA LINC00339 caused by a genetic variant (rs6426749) on chromosome 1p36.12 suppresses the expression of Cdc42 and elevates the risks of osteoporosis incidence [175]. BDNF-AS (brain-derived neurotrophic factor antisense) plays an inhibitory role in human retinoblastoma. BDNF-AS overexpression leads to cell-cycle arrest and Cdc42 downregulation through a yet unknown mechanism [176].

3.3. LncRNA and PAK1

As mentioned above, PAK1 is activated by the lncRNA H19 in HCC cells [171]. H19 is highly expressed in HCC and esophageal squamous cell carcinoma [177,178]. H19 knockdown significantly inhibits EMT, thus providing a new strategy for treating HCC [171].

3.4. LncRNA and ROCK

The lncRNA SNHG5 (small nucleolar RNA host gene 5) is dysregulated in several types of cancer [179–181]. High levels of SNHG5 function as a sponge for miR-26a and competitively bind miR-26a with ROCK, promoting osteosarcoma cell proliferation, invasion, and migration in osteosarcoma [182].

Table 3 summarizes the above lncRNAs that function as ceRNAs in the regulation of actin cytoskeleton regulators during cancer progression.

| LncRNA   | miRNA     | Cancer                        | Reference |
|----------|-----------|-------------------------------|-----------|
| XIST     | miR-133a-3p | colorectal cancer             | [150]     |
| LOC554202| miR-31    | laryngeal squamous cell carcinoma | [151] |
| NORAD    | miR-125a-3p | pancreatic cancer             | [152]     |
| MALAT1   | miR-509   | Osteosarcoma                  | [161]     |
| TP73-AS1 | miR-142   | Osteosarcoma                  | [162]     |
| UCA1     | miR-126   | myelogenous leukemia          | [163]     |
| FTH1P3   | miR-224-5p| uveal melanoma                | [164]     |
| XIST     | miR-137   | Glioma                        | [165]     |
| H19      | miR-15b   | hepatocellular carcinoma      | [171]     |
| MALAT1   | miR-1     | breast cancer                 | [172]     |
| SNHG15   | miR-153   | Glioma                        | [173]     |
| H19      | miR-15b   | hepatocellular carcinoma      | [171]     |
| ROCK     | SNHG5     | Osteosarcoma                  | [182]     |
| COFILIN  | GAS5      | Glioma                        | [147]     |

4. Ubiquitination and IncRNA in Actin Cytoskeleton Regulation

In the last few years, lncRNA regulation of ubiquitination has gradually drawn significant research attention. LncRNAs exert either a positive or negative effect on ubiquitination by various mechanisms. Here, we briefly summarize these mechanisms as follows. (1) LncRNA acts as ceRNA for miRNA of ligases and promotes expression of these E3s [183–188]. For example, MALAT1 promotes FBXW7 expression by acting as ceRNA for miR-155 in glioma cells [185]. The regulations of ubiquitination by lncRNAs of actin cytoskeleton regulators occur via these means. (2) LncRNA binds to the substrate and blocks its interaction with E3 [189–191]. For instance, the lncRNA HOTAIR binds with the androgen receptor and blocks its binding to E3 MDM2 (mouse double minute 2) [189]. (3) LncRNA binds to E3. LincRNA-p21 enhances the activity of p53 by directly binding MDM2. Intriguingly, lincRNA-p21 is also a transcriptional target of p53, which forms positive feedback that promotes the activity of p53 [192]. (4) LncRNA enhances the interaction between E3 and its target [193]. For example, the lncRNA
CDST (cervical cancer DExH-box helicase 9 suppressive transcript) acts as a scaffold between DHX9 (DExH-box helicase 9) and MDM2 to promote the degradation of DHX9 [193]. (5) LncRNA directly links the substrate to UPS components [194]. The lncRNA NRON inhibits HIV-1 replication by directly attaching viral transactivator protein Tat to Cul4B and PSMD11 (proteasome 26S subunit) and promotes the degradation of Tat [194]. (6) LncRNA recruits deubiquitinase and inhibits ubiquitination [195]. The lncRNA LINC00473 inhibits ubiquitination by recruitment of deubiquitinase USP9X and thereby promotes proliferation and invasion of HCC cells [195]. (7) LncRNA regulates ubiquitinase via other PTMs of the target protein, such as methylation [196] and phosphorylation [197]. Phosphorylation of β-catenin leads to its ubiquitination and degradation. Its E3 ligase β-TrCP catalyzes the ubiquitination of β-catenin at K19 and K49. Lnc-b-Catm, which is highly expressed in liver cancer stem cells and recruits EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) to directly catalyze K49 methylation of β-catenin, inhibits the phosphorylation and subsequent ubiquitination of β-catenin [196]. The lncRNA MEG3 promotes the phosphorylation of EZH2 at Thr-345 and Thr-487, and consequently lowers protein levels of EZH2 by promoting its ubiquitination and degradation [197]. Therefore, lncRNAs play an essential role in ubiquitination and proteasome-dependent protein degradation. Understanding how lncRNAs regulate ubiquitination helps us understand how lncRNAs are involved in cancer progression. Meanwhile, based on these mechanisms, the lncRNAs provide potential therapeutic targets for multiple cancer treatment strategies.

So far, several E3s that affect the actin filament regulation pathway have been proven to be controlled by lncRNAs. For instance, SCF^FBXW7^ and SCF^FBXL19^ are regulated by lncRNAs. The relatively well-studied FBXW7 belongs to the F-box protein, which are part of the SCF family ligase complexes. SCF^FBXW7^ is regarded as a tumor suppressor of multiple human cancers because it degrades several proto-oncogenes, Notch and Myc [198]. The lncRNA MIF (c-Myc inhibitory factor) is a ceRNA for miR-586 and increases FBXW7 levels, which subsequently promotes c-Myc degradation and inhibits aerobic glycolysis and tumor progression [183]. It is noteworthy that a feedback loop exists between MIF and c-Myc; overexpression of c-Myc induces transcription of MIF. The lncRNA MT1JP (metallothionein 1J, pseudogene) increases expression levels of FBXW7 and inhibits proliferation and invasion of gastric cancer cells [199]. Moreover, MT1JP regulates FBXW7 and inhibits gastric cancer via binding to miR-92a-3p [184]. MALAT1 also promotes FBXW7 expression by acting as a sponge of miR-155 in glioma cells [185]. The lncRNA TINCR (Terminal differentiation-induced lncRNA) suppresses proliferation and invasion of lung cancer cells by serving as a ceRNA to miR-544a and upregulating FBXW7 [186]. The lncRNA CASC2 (cancer susceptibility candidate 2) acts as a sponge of miR-367 and upregulates FBXW7, thereby inhibits EMT in HCC cells [187]. Intriguingly, although there is currently no evidence that lncRNA interacts with FBXL19, an antisense transcript of FBXL19, FBXL19-AS1, was previously discovered to be oncogenic in colorectal cancer and osteosarcoma [200,201]. FBXL19-AS1 acts as a sponge of miRNA in cancer; however, whether there is any pathological or physiological interaction between FBXL19-AS1 and FBXL19 mRNA still needs further study. The lncRNA SPRIGHTLY promotes cellular proliferation in melanoma cells. XIAP, targeting Rac1 for proteasomal degradation, is significantly upregulated in SPRIGHTLY-overexpressing melanocytes [188].

Theoretically, lncRNAs may be capable of regulating proteins involved in the ubiquitination process, while ubiquitination directly modifies proteins but not RNAs. Thus, lncRNA is likely to be regulated by ubiquitination via ubiquitination-dependent degradation of upstream transcription factors or proteins that interact with lncRNA. However, little research on this mechanism has been published so far.

5. Conclusions

The actin cytoskeleton plays an important role in modulating cell motility and cell morphology, thus the regulation of actin regulatory factors is crucial to normal cell function. Though various diseases are related to this topic, most present research focuses on this regulation in neuron diseases and, especially, tumor progression and metastasis. As is well known, ubiquitination-dependent
degradation is a major mechanism by which appropriate cellular protein levels are maintained. It is easy to understand that abnormal ubiquitination of the actin cytoskeleton regulators may lead to higher metastasis potentiality, but it is more likely to lead to tumor inhibition. For example, the E3 ligase HACE1 is a tumor suppressor in natural killer cell malignancies and breast cancer [116].

Ubiquitination is one of the best understood PTMs. Nevertheless, some questions remain unanswered. For instance, ubiquitination of several regulators has been established, and its role in the progression of certain diseases has been confirmed, but the enzymes involved in the ubiquitination of some particular regulators remain to be identified. Much research has focused on the functions of IncRNAs because of their simultaneous participation in multiple steps of cancer progression or simultaneous involvement in multiple types of cancer, as is the case for MALAT1 [161,172,173,185]. As mentioned above, IncRNAs can affect ubiquitination by many mechanisms. However, IncRNAs often act as ceRNA and increase certain protein level to change actin cytoskeleton in cancer cells (Table 3), which indicates that this mechanism may widely exist. Interestingly, E3s, like MDM2, may be regulated by different IncRNAs in various ways [189,192,193]. Whether these IncRNAs are related or competing with each other is also needed to be elucidated. In this review, we briefly discussed how IncRNA regulates the actin cytoskeleton via interaction with ubiquitination processes. Ubiquitination and IncRNA regulation of these regulators are essential and require further study. Further research can help us understand more about these diseases and open possibilities for clinical applications.

**Funding:** This work was supported by grants from National Natural Science Foundation of China, grant number 81872377; Tianjin Natural Science Foundation of China, grant number 18JCJQJC25600; and National Student’s Platform for Innovation and Entrepreneurship Training Program, grant number 201710062002.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| ADF          | actin-depolymerizing factor |
| Ser3         | serine residue at position 3 |
| TESK         | testicular protein kinase |
| NIK          | Nck-interacting kinase |
| NRK          | Nck-interacting kinase related kinase |
| NESK         | Nck-interacting kinase related kinase/NIK-like embryo-specific kinase |
| SSH          | slingshot family protein phosphate |
| UPS          | ubiquitin-proteasome system |
| HECT         | homologous to E6-AP C-terminus |
| RBR          | RING-between-RING |
| RINGCRBP2    | Cellular retinoic acid binding protein 2 |
| PAK          | p21-activated kinase |
| ROCK         | Rho-associated coiled-coil containing kinase |
| APC/C        | anaphase-promoting complex/cyclosome |
| APC/C-Cdh1   | APC/C with its cofactor Cdh1 |
| HSV-1        | herpes simplex virus 1 |
| Smurf1       | Smad ubiquitination regulatory factor 1 |
| PKCzeta      | protein kinase C zeta |
| EMT          | epithelial-to-mesenchymal transition |
| Par6         | partitioning-defective 6 |
| RASSF1A      | Ras association domain family member 1 |
| SCF          | skp1-cul1-f-box |
| SCFFbxl19    | Skp1-Cul1-F-box FBXL19 |
| FBXL19       | F-box and leucine rich repeat protein 19 |
| Erk2         | extracellular signal regulated kinase 2 |
| Fbxw7        | F-box and WD repeat domain-containing 7 |
| SCFFbxw7     | Skp1-Cul1-F-box Fbxw7 |
SQSTM1 sequestosome 1, also known as p62
HACE1 HECT domain and ankyrin repeat Containing E3 ubiquitin protein kinase 1
IAP Inhibitor of apoptosis protein
ROS reactive oxygen species
HGF hepatocyte growth factor
BIR Baculovirus IAP Repeat
XIAP X-linked IAP
cIAP1 cellular IAP1
TUG1 taurine up-regulated gene 1
EZH2 enhancer of zeste homolog 2
cRNA competitive endogenous RNAs
GAS5 growth arrest-specific 5
LERFS lowly expressed in rheumatoid fibroblast-like synoviocytes
XIST X-inactive-specific transcript
CXCR4 chemokine receptor 4
NORAD non-coding RNA activated by DNA damage
PCGEM1 prostate cancer gene expression marker 1
TBILA TGF-β-induced lncRNA
SchLAH seven chromosome locus associated with hepatocellular carcinoma
HCC hepatocellular carcinoma
MALAT1 metastasis associated in lung adenocarcinoma transcript 1
TDNs tetrahedral DNA nanostructures
UCA1 urothelial cancer associated 1
FTH1P3 ferritin heavy chain 1 pseudogene 3
SNHG15 small nucleolar RNA host gene 15
BDNF-AS brain-derived neurotrophic factor antisense
SNHG5 small nucleolar RNA host gene 5
MIF c-Myc inhibitory factor
CCDST cervical cancer DExH-box helicase 9 suppressive transcript
DHX9 DExH-box helicase 9
MDM2 mouse double minute 2
PSMD11 proteasome 26S subunit
MT1JP metallothionein 1J, pseudogene
TINCR Terminal differentiation-induced lncRNA
CASC2 cancer susceptibility candidate 2

References
1. Pollard, T.D.; Cooper, J.A. Actin, a central player in cell shape and movement. *Science* 2009, 326, 1208–1212. [CrossRef] [PubMed]
2. Akhshi, T.K.; Wernike, D.; Piekny, A. Microtubules and actin crosstalk in cell migration and division. *Cytoskeleton* 2014, 71, 1–23. [CrossRef] [PubMed]
3. Pollard, T.D.; Borisy, G.G. Cellular motility driven by assembly and disassembly of actin filaments. *Cell* 2003, 112, 453–465. [CrossRef]
4. Hall, A. The cytoskeleton and cancer. *Cancer Metastasis Rev.* 2009, 28, 5–14. [CrossRef] [PubMed]
5. Pollard, T.D.; Blanchon, L.; Mullins, R.D. Molecular mechanisms controlling actin filament dynamics in nonmuscle cells. *Annu. Rev. Biophys. Biomol. Struct.* 2000, 29, 545–576. [CrossRef] [PubMed]
6. Dawe, H.R.; Minamide, L.S.; Bamburg, J.R.; Cramer, L.P. ADF/cofilin controls cell polarity during fibroblast migration. *Curr. Biol.* 2003, 13, 252–257. [CrossRef]
7. Mizuno, K. Signaling mechanisms and functional roles of cofilin phosphorylation and dephosphorylation. *Cell Signal* 2013, 25, 457–469. [CrossRef]
8. Wang, W.; Eddy, R.; Condeelis, J. The cofilin pathway in breast cancer invasion and metastasis. *Nat. Rev. Cancer* 2007, 7, 429–440. [CrossRef]
9. Yang, N.; Higuchi, O.; Ohashi, K.; Nagata, K.; Wada, A.; Kangawa, K.; Nishida, E.; Mizuno, K. Cofilin phosphorylation by LIM-kinase 1 and its role in Rac-mediated actin reorganization. *Nature* 1998, 393, 809–812. [CrossRef]

10. Agnew, B.J.; Minamide, L.S.; Bamburg, J.R. Reactivation of phosphorylated actin depolymerizing factor and identification of the regulatory site. *J. Biol. Chem.* 1995, 270, 17582–17587. [CrossRef]

11. Moriyama, K.; Iida, K.; Yahara, I. Phosphorylation of Ser-3 of cofilin regulates its essential function on actin. *Genes Cells* 1996, 1, 73–86. [CrossRef] [PubMed]

12. Arber, S.; Barbayannis, F.A.; Hanser, H.; Schneider, C.; Stanyon, C.A.; Bernard, O.; Caroni, P. Regulation of actin dynamics through phosphorylation of cofilin by LIM-kinase. *Nature* 1998, 393, 805–809. [CrossRef] [PubMed]

13. Sumi, T.; Matsumoto, K.; Takai, Y.; Nakamura, T. Cofilin phosphorylation and actin cytoskeletal dynamics regulated by rho- and Cdc42-activated LIM-kinase 2. *J. Cell Biol.* 1999, 147, 1519–1532. [CrossRef] [PubMed]

14. Toshima, J.; Toshima, J.Y.; Amano, T.; Yang, N.; Narumiya, S.; Mizuno, K. Cofilin phosphorylation by protein kinase testicular protein kinase 1 and its role in integrin-mediated actin reorganization and focal adhesion formation. *Mol. Biol. Cell.* 2001, 12, 1131–1145. [CrossRef]

15. Toshima, J.; Toshima, J.Y.; Takeuchi, K.; Mori, R.; Mizuno, K. Cofilin phosphorylation and actin reorganization activities of testicular protein kinase 2 and its predominant expression in testicular Sertoli cells. *J. Biol. Chem.* 2001, 276, 31449–31458. [CrossRef]

16. Nakano, K.; Kanai-Azuma, M.; Kanai, Y.; Moriyama, K.; Yazaki, K.; Hayashi, Y.; Kitamura, N. Cofilin phosphorylation and actin polymerization by NRK/NECK, a member of the germinal center kinase family. *Exp. Cell Res.* 2003, 287, 219–227. [CrossRef]

17. Ohta, Y.; Kousaka, K.; Nagata-Ohashi, K.; Ohashi, K.; Muramoto, A.; Shima, Y.; Niwa, R.; Uemura, T. Control of actin reorganization by Slingshot, a family of phosphatases that dephosphorylate ADF/cofilin. *Cell* 2002, 108, 233–246. [CrossRef]

18. Ohta, Y.; Kousaka, K.; Nagata-Ohashi, K.; Ohashi, K.; Muramoto, A.; Shima, Y.; Niwa, R.; Uemura, T.; Mizuno, K. Differential activities, subcellular distribution and tissue expression patterns of three members of Slingshot family phosphatases that dephosphorylate cofilin. *Genes Cells* 2003, 8, 811–824. [CrossRef]

19. Ambach, A.; Saunus, J.; Konstandin, M.; Wesselborg, S.; Meuer, S.C.; Samstag, Y. The serine phosphatases PP1 and PP2A associate with and activate the actin-binding protein cofilin in human T lymphocytes. *Eur. J. Immunol.* 2000, 30, 3422–3431. [CrossRef]

20. Gohla, A.; Birkenfeld, J.; Bokoch, G.M. Chronophin, a novel HAD-type serine protein phosphatase, regulates cofilin-dependent actin dynamics. *Nat. Cell Biol.* 2005, 7, 21–29. [CrossRef]

21. Oleinik, N.V.; Krupenko, N.I.; Krupenko, S.A. ALDH1L1 inhibits cell motility via dephosphorylation of cofilin by PP1 and PP2A. *Oncogene* 2010, 29, 6233–6244. [CrossRef] [PubMed]

22. Frantz, C.; Barreiro, G.; Dominguez, L.; Chen, X.; Eddy, R.; Condeelis, J.; Kelly, M.J.; Jacobson, M.P.; Barber, D.L. Cofilin is a pH sensor for actin free barbed end formation: Role of phosphoinositide binding. *J. Cell Biol.* 2008, 183, 865–879. [CrossRef] [PubMed]

23. Yonezawa, N.; Nishida, E.; Iida, K.; Yahara, I. Inhibition of the interactions of cofilin, destrin, and deoxyribonuclease I with actin by phosphoinositides. *J. Biol. Chem.* 1990, 265, 8382–8386. [PubMed]

24. Oser, M.; Yamaguchi, H.; Mader, C.C.; Bravo-Cordero, J.J.; Arias, M.; Chen, X.; Desmarais, V.; van Rheenen, J.; Koleske, A.J.; Condeelis, J. Cortactin regulates cofilin and N-WASP activities to control the stages of invadopodium assembly and maturation. *J. Cell Biol.* 2009, 186, 571–587. [CrossRef] [PubMed]

25. Ono, S. Regulation of actin filament dynamics by actin depolymerizing factor/cofilin and actin-interacting protein 1: New blades for twisted filaments. *Biochemistry* 2003, 42, 13363–13370. [CrossRef] [PubMed]

26. Moriyama, K.; Yahara, I. Human CAP1 is a key factor in the recycling of cofilin and actin for rapid actin turnover. *J. Cell Sci.* 2002, 115, 1591–1601.

27. Vega, F.M.; Ridley, A.J. Rho GTPases in cancer cell biology. *FEBS Lett.* 2008, 582, 2093–2101. [CrossRef]

28. Nobes, C.D.; Hall, A. Rho, rac, and cdc42 GTPases regulate the assembly of multimolecular focal complexes associated with actin stress fibers, lamellipodia, and filopodia. *Cell* 1995, 81, 53–62. [CrossRef]

29. Aronheim, A.; Broder, Y.C.; Cohen, A.; Fritsch, A.; Belisle, B.; Abo, A. Chp, a homologue of the GTPase Cdc42Hs, activates the JNK pathway and is implicated in reorganizing the actin cytoskeleton. *Curr. Biol.* 1998, 8, 1125–1128. [CrossRef]

30. Shimizu, T.; Ibara, K.; Maesaki, R.; Amano, M.; Kaibuchi, K.; Hakoshima, T. Parallel coiled-coil association of the RhoA-binding domain in Rho-kinase. *J. Biol. Chem.* 2003, 278, 46046–46051. [CrossRef]
31. Burns, S.; Thrasher, A.J.; Blundell, M.P.; Machesky, L.; Jones, G.E. Configuration of human dendritic cell cytoskeleton by Rho GTPases, the WAS protein, and differentiation. *Blood* **2001**, *98*, 1142–1149. [CrossRef] [PubMed]

32. Rafiq, N.B.; Lieu, Z.Z.; Jiang, T.; Yu, C.H.; Matsudaira, P.; Jones, G.E.; Bershadsky, A.D. Podosome assembly is controlled by the GTPase ARF1 and its nucleotide exchange factor ARNO. *J. Cell Biol.* **2017**, *216*, 181–197. [CrossRef] [PubMed]

33. Tatin, F.; Grise, F.; Reuzeau, E.; Genot, E.; Moreau, V. Sodium fluoride induces podosome formation in endothelial cells. *Bioll. Cell* **2010**, *102*, 489–498. [CrossRef] [PubMed]

34. Granot-Attas, S.; Luxenburg, C.; Finkelshtein, E.; Elson, A. Protein tyrosine phosphatase epsilon regulates integrin-mediated podosome stability in osteoclasts by activating Src. *Mol. Biol. Cell* **2009**, *20*, 4324–4334. [CrossRef] [PubMed]

35. Linder, S.; Nelson, D.; Weiss, M.; Aepfelbacher, M. Wiskott-Aldrich syndrome protein regulates podosomes in primary human macrophages. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 9648–9653. [CrossRef] [PubMed]

36. Linder, S.; Higgs, H.; Hufner, K.; Schwarz, K.; Pannicke, U.; Aepfelbacher, M. The polarization defect of Wiskott-Aldrich syndrome macrophages is linked to dislocalization of the Arp2/3 complex. *J. Immunol.* **2000**, *165*, 221–225. [CrossRef] [PubMed]

37. Duan, R.; Jin, P.; Luo, F.; Zhang, G.; Anderson, N.; Chen, E.H. Group I PAKs function downstream of Rac to promote podosome invasion during myoblast fusion in vivo. *J. Cell Biol.* **2012**, *199*, 169–185. [CrossRef] [PubMed]

38. Webb, B.A.; Eves, R.; Crawley, S.W.; Zhou, S.; Cote, G.P.; Mak, A.S. PAK1 induces podosome formation in A7r5 vascular smooth muscle cells in a PAK-interacting exchange factor-dependent manner. *Am. J. Physiol. Cell Physiol.* **2005**, *289*, C898–C907. [CrossRef] [PubMed]

39. Gringel, A.; Walz, D.; Rosenberger, G.; Minden, A.; Kutsche, K.; Kopp, P.; Linder, S. PAK4 and alphaPIX determine podosome size and number in macrophages through localized actin regulation. *J. Cell Physiol.* **2006**, *209*, 568–579. [CrossRef] [PubMed]

40. Georgess, D.; Mazzorana, M.; Terrado, J.; Delprat, C.; Chamot, C.; Guasch, R.M.; Perez-Roger, I.; Jurdic, P.; Machuca-Gayet, I. Comparative transcriptomics reveals RhoE as a novel regulator of actin dynamics in bone-resorbing osteoclasts. *Mol. Biol. Cell* **2014**, *25*, 380–396. [CrossRef]

41. Pan, Y.R.; Cho, K.H.; Lee, H.H.; Chang, Z.F.; Chen, H.C. Protein tyrosine phosphatase SHP2 suppresses podosome rosette formation in Src-transformed fibroblasts. *J. Cell Sci.* **2013**, *126*, 657–666. [CrossRef] [PubMed]

42. Sedgwick, A.E.; Clancy, J.W.; Olivia Balmert, M.; D’Souza-Schorey, C. Extracellular microvesicles and invadopodia mediate non-overlapping modes of tumor cell invasion. *Sci. Rep.* **2015**, *5*, 14748. [CrossRef] [PubMed]

43. Daubon, T.; Rochelle, T.; Bourmeyster, N.; Genot, E. Invadopodia and rolling-type motility are specific features of highly invasive p190(bcr-abl) leukemic cells. *Eur. J. Cell Biol.* **2012**, *91*, 978–987. [CrossRef] [PubMed]

44. Hwang, Y.S.; Lee, J.; Zhang, X.; Lindholm, P.F. Lyso phosphatidic acid activates the RhoA and NF-kappaB through Akt/IkappaBalpha signaling and promotes prostate cancer invasion and progression by enhancing functional invadopodia formation. *Tumour Biol.* **2016**, *37*, 6775–6785. [CrossRef] [PubMed]

45. Struckhoff, A.P.; Rana, M.K.; Worthylake, R.A. RhoA can lead the way in tumor cell invasion and metastasis. *Front. Biosci.* **2011**, *16*, 1915–1926. [CrossRef]

46. Sakurai-Yageta, M.; Recchi, C.; Le Dez, G.; Sibarita, J.B.; Daviet, L.; Camonis, J.; D’Souza-Schorey, C.; Chavrier, P. The interaction of IQGAP1 with the exocyst complex is required for tumor cell invasion downstream of Cdc42 and RhoA. *J. Cell Biol.* **2008**, *181*, 985–998. [CrossRef]

47. Cheerathodi, M.; Avci, N.G.; Guerrero, P.A.; Tang, L.K.; Popp, J.; Morales, J.E.; Chen, Z.; Carnero, A.; Lang, F.F.; Ballif, B.A.; et al. The Cytoskeletal Adapter Protein Spinophilin Regulates Invadopodia Dynamics and Tumor Cell Invasion in Glioblastoma. *Mol. Cancer Res.* **2016**, *14*, 1277–1287. [CrossRef]

48. Moshefegh, Y.; Bravo-Cordero, J.J.; Miskolczi, V.; Condeelis, J.; Hodgson, L. A Trio-Rac1-Pak1 signalling axis drives invadopodia disassembly. *Nat. Cell Biol.* **2014**, *16*, 574–586. [CrossRef]

49. Lin, C.W.; Sun, M.S.; Liao, M.Y.; Chung, C.H.; Chi, Y.H.; Chiou, L.T.; Yu, J.; Lou, K.L.; Wu, H.C. Podocalyxin-like 1 promotes invadopodia formation and metastasis through activation of Rac1/Cdc42/cortactin signaling in breast cancer cells. *Carcinogenesis* **2014**, *35*, 2425–2435. [CrossRef]
Nakahara, H.; Otani, T.; Sasaki, T.; Miura, Y.; Takai, Y.; Kogo, M. Involvement of Cdc42 and Rac small G proteins in invadopodia formation of RPMI7951 cells. *Genes Cells* **2003**, *8*, 1019–1027. [CrossRef]

Yamaguchi, H.; Lorenz, M.; Kempiak, S.; Sarmiento, C.; Coniglio, S.; Symons, M.; Segall, J.; Eddy, R.; Miki, H.; Takenawa, T.; et al. Molecular mechanisms of invadopodium formation: The role of the N-WASP-Arp2/3 complex pathway and cofillin. *J. Cell Biol.* **2005**, *168*, 441–452. [CrossRef] [PubMed]

Nicholas, N.S.; Pipili, A.; Lesjak, M.S.; Ameer-Beg, S.M.; Geh, J.L.; Healy, C.; MacKenzie Ross, A.D.; Parsons, M.; Nestle, F.O.; Lacy, K.E.; et al. PAK4 suppresses PDZ-RhoGEF activity to drive invadopodia maturation in melanoma cells. *Oncoarget* **2016**, *7*, 70881–70897. [CrossRef] [PubMed]

Martin-Villar, E.; Borda-d’Agua, B.; Carrasco-Ramirez, P.; Renart, J.; Parsons, M.; Quintanilla, M.; Jones, G.E. Podoplanin mediates ECM degradation by squamous carcinoma cells through control of invadopodia stability. *Oncogene* **2015**, *34*, 4531–4544. [CrossRef] [PubMed]

Semprucci, E.; Tocci, P.; Cianfrocca, R.; Sestito, R.; Caprara, V.; Veglione, M.; Castro, V.D.; Spadaro, F.; Ferrandina, G.; Bagnato, A.; et al. Endothelin A receptor drives invadopodia function and cell motility through the beta-arrestin/PDZ-RhoGEF pathway. *Oncoarget* **2016**, *35*, 3432–3442. [CrossRef] [PubMed]

Berger, C.N.; Crepin, V.F.; Jepson, M.A.; Arbeloa, A.; Frankel, G. The mechanisms used by enteropathogenic *Escherichia coli* to control filopodia dynamics. *Cell Microbiol.* **2009**, *11*, 109–129. [CrossRef] [PubMed]

Huang, Z.H.; Wang, Y.; Yuan, X.B.; He, C. RhoA-ROCK-Myosin pathway regulates morphological plasticity of cultured olfactory ensheathing cells. *Exp. Cell Res.* **2011**, *317*, 2823–2834. [CrossRef]

Pickering, K.; Alves-Silva, J.; Goberdhan, D.; Millard, T.H. Par3 antagonized by CRMP-1. *J. Clin. Invest.* **2011**, *121*, 3189–3205. [CrossRef]

Podoplanin mediates ECM degradation by squamous carcinoma cells through control of invadopodia stability. *Oncogene* **2015**, *34*, 4531–4544. [CrossRef] [PubMed]

Semprucci, E.; Tocci, P.; Cianfrocca, R.; Sestito, R.; Caprara, V.; Veglione, M.; Castro, V.D.; Spadaro, F.; Ferrandina, G.; Bagnato, A.; et al. Endothelin A receptor drives invadopodia function and cell motility through the beta-arrestin/PDZ-RhoGEF pathway. *Oncoarget* **2016**, *35*, 3432–3442. [CrossRef] [PubMed]

Scott, R.W.; Hooper, S.; Crighton, D.; Li, A.; Konig, I.; Munro, P.; Croft, D.R.; et al. LIM kinases are required for invasive path generation by tumor and tumor-associated stromal cells. *J. Cell Biol.* **2010**, *191*, 169–185. [CrossRef]

Sudarov, A.; Gooden, F.; Tseng, D.; Gan, W.B.; Ross, M.E. Lis1 controls dynamics of neuronal filopodia and spines to impact synaptogenesis and social behaviour. *EMBO Mol. Med.* **2013**, *5*, 591–607. [CrossRef]

Chen, T.J.; Gehler, S.; Letourneau, P.C. Cdc42 participates in the regulation of ADF/cofilin and retinal growth cone filopodia by brain derived neurotrophic factor. *J. Neurobiol.* **2006**, *66*, 103–114. [CrossRef]

Jacquemet, G.; Green, D.M.; Bridgewater, R.E.; von Kriegsheim, A.; Humphries, M.J.; Norman, J.C.; Caswell, P.T. RCP-driven alpha5beta1 recycling suppresses Rac and promotes RhoA activity via the RacGAP1-IQGAP1 complex. *J. Cell Biol.* **2013**, *202*, 917–935. [CrossRef]

Berger, C.N.; Crepin, V.F.; Jepson, M.A.; Arbeloa, A.; Frankel, G. The mechanisms used by enteropathogenic *Escherichia coli* to control filopodia dynamics. *Cell Microbiol.* **2009**, *11*, 309–322. [CrossRef]

Huang, Z.H.; Wang, Y.; Yuan, X.B.; He, C. RhoA-ROCK-Myosin pathway regulates morphological plasticity of cultured olfactory ensheathing cells. *Exp. Cell Res.* **2011**, *317*, 2823–2834. [CrossRef]

Pickering, K.; Alves-Silva, J.; Goberdhan, D.; Millard, T.H. Par3/Bazooka and phosphoinositides regulate actin protrusion formation during Drosophila dorsal closure and wound healing. *Development* **2013**, *140*, 800–809. [CrossRef]

Johnston, S.A.; Bramble, J.P.; Yeung, C.L.; Mendes, P.M.; Machesky, L.M. Arp2/3 complex activity in filopodia of spreading cells. * BMC Cell Biol.* **2008**, *9*, 65. [CrossRef]

Alvarez Julia, A.; Frasch, A.C.; Fuchsova, B. Neuronal filopodium formation induced by the membrane glycoprotein M6a (Gpm6a) is facilitated by coronin-1a, Rac1, and p21-activated kinase 1 (Pak1). *J. Neurochem.* **2016**, *137*, 46–61. [CrossRef]

Wakayama, Y.; Fukuhara, S.; Ando, K.; Matsuda, M.; Mochizuki, N. Cdc42 mediates Bmp-induced sprouting angiogenesis through Fmnl3-driven assembly of endothelial filopodia in zebrafish. *Dev. Cell* **2015**, *32*, 109–122. [CrossRef]
90. Frame, M.C. Src in cancer: Deregulation and consequences for cell behaviour. J. Biol. Chem. 2008, 283, 20545–20547. [CrossRef]

91. Heasman, S.J.; Ridley, A.J. Mammalian Rho GTPases: New insights into their functions from in vivo studies. Nat. Rev. Mol. Cell Biol. 2008, 9, 690–701. [CrossRef]

92. Jaffe, A.B.; Hall, A. Rho GTPases: Biochemistry and biology. Annu Rev. Cell Dev. Biol. 2005, 21, 247–269. [CrossRef]
93. Watanabe, N.; Madaule, P.; Reid, T.; Ishizaki, T.; Watanabe, G.; Kakizuka, A.; Saito, Y.; Nakao, K.; Jockusch, B.M.; Narumiya, S. p140mDia, a mammalian homolog of Drosophila diaphanous, is a target protein for Rho small GTPase and is a ligand for profilin. *EMBO J.* 1997, 16, 3044–3056. [CrossRef]

94. Wang, H.R.; Zhang, Y.; Ozdamar, B.; Ogunjimi, A.A.; Alexandrova, E.; Thomsen, G.H.; Wrana, J.L. Regulation of cell polarity and protrusion formation by targeting RhoA for degradation. *Science* 2003, 302, 1775–1779. [CrossRef]

95. Ozdamar, B.; Bose, R.; Barrios-Rodiles, M.; Wang, H.R.; Zhang, Y.; Wrana, J.L. Regulation of the polarity protein Par6 by TGFbeta receptors controls epithelial cell plasticity. *Science* 2005, 307, 1603–1609. [CrossRef]

96. Deglincerti, A.; Liu, Y.; Colak, D.; Hengst, U.; Xu, G.; Jaffrey, S.R. Coupled local translation and degradation regulate growth cone collapse. *Nat. Commun.* 2015, 6, 6888. [CrossRef]

97. Kwei, K.A.; Shain, A.H.; Bair, R.; Montgomery, K.; Karikari, C.A.; van de Rijn, M.; Hidalgo, M.; Maitra, A.; Bashyam, M.D.; Pollack, J.R. SMURF1 amplification promotes invasiveness in pancreatic cancer. *PLoS ONE* 2011, 6, e23924. [CrossRef]

98. Kwon, A.; Lee, H.L.; Woo, K.M.; Ryoo, H.M.; Baek, J.H. SMURF1 plays a role in EGF-induced breast cancer cell migration and invasion. *Mol. Cells* 2013, 36, 548–555. [CrossRef]

99. Bose, R.; Wrana, J.L. Regulation of Par6 by extracellular signals. *Curr. Opin. Cell Biol.* 2006, 18, 206–212. [CrossRef]

100. Lee, M.G.; Jeong, S.I.; Ko, K.P.; Park, S.K.; Ryu, B.K.; Kim, I.Y.; Kim, J.K.; Chi, S.G. RASSF1A Directly Antagonizes RhoA Activity through the Assembly of a Smurf1-Mediated Destruction Complex to Suppress Tumorigenesis. *Cancer Res.* 2016, 76, 1847–1859. [CrossRef]

101. Cheng, P.L.; Lu, H.; Shelly, M.; Gao, H.; Poo, M.M. Phosphorylation of E3 ligase Smurf1 switches its substrate preference in support of axon development. *Neuron* 2011, 69, 231–243. [CrossRef]

102. Wei, J.; Mialiki, R.K.; Dong, S.; Khoo, A.; Mallampalli, R.K.; Zhao, Y.; Zhao, J. A new mechanism of RhoA ubiquitination and degradation: Roles of SCF(FBXL19) E3 ligase and Erk2. *Biochim. Biophys. Acta* 2013, 1833, 2757–2764. [CrossRef]

103. Li, H.; Wang, Z.; Zhang, W.; Qian, K.; Xu, W.; Zhang, S. Fbxw7 regulates tumor apoptosis, growth arrest and the epithelial-to-mesenchymal transition in part through the RhoA signaling pathway in gastric cancer. *Cancer Lett.* 2016, 370, 39–55. [CrossRef]

104. Furukawa, M.; He, Y.J.; Borchers, C.; Xiong, Y. Targeting of protein ubiquitination by BTB-Cullin 3-Roc1 ubiquitin ligases. *Nat. Cell Biol.* 2003, 5, 1001–1007. [CrossRef]

105. Perez-Torrado, R.; Yamada, D.; Defossez, P.A. Born to bind: The BTB protein-protein interaction domain. *Bioessays* 2006, 28, 1194–1202. [CrossRef]

106. Chen, Y.; Yang, Z.; Meng, M.; Zhao, Y.; Dong, N.; Yan, H.; Liu, L.; Ding, M.; Peng, H.B.; Shao, F. Cullin mediates degradation of RhoA through evolutionarily conserved BTB adaptors to control actin cytoskeleton structure and cell movement. *Mol. Cell* 2009, 35, 841–855. [CrossRef]

107. Belaid, A.; Cerezo, M.; Chargui, A.; Corcelle-Termeau, E.; Pedetour, F.; Giuliano, S.; Ilie, M.; Rubera, I.; Tauc, M.; Barale, S.; et al. Autophagy plays a critical role in the degradation of active RHOA, the control of cell cytokinesis, and genomic stability. *Cancer Res.* 2013, 73, 4311–4322. [CrossRef]

108. Belaid, A.; Ndiaye, P.D.; Cerezo, M.; Cailleteau, L.; Brest, P.; Kliowsky, D.J.; Carle, G.F.; Hofman, P.; Mograbi, B. Autophagy and SQSTM1 on the RHOA(d) again: Emerging roles of autophagy in the degradation of signaling proteins. *Autophagy* 2014, 10, 201–208. [CrossRef]

109. Orvedahl, A.; Sumpter, R., Jr.; Xiao, G.; Ng, A.; Kou, Z.; Tang, Y.; Narimatsu, M.; Gilpin, C.; Sun, Q.; Roth, M.; et al. Image-based genome-wide siRNA screen identifies selective autophagy factors. *Nature* 2011, 480, 113–117. [CrossRef]

110. Kovacevic, I.; Sakaue, T.; Majolee, J.; Pronk, M.C.; Maekawa, M.; Geerts, D.; Fernandez-Borja, M.; Higashiyama, S.; Hordijk, P.L. The Cullin-3-Rbx1-KCTD10 complex controls endothelial barrier function via K63 ubiquitination of RhoB. *J. Cell Biol.* 2018, 217, 1015–1032. [CrossRef]

111. Murakami, A.; Maekawa, M.; Kawai, K.; Nakayama, J.; Araki, N.; Semba, K.; Taguchi, T.; Kamei, Y.; Takada, Y.; Higashiyama, S. Cullin-3/KCTD10 E3 complex is essential for Rac1 activation through RhoB degradation in human epidermal growth factor receptor 2-positive breast cancer cells. *Cancer Sci.* 2019, 110, 650–661. [CrossRef]
112. Wang, M.; Guo, L.; Wu, Q.; Zeng, T.; Lin, Q.; Qiao, Y.; Wang, Q.; Liu, M.; Zhang, X.; Ren, L.; et al. ATR/Chkl/Smurf1 pathway determines cell fate after DNA damage by controlling RhoB abundance. Nat. Commun. 2014, 5, 4901. [CrossRef]

113. Andrio, E.; Lotte, R.; Hamamou, D.; Cherfils, J.; Doye, A.; Daugaard, M.; Sorensen, P.H.; Bost, F.; Ruimy, R.; Mettouchi, A.; et al. Identification of cancer-associated missense mutations in hache1 that impair cell growth control and Rac1 ubiquitylation. Sci. Rep. 2017, 7, 44779. [CrossRef]

114. Oberoi-Khanuja, T.K.; Murali, A.; Rajalingam, K. IAPs on the move: Role of inhibitors of apoptosis proteins in cell migration. Cell Death Dis. 2013, 4, e784. [CrossRef]

115. Zhao, J.; Mialki, R.K.; Wei, J.; Coon, T.A.; Zhou, C.; Chen, B.B.; Mallampalli, R.K.; Zhao, Y. SCF E3 ligase F-box protein complex SCF(FBXL19) regulates cell migration by mediating Rac1 ubiquitination and degradation. FASEB J. 2013, 27, 2611–2619. [CrossRef]

116. Murali, A.; Shin, J.; Yurugi, H.; Krishnan, A.; Akutsu, M.; Carpy, A.; Macek, B.; Rajalingam, K. Ubiquitin-dependent regulation of Cdc42 by XIAP. Cell Death Dis. 2017, 8, e2900. [CrossRef]

117. Bobo-Jimenez, V.; Delgado-Esteban, M.; Angibaud, J.; Sanchez-Moran, I.; de la Fuente, A.; Yajeya, J.; Nagerl, U.V.; Castillo, J.; Bolanos, J.P.; Almeida, A. APC/CCdh1-Rock2 pathway controls dendritic integrity and memory. Proc. Natl. Acad. Sci. USA 2017, 114, 4513–4518. [CrossRef]

118. Wang, R.; Yang, Q.; Xiao, W.; Si, R.; Sun, F.; Pan, Q. Cellular retinoic acid binding protein 2 inhibits osteogenic differentiation by modulating LIMK1 in C2C12 cells. Dev. Growth Diff. 2015, 57, 581–589. [CrossRef]

119. Cetinbas, N.; Daugaard, M.; Mullen, A.R.; Hajej, S.; Rotblat, B.; Lopez, A.; Li, A.; DeBerardinis, R.J.; Sorensen, P.H. Loss of the tumor suppressor Hace1 leads to ROS-dependent glutamine addiction. Oncogene 2015, 34, 4005–4010. [CrossRef]

120. Daugaard, M.; Nitsch, R.; Razaghi, B.; McDonald, L.; Jarrar, A.; Torrino, S.; Castillo-Lluva, S.; Rotblat, B.; Li, L.; Malliri, A.; et al. Hace1 controls ROS generation of vertebrate Rac1-dependent NADPH oxidase complexes. Nat. Commun. 2017, 4, 2180. [CrossRef]

121. Zhang, L.; Anglesio, M.S.; O’Sullivan, M.; Zhang, F.; Yang, G.; Sarao, R.; Mai, P.N.; Cronin, S.; Hara, H.; Melynk, N.; et al. The E3 ligase HACE1 is a critical chromosome 6q21 tumor suppressor involved in multiple cancers. Nat. Med. 2007, 13, 1060–1069. [PubMed]

122. Goka, E.T.; Lippman, M.E. Loss of the E3 ubiquitin ligase HACE1 results in enhanced Rac1 signaling contributing to breast cancer progression. Oncogene 2015, 34, 5395–5405. [CrossRef] [PubMed]

123. Castillo-Lluva, S.; Tan, C.T.; Daugaard, M.; Sorensen, P.H.; Malliri, A. The tumour suppressor HACE1 controls cell migration by regulating Rac1 degradation. Oncogene 2013, 32, 1735–1742. [CrossRef] [PubMed]

124. Iimura, A.; Yamazaki, F.; Suzuki, T.; Endo, T.; Nishida, E.; Kusakabe, M. The E3 ubiquitin ligase Hace1 is required for early embryonic development in Xenopus laevis. BMC Dev. Biol. 2016, 16, 31. [CrossRef]

125. Dohi, T.; Okada, K.; Xia, F.; Wilford, C.E.; Samuel, T.; Welsh, K.; Marusawa, H.; Zou, H.; Armstrong, R.; Matsuzawa, S.; et al. An IAP-IAP complex inhibits apoptosis. J. Biol. Chem. 2004, 279, 34087–34090. [PubMed]

126. Gyrd-Hansen, M.; Meier, P. IAPs: From caspase inhibitors to modulators of NF-kappaB, inflammation and cancer. Nat. Rev. Cancer 2010, 10, 561–574. [CrossRef] [PubMed]

127. Oberoi, T.K.; Dogan, T.; Hocking, J.C.; Scholz, R.P.; Mooz, J.; Anderson, C.L.; Karreman, C.; Meyer zu Heringdorf, D.; Schmidt, G.; Ruonala, M.; et al. IAPs regulate the plasticity of cell migration by directly targeting Rac1 for degradation. EMBO J. 2012, 31, 14–28. [CrossRef]

128. Hornburger, M.C.; Mayer, B.A.; Leonhardt, S.; Willer, E.A.; Zahler, S.; Beyerle, A.; Rajalingam, K.; Vollmar, A.M.; Furst, R. A novel role for inhibitor of apoptosis (IAP) proteins as regulators of endothelial barrier function by mediating RhoA activation. FASEB J. 2014, 28, 1938–1946. [CrossRef]

129. Rane, C.K.; Minden, A. P21 activated kinases: Structure, regulation, and functions. Small GTPases 2014, 5, e28003. [CrossRef]

130. Weisz Hubsman, M.; Volinsky, N.; Manser, E.; Yablonski, D.; Aronheim, A. Autophosphorylation-dependent degradation of Pak1, triggered by the Rho-family GTPase. Chp. Biochem. J. 2007, 404, 487–497. [CrossRef] [PubMed]

131. Dou, Q.; Chen, H.N.; Wang, K.; Yuan, K.; Lei, Y.; Li, K.; Lan, J.; Chen, Y.; Huang, Z.; Xie, N.; et al. Ivermectin Induces Cytostatic Autophagy by Blocking the PAK1/Akt Axis in Breast Cancer. Cancer Res. 2016, 76, 4457–4469. [CrossRef] [PubMed]
132. Wang, K.; Gao, W.; Dou, Q.; Chen, H.; Li, Q.; Nice, E.C.; Huang, C. Ivermectin induces PAK1-mediated cytostatic autophagy in breast cancer. *Autophagy* 2016, 12, 2498–2499. [CrossRef] [PubMed]

133. Julian, L.; Olson, M.F. Rho-associated coiled-coil containing kinases (ROCK): Structure, regulation, and functions. *Small GTPases* 2014, 5, e29846. [CrossRef] [PubMed]

134. Prunier, C.; Prudent, R.; Kapur, R.; Sadoul, K.; Lafanechere, L. LIM kinases: Cofilin and beyond. *Oncotarget* 2017, 8, 41749–41763. [CrossRef] [PubMed]

135. Tursun, B.; Schluter, A.; Peters, M.A.; Viehweger, B.; Ostendorff, H.P.; Soosairajah, J.; Drung, A.; Bossenz, M.; Johnsen, S.A.; Schweizer, M.; et al. The ubiquitin ligase Rnf6 regulates local LIM kinase 1 levels in axonal growth cones. *Genes Dev.* 2005, 19, 2307–2319. [CrossRef] [PubMed]

136. Lim, M.K.; Kawamura, T.; Ohsawa, Y.; Ohtsubo, M.; Asakawa, S.; Takayanagi, A.; Shimizu, N. Parkin interacts with LIM Kinase 1 and reduces its cofilin-phosphorylation activity via ubiquitination. *Exp. Cell Res.* 2007, 313, 2858–2874. [CrossRef] [PubMed]

137. Xiang, Y.; Zheng, K.; Zhong, M.; Chen, J.; Wang, X.; Wang, Q.; Wang, S.; Ren, Z.; Fan, J.; Wang, Y. Ubiquitin-proteasome-dependent slingshot 1 downregulation in neuronal cells inactivates cofilin to facilitate HSV-1 replication. *Virology* 2014, 449, 88–95. [CrossRef]

138. Pei, H.; Hu, W.; Guo, Z.; Chen, H.; Ma, J.; Mao, W.; Li, B.; Wang, A.; Wan, J.; Zhang, J.; et al. Long Noncoding RNA CRYBG3 Blocks Cytokinesis by Directly Binding G-Actin. *Cancer Res.* 2018, 78, 4563–4572. [CrossRef]

139. Chen, R.; Kong, P.; Zhang, F.; Shu, Y.N.; Nie, X.; Dong, L.H.; Lin, Y.L.; Xie, X.L.; Zhao, L.L.; Zhang, X.J.; et al. EZH2-mediated alpha-actin methylation needs lncRNA TUG1, and promotes the cortex cytoskeleton formation in VSMCs. *Gene* 2017, 616, 52–57. [CrossRef]

140. Song, J.; Shu, H.; Zhang, L.; Xiong, J. Long noncoding RNA GAS5 inhibits angiogenesis and metastasis of colorectal cancer through the Wnt/beta-catenin signaling pathway. *J. Cell Biochem.* 2019, 120, 6937–6951. [CrossRef]

141. Zong, Y.; Zhang, Y.; Sun, X.; Xu, T.; Cheng, X.; Qin, Y. miR-221/222 promote tumor growth and suppress apoptosis by targeting lncRNA GAS5 in breast cancer. *Biosci. Rep.* 2019, 39. [CrossRef] [PubMed]

142. Li, J.; Yang, C.; Li, Y.; Chen, A.; Li, L.; You, Z. LncRNA GAS5 suppresses ovarian cancer by inducing inflammasome formation. *Biosci. Rep.* 2017, 38. [CrossRef] [PubMed]

143. Liu, B.; Wu, S.; Ma, J.; Yan, S.; Xiao, Z.; Wan, L.; Zhang, F.; Shang, M.; Mao, A. lncRNA GAS5 Reverses EMT and Tumor Stem Cell-Mediated Gemcitabine Resistance and Metastasis by Targeting miR-221/SOCS3 in Pancreatic Cancer. *Mol. Ther. Nucleic Acids* 2018, 13, 472–482. [CrossRef] [PubMed]

144. Zeng, B.; Li, Y.; Jiang, F.; Wei, C.; Chen, G.; Zhang, W.; Zhao, W.; Yu, D. LncRNA GAS5 suppresses proliferation, migration, invasion, and epithelial-mesenchymal transition in oral squamous cell carcinoma by regulating the miR-21/PTEN axis. *Exp. Cell Res.* 2019, 374, 365–373. [CrossRef] [PubMed]

145. Chi, X.; Ding, B.; Zhang, L.; Zhang, J.; Wang, J.; Zhang, W. lncRNA GAS5 promotes M1 macrophage polarization via miR-455-5p/SOCS3 pathway in childhood pneumonia. *J. Cell Physiol.* 2018, 234, 13242–13251. [CrossRef]

146. Dai, X.; Yi, M.; Wang, D.; Chen, Y.; Xu, X. Changqin NO. 1 inhibits neuronal apoptosis via suppressing GAS5 expression in traumatic brain injury mice model. *Biol. Chem.* 2018. [CrossRef]

147. Zhao, X.; Wang, P.; Liu, J.; Zheng, J.; Liu, Y.; Chen, J.; Xue, Y. Gas5 Exerts Tumor-suppressive Functions in Human Gloma Cells by Targeting miR-222. *Mol. Ther.* 2015, 23, 1899–1911. [CrossRef]

148. Pan, B.; Shi, Z.J.; Yan, J.Y.; Li, J.H.; Feng, S.Q. Long non-coding RNA NONMMUG014387 promotes Schwann cell proliferation after peripheral nerve injury. *Neural. Regen Res.* 2017, 12, 2084–2091.

149. Zou, Y.; Xu, S.; Xiao, Y.; Qiu, Q.; Shi, M.; Wang, J.; Liang, L.; Zhan, Z.; Yang, X.; Olsen, N.; et al. Long noncoding RNA LERFS negatively regulates rheumatoid synovial aggression and proliferation. *J. Clin. Invest.* 2018, 128, 4510–4524. [CrossRef]

150. Yu, X.; Wang, D.; Wang, X.; Sun, S.; Zhang, Y.; Wang, S.; Miao, R.; Xu, X.; Qu, X. CXCL12/CXCR4 promotes inflammation-driven colorectal cancer progression through activation of RhoA signaling by sponging miR-133a-3p. *J. Exp. Clin. Cancer Res.* 2019, 38, 32. [CrossRef]

151. Yang, S.; Wang, J.; Ge, W.; Jiang, Y. Long non-coding RNA LOC554202 promotes laryngeal squamous cell carcinoma progression through regulating miR-31. *J. Cell Biochem.* 2018, 119, 6953–6960. [CrossRef] [PubMed]
160. Shi, S.; Peng, Q.; Shao, X.; Xie, J.; Lin, S.; Zhang, T.; Li, Q.; Li, X.; Lin, Y. Self-Assembled Tetrahedral DNA
161. Zhang, Y.; Dai, Q.; Zeng, F.; Liu, H. MALAT1 Promotes the Proliferation and Metastasis of Osteosarcoma
159. Cai, X.; Liu, Y.; Yang, W.; Xia, Y.; Yang, C.; Yang, S.; Liu, X. Long noncoding RNA MALAT1 as a potential
158. Zhang, J.Y.; Weng, M.Z.; Song, F.B.; Xu, Y.G.; Liu, Q.; Wu, J.Y.; Qin, J.; Jin, T.; Xu, J.M. Long noncoding RNA
157. Ji, D.; Zhong, X.; Jiang, X.; Leng, K.; Xu, Y.; Li, Z.; Huang, L.; Li, J.; Cui, Y. The role of long non-coding RNA
156. Augo
155. Ge, Z.; Cheng, Z.; Yang, X.; Huo, X.; Wang, N.; Wang, C.; Gu, D.; Zhao, F.; Yao, M.; et al. Long noncoding RNA AFAP1-AS1 in human malignant tumors. Pathol. Res. Pract. 2018, 214, 1524–1531. [CrossRef]
154. Lu, Z.; Li, Y.; Che, Y.; Huang, J.; Sun, S.; Mao, S.; Lei, Y.; Li, N.; Sun, N.; He, J. The TGFbeta-induced lncRNA TBILA promotes non-small cell lung cancer progression in vitro and in vivo via cis-regulating HGAL and activating SI00A7/JAB1 signaling. Cancer Lett. 2018, 432, 156–168. [CrossRef] [PubMed]
153. Chen, S.; Wang, L.L.; Sun, K.X.; Liu, Y.; Guan, X.; Zong, Z.H.; Zhao, Y. LncRNA PCGEM1 Induces Ovarian Carcinoma Tumorigenesis and Progression Through RhoA Pathway. Cell Physiol. Biochem. 2018, 47, 1578–1588. [CrossRef] [PubMed]
152. Li, H.; Wang, X.; Wen, C.; Huo, Z.; Wang, W.; Zhan, Q.; Cheng, D.; Chen, H.; Deng, X.; Peng, C.; et al. Long noncoding RNA NORAD, a novel competing endogenous RNA, enhances the hypoxia-induced epithelial-mesenchymal transition to promote metastasis in pancreatic cancer. Mol. Cancer 2017, 16, 169. [CrossRef] [PubMed]
151. Chen, S.; Wang, L.L.; Sun, K.X.; Liu, Y.; Guan, X.; Zong, Z.H.; Zhao, Y. LncRNA PCGEM1 Induces Ovarian Carcinoma Tumorigenesis and Progression Through RhoA Pathway. Cell Physiol. Biochem. 2018, 47, 1578–1588. [CrossRef] [PubMed]
150. Li, H.; Wang, X.; Wen, C.; Huo, Z.; Wang, W.; Zhan, Q.; Cheng, D.; Chen, H.; Deng, X.; Peng, C.; et al. Long noncoding RNA NORAD, a novel competing endogenous RNA, enhances the hypoxia-induced epithelial-mesenchymal transition to promote metastasis in pancreatic cancer. Mol. Cancer 2017, 16, 169. [CrossRef] [PubMed]
149. Lu, Z.; Li, Y.; Che, Y.; Huang, J.; Sun, S.; Mao, S.; Lei, Y.; Li, N.; Sun, N.; He, J. The TGFbeta-induced lncRNA TBILA promotes non-small cell lung cancer progression in vitro and in vivo via cis-regulating HGAL and activating SI00A7/JAB1 signaling. Cancer Lett. 2018, 432, 156–168. [CrossRef] [PubMed]
148. Ge, Z.; Cheng, Z.; Yang, X.; Huo, X.; Wang, N.; Wang, C.; Gu, D.; Zhao, F.; Yao, M.; et al. Long noncoding RNA AFAP1-AS1 in human malignant tumors. Pathol. Res. Pract. 2018, 214, 1524–1531. [CrossRef]
147. Augo
146. Augo
145. Ge, Z.; Cheng, Z.; Yang, X.; Huo, X.; Wang, N.; Wang, H.; Wang, C.; Gu; D.; Zhao, F.; Yao, M.; et al. Long noncoding RNA AFAP1-AS1 in human malignant tumors. Pathol. Res. Pract. 2018, 214, 1524–1531. [CrossRef] [PubMed]
144. Ji, D.; Zhong, X.; Jiang, X.; Leng, K.; Xu, Y.; Li, Z.; Huang, L.; Li, J.; Cui, Y. The role of long non-coding RNA AFAP1-AS1 in human malignant tumors. Pathol. Res. Pract. 2018, 214, 1524–1531. [CrossRef]
143. Zhang, J.Y.; Weng, M.Z.; Song, F.B.; Xu, Y.G.; Liu, Q.; Wu, J.Y.; Qin, J.; Jin, T.; Xu, J.M. Long noncoding RNA AFAP1-AS1 indicates a poor prognosis of hepatocellular carcinoma and promotes cell proliferation and invasion via upregulation of the RhoA/Rac2 signaling. Int. J. Oncol. 2016, 48, 1590–1598. [CrossRef]
142. Cai, X.; Liu, Y.; Yang, W.; Xia; Y.; Yang, C.; Yang, S.; Liu, X. Long noncoding RNA MALAT1 as a potential therapeutic target in osteosarcoma. J. Orthop Res. 2016, 34, 932–941. [CrossRef]
141. Shi, S.; Peng, Q.; Shao, X.; Xie; J.; Lin, S.; Zhang, T.; Li, Q.; Li, X.; Lin, Y. Self-Assembled Tetrahedral DNA Nanostructures Promote Adipose-Derived Stem Cell Migration via LncRNA XLOC 010623 and RHOA/ROCK2 Signal Pathway. ACS Appl. Mater. Interfaces 2016, 8, 19353–19363. [CrossRef] [PubMed]
140. Zhang, Y.; Dai, Q.; Zeng, F.; Liu, H. MALAT1 Promotes the Proliferation and Metastasis of Osteosarcoma Cells By Activating the Rac1/JNK Pathway Via Targeting MiR-509. Oncol. Res. 2018. [CrossRef] [PubMed]
139. Yang, G.; Song, R.; Wang, L.; Wu, X. Knockdown of long non-coding RNA TP73-AS1 inhibits osteosarcoma cell proliferation and invasion through sponging miR-142. Biomed. Pharmacother. 2018, 103, 1238–1245. [CrossRef] [PubMed]
138. Sun, M.D.; Zheng, Y.Q.; Wang, L.P.; Zhao, H.T.; Yang, S. Long noncoding RNA UCA1 promotes cell proliferation, migration and invasion of human leukemia cells via sponging miR-126. Eur. Rev. Med. Pharmacol. Sci. 2018, 22, 2233–2245. [PubMed]
137. Zheng, X.; Tang, H.; Zhao, X.; Sun, Y.; Jiang, Y.; Liu, Y. Long non-coding RNA FTH1P3 facilitates uveal melanoma cell growth and invasion through miR-224-5p. PLoS ONE 2017, 12, e0184746. [CrossRef] [PubMed]
136. Wang, Z.; Yuan, J.; Li, L.; Yang, Y.; Xu, X.; Wang, Y. Long non-coding RNA XIST exerts oncogenic functions in human glioma by targeting miR-137. Am. J. Transl. Res. 2017, 9, 1845–1855. [PubMed]
135. Yu, F.; Lu, Z.; Cai, J.; Huang, K.; Chen, B.; Li, G.; Dong, P.; Zheng, J. MALAT1 functions as a competing endogenous RNA to mediate Rac1 expression by sequestering miR-101b in liver fibrosis. Cell Cycle 2015, 14, 3885–3896. [CrossRef]
134. Gao, Y.; Wang, G.; Zhang, C.; Lin, M.; Liu, X.; Zeng, Y.; Liu, J. Long non-coding RNA linc-cdh4-2 inhibits the migration and invasion of HCC cells by targeting R-cadherin pathway. Biochem. Biophys. Res. Commun. 2016, 480, 348–354. [CrossRef]
133. Lei, T.; Lv, Z.Y.; Fu, J.F.; Wang, Z.; Fan, Z.; Wang, Y. LncRNA NBAT-1 is down-regulated in lung cancer and influences cell proliferation, apoptosis and cell cycle. Eur. Rev. Med. Pharmacol. Sci. 2018, 22, 1958–1962. [CrossRef]
132. Wang, C.; Yan, G.; Zhang, Y.; Jia, X.; Bu, P. Long non-coding RNA MEG3 suppresses migration and invasion of thyroid carcinoma by targeting of Rac1. Neoplasma 2015, 62, 541–549. [CrossRef]
131. Dai, J.; Ma, J.; Yu, B.; Zhu, Z.; Hu, Y. Long Noncoding RNA TUNAR Represses Growth, Migration, and Invasion of Human Glioma Cells Through Regulating miR-200a and Rac1. Oncol. Res. 2018, 27, 107–115. [CrossRef]
171. Zhou, Y.; Fan, R.G.; Qin, C.L.; Jia, J.; Wu, X.D.; Zha, W.Z. LncRNA-H19 activates CDC42/PAK1 pathway to promote cell proliferation, migration and invasion by targeting miR-15b in hepatocellular carcinoma. *Genomics* 2018. [CrossRef] [PubMed]

172. Chou, J.; Wang, B.; Zheng, T.; Li, X.; Zheng, L.; Hu, J.; Zhang, Y.; Xing, Y.; Xi, T. MALAT1 induced migration and invasion of human breast cancer cells by competitively binding miR-1 with cdc42. *Biochem. Biophys. Res. Commun.* 2016, 472, 262–269. [CrossRef] [PubMed]

173. Ma, Y.; Xue, Y.; Liu, X.; Qu, C.; Cai, H.; Wang, P.; Li, Z.; Li, Z.; Liu, Y. SNHG15 affects the growth of glioma microvascular endothelial cells by negatively regulating miR-153. *Oncol. Rep.* 2017, 38, 3265–3272. [CrossRef] [PubMed]

174. Ma, T.; Ma, H.; Zou, Z.; He, X.; Liu, Y.; Shuai, Y.; Xie, M.; Zhang, Z. The Long Intergenic Noncoding RNA 00707 promotes Lung Adenocarcinoma Cell Proliferation by Regulating Cdc42. *Cell Physiol. Biochem.* 2018, 45, 1566–1580. [CrossRef] [PubMed]

175. Chen, X.F.; Zhu, D.L.; Yang, M.; Hu, W.X.; Duan, Y.Y.; Lu, B.J.; Rong, Y.; Dong, S.S.; Hao, R.H.; Chen, J.B.; et al. An Osteoporosis Risk SNP at 1p36.12 Acts as an Allele-Specific Enhancer to Modulate LINC00339 Expression via Long-Range Loop Formation. *Am. J. Hum. Genet.* 2018, 102, 776–793. [CrossRef]

176. Shang, W.; Yang, Y.; Zhang, J.; Wu, Q. Long noncoding RNA BDNF-AS is a potential biomarker and regulates cancer development in human retinoblastoma. *Biochem. Biophys. Res. Commun.* 2018, 497, 1142–1148. [CrossRef] [PubMed]

177. Chou, J.; Wang, B.; Zheng, T.; Li, X.; Zheng, L.; Hu, J.; Zhang, Y.; Xing, Y.; Xi, T. MALAT1 induced migration and invasion of human breast cancer cells by competitively binding miR-1 with cdc42. *Biochem. Biophys. Res. Commun.* 2016, 472, 262–269. [CrossRef] [PubMed]

178. Zhao, W.; Mazar, J.; Lee, B.; Sawada, J.; Li, J.L.; Shelley, J.; Govindarajan, S.; Towler, D.; Mattick, J.S.; Komatsu, M.; et al. The Long Noncoding RNA SPRIGHTLY Regulates Cell Proliferation in Primary Human Melanocytes. *J. Invest. Dermatol.* 2016, 136, 819–828. [CrossRef] [PubMed]
189. Zhang, A.; Zhao, J.C.; Kim, J.; Fong, K.W.; Yang, Y.A.; Chakravarti, D.; Mo, Y.Y.; Yu, J. LncRNA HOTAIR Enhances the Androgen-Receptor-Mediated Transcriptional Program and Drives Castration-Resistant Prostate Cancer. *Cell Rep.* 2015, 13, 209–221. [CrossRef] [PubMed]

190. Jiang, R.; Tang, J.; Chen, Y.; Deng, L.; Ji, J.; Xie, Y.; Wang, K.; Jia, W.; Chu, W.M.; Sun, B. The long noncoding RNA lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion. *Nat. Commun.* 2017, 8, 15129. [CrossRef]

191. Yu, T.; Zhao, Y.; Hu, Z.; Li, J.; Chu, D.; Zhang, J.; Li, Z.; Chen, B.; Zhang, X.; Pan, H.; et al. MetaLnc9 Facilitates Lung Cancer Metastasis via a PGK1-Activated AKT/mTOR Pathway. *Cancer Res.* 2017, 77, 5782–5794. [CrossRef] [PubMed]

192. Wu, G.; Cai, J.; Han, Y.; Chen, J.; Huang, Z.P.; Chen, C.; Cai, Y.; Huang, H.; Yang, Y.; Liu, Y.; et al. LincRNA-p21 regulates neointima formation, vascular smooth muscle cell proliferation, apoptosis, and atherosclerosis by enhancing p53 activity. *Circulation* 2014, 130, 1452–1465. [CrossRef] [PubMed]

193. Ding, X.; Jia, X.; Wang, C.; Xu, J.; Gao, S.J.; Lu, C. A DHX9-lncRNA-MDM2 interaction regulates cell invasion and angiogenesis of cervical cancer. *Cell Death Differ.* 2018. [CrossRef] [PubMed]

194. Li, J.; Chen, C.; Ma, X.; Geng, G.; Liu, B.; Zhang, Y.; Zhang, S.; Zhong, F.; Liu, C.; Yin, Y.; et al. Long noncoding RNA NRON contributes to HIV-1 latency by specifically inducing tat protein degradation. *Nat. Commun.* 2016, 7, 11730. [CrossRef] [PubMed]

195. Chen, H.; Yang, F.; Li, X.; Gong, Z.J.; Wang, L.W. Long noncoding RNA LNC473 inhibits the ubiquitination of survivin via association with USP9X and enhances cell proliferation and invasion in hepatocellular carcinoma cells. *Biochem. Biophys. Res. Commun.* 2018, 499, 702–710. [CrossRef]

196. Zhu, P.; Wang, Y.; Huang, G.; Ye, B.; Liu, B.; Wu, J.; Du, Y.; He, L.; Fan, Z. Inc-beta-Catm elicits EZH2-dependent beta-catenin stabilization and sustains liver CSC self-renwal. *Nat. Struct. Mol. Biol.* 2016, 23, 631–639. [CrossRef]

197. Jin, L.; Cai, Q.; Wang, S.; Wang, S.; Mondal, T.; Wang, J.; Quan, Z. Long noncoding RNA MEG3 regulates LATS2 by promoting the ubiquitination of EZH2 and inhibits proliferation and invasion in gallbladder cancer. *Cell Death Dis.* 2018, 9, 1017. [CrossRef]

198. Welcker, M.; Clurman, B.E. FBW7 ubiquitin ligase: A tumour suppressor at the crossroads of cell division, growth and differentiation. *Nat. Rev. Cancer* 2008, 8, 83–93. [CrossRef]

199. Lv, Z.; Zhang, Y.; Yu, X.; Lin, Y.; Ge, Y. The function of long non-coding RNA MT1JP in the development and progression of gastric cancer. *Pathol. Res. Pract.* 2018, 214, 1218–1223. [CrossRef]

200. Pan, R.; He, Z.; Ruan, W.; Li, S.; Chen, H.; Chen, Z.; Liu, F.; Tian, X.; Nie, Y. LncRNA FBXL19-AS1 regulates osteosarcoma cell proliferation, migration and invasion by sponging miR-346. *Onco. Targets Ther.* 2018, 11, 8409–8420. [CrossRef]

201. Shen, B.; Yuan, Y.; Zhang, Y.; Yu, S.; Peng, W.; Huang, X.; Feng, J. Long non-coding RNA FBXL19-AS1 plays oncogenic role in colorectal cancer by sponging miR-203. *Biochem. Biophys. Res. Commun.* 2017, 488, 67–73. [CrossRef] [PubMed]

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).