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Review Article

Functions of the Tumor Suppressors p53 and Rb in Actin Cytoskeleton Remodeling

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Mechanical microenvironments, such as extracellular matrix stiffness and strain, have crucial roles in cancer progression. Cells sense their microenvironments with mechanosensing biomolecules, which is accompanied by the modulation of actin cytoskeleton structures, and the signals are subsequently transduced downstream as biochemical signals. The tumor suppressors p53 and retinoblastoma protein (Rb) are known to prevent cancer progression. The p53 and Rb signaling pathways are disrupted in many types of cancers. Here, we review recent findings about the roles of these tumor suppressors in the regulation of mechanosensing biomolecules and the actin cytoskeleton. We further discuss how dysfunction in the p53- and/or Rb-mediated mechanosignaling pathways is potentially involved in cancer progression. These pathways might provide good targets for developing anticancer therapies.

1. Introduction

During cancer progression, cells acquire several abilities, including continual unregulated proliferation, resistance to cell death, invasiveness, and epithelial-mesenchymal transition (EMT) [1–3]. Remodeling of the actin cytoskeleton is also associated with cancer progression [4, 5]. Actin is one of the most abundant proteins in eukaryotic cells. Globular actin (G-actin) monomers polymerize into actin filaments (F-actin), which is then depolymerized, in a steady-state equilibrium. Actin polymerization is regulated by actin nucleators, including the formins, actin-related protein 2/3 (Arp2/3) complex, and spire [6–8]. The activation of these actin nucleators is regulated by Rho GTPases, including Rho, Rac, and Cdc42, which typically induce the formation of stress fibers, lamellipodia, and filopodia, respectively [9]. Actin depolymerization is enhanced by gelsolin and actin-depolymerizing factor (ADF)/cofilin, while spontaneous depolymerization is slow [10]. Gelsolin is activated by calcium ions but inhibited by phosphatidylinositol 4,5-bisphosphate. Activation of ADF/cofilin is regulated by its phosphorylation. Kinases, including LIM kinase (LIMK), testicular protein kinase (TESK), and integrin-linked kinase (ILK), induce the activation of ADF/cofilin, while phosphatases, such as slingshot and chronophin, induce its inactivation [11–13].

The invasion of cancer cells is associated with the formation of several actin-mediated structures, including lamellipodia, filopodia, podosomes, and invadopodia [14, 15]. Podosomes and invadopodia degrade the extracellular matrix (ECM), which facilitates invasion into other tissues. Protrusions of lamellipodia and filopodia are likely to promote cancer cell invasion through the generation of traction forces that are required for mesenchymal-mode migration. Blebs are also formed during the migration of cancer cells and promote their invasion [16, 17]. The formation of blebs is initiated upon disruption of the actin cortex and driven by intracellular pressure generated in the cytoplasm. In association with reassembly of the actin cortex, the blebs are then retracted by

actomyosin contraction, generating traction forces that move the cells forward. While membrane blebbing is typically associated with apoptotic cell death [18], aggressive cancer cells appear to form and use blebs for invasion independently of cell death [16, 17]. In addition to invasion, the insensitivity of aggressive cancer cells to antitumor drug-induced apoptosis might also be affected by actin cytoskeletal structures. Stress fibers, lamellipodia, and filopodia are considered to promote the survival of cancer cells.

Actomyosin contraction is essential for sensing the mechanical environments surrounding cells [19]. At the sites of cell-ECM adhesion, the formation of focal adhesion complexes, including integrins, focal adhesion kinase (FAK), p130 Crk-associated substrate (p130Cas; also known as Bcar1), and paxillin, promotes actin polymerization and activates myosin [20–24]. Activated actomyosin generates a contractile force that induces conformational changes in several focal adhesion proteins to enhance downstream signaling [25]. Furthermore, α-catenin has been identified as a mechanosensing protein in adherens junction (AJ) complexes at cell-cell junctions [26]. The homophilic interaction of cadherin ectodomains induces the assembly of AJ complexes and local actin polymerization. While actin filaments link to cadherins via β-catenin and α-catenin, an actomyosin-generated force transmitted to this linkage causes conformational changes in α-catenin, which promotes its binding to vinculin [27]. This results in the recruitment of various proteins, including zyxin and Arp2/3, to AJs and a further increase in actin polymerization [26, 28]. The expression and activity of proteins in focal adhesions and AJ complexes are often altered during cancer progression.

Actin dynamics influence cellular behavior not only by regulating cytoskeletal organization but also by controlling gene expression. For example, in skeletal muscle differentiation, disassembly of actin filaments is required for the muscle-specific gene expression induced by serum response factor (SRF) [29–32]. G-actin binds to megakaryocytic acute leukemia (MAL; also known as MKL1/MRTF-A), a cofactor of SRF, and sequesters it from the nucleus, therefore, causing alterations in the equilibrium between actin polymerization and depolymerization perturb differentiation [33].

Cancer progression is associated with the accumulation of gene mutations and cancer is generally considered to be a genomic disease. *TP53*, which encodes the p53 transcription factor, is mutated in more than 50% of human cancers [34]. This protein exerts its biological activities, such as cell cycle arrest and induction of apoptosis or senescence, by upregulating the expression of various target genes [35–37]. Stresses, such as DNA damage, induce the stabilization and activation of p53 by affecting its posttranscriptional modifications such as phosphorylation and acetylation [38, 39]. The expression level of p53 is low under low stress conditions. However, it still contributes to cellular homeostasis involving differentiation and cell cycle progression.

Germline mutations in the retinoblastoma (*Rb*) gene occur frequently in retinoblastoma, which is the most common cancer of the developing retina in early childhood [40]. Somatic mutations in Rb are also observed in several cancers, including small-cell lung cancer and bladder cancer [41].

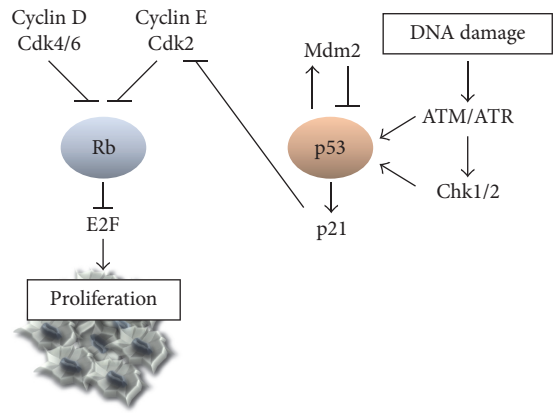

Figure 1: p53 suppresses the cell proliferation mediated by the Rb-E2F pathway. Phosphorylation of Rb by CDK4/6-cyclin D and CDK2-cyclin E causes the dissociation of Rb from E2F to promote cell cycle progression. In response to DNA damage, ataxia telangiectasia mutated (ATM) or ataxia telangiectasia and Rad3-related protein (ATR) are activated and phosphorylate p53 either directly or through Chk1/2. Phosphorylated p53 dissociates from Mdm2 and is thereby stabilized. Active p53 then induces the transcription of its target genes involving $p21^{WAF1}$, resulting in the inhibition of CDK2-cyclin E activity.

Furthermore, inactivation of Rb by hyperphosphorylation via the constitutive activation of its kinases has been implicated in tumor initiation and progression [40, 42, 43]. Phosphorylation of Rb by cell cycle kinase complexes, that is, cyclin-dependent kinase (CDK) 4/6-cyclin D and Cdk-2-cyclin E, releases the transcriptional repression of E2F, resulting in cell cycle progression. The activity of Cdk-2-cyclin E is inhibited by the CDK-inhibitor $p21^{WAF1}$, a transcriptional target of p53 (Figure 1) [44]. Rb also plays a critical role in the development of several tissues, including muscle and bone, by regulating other transcriptional factors such as MyoD and RUNX2 [43].

While various molecules that constitute the actin cytoskeleton, focal adhesions, and AJs are involved in sensing the mechanical microenvironments surrounding cells, little is known about the contribution of p53 and Rb to mechanosensing. In this review, we summarize the roles of p53 and Rb in the regulation of the actin cytoskeleton and mechanosensing proteins, which provides insights into the mechanisms of cancer progression.

2. p53 Regulates Integrin Expression and Activation

Integrins, which are heterodimers composed of α and β subunits, form a connection between the ECM and actin cytoskeleton, and their downstream signaling molecules drive actin polymerization [45–47]. In humans, 18 types of α subunits and 8 types of β subunits have been identified, and they assemble into 24 types of integrins that bind specifically to their ligands, including fibronectin, laminin, and collagen [48]. The binding of a ligand to the extracellular domain of integrin induces the recruitment of focal adhesion proteins, including FAK, p130Cas, and paxillin, at the cytoplasmic side,

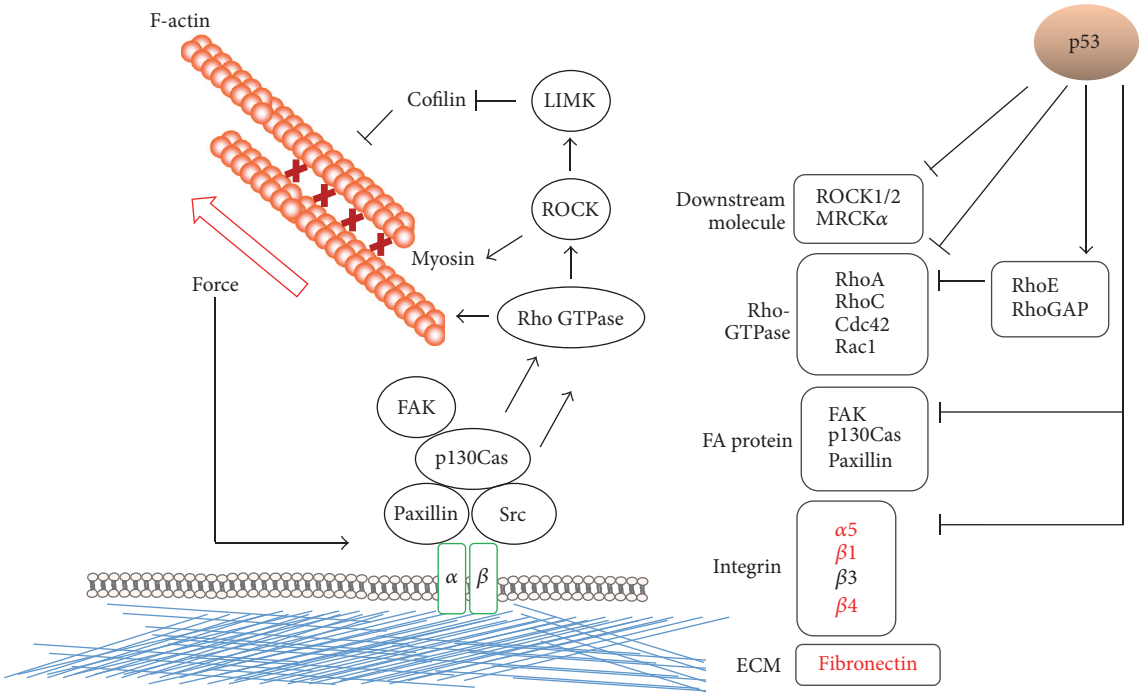

FIGURE 2: Effects of p53 on molecules in mechanosensing pathways. Cells sense ECM stiffness and modulate actin cytoskeleton structures through the integrin signaling pathways. p53 wild-type suppresses cancer progression through downregulation of the molecules in the integrin signaling pathways. Conversely, several p53 mutants exert gain-of-function effects on the upregulation of molecules in the integrin signaling pathways. The molecules indicated by red letters are upregulated by p53 GOF mutants.

leading to the activation of Rho GTPases and stimulation of actin polymerization [20–24]. The cytoplasmic domain of integrin links to actin filaments through several adaptor proteins. Actomyosin contraction potentially modulates the affinity of integrin to its ligands by changing the conformation of integrin.

Integrin signaling plays a fundamental role in tumor cell invasion and metastasis. The expression levels of several integrins, including $\alpha5\beta1$, $\alpha6\beta4$, $\alpha4\beta1$, $\alpha v\beta3$, $\alpha v\beta5$, $\alpha v\beta6$, and $\alpha2\beta1$, in cancer cells correlate with their aggressiveness [46, 49, 50]. It has been revealed that p53 regulates the expression of integrins $\alpha5$, $\beta1$, $\beta3$, and $\beta4$ (Figure 2) [51–56]. Janouskova et al. showed that Nutlin-3a, an MDM2 antagonist that acts as a p53 activator, decreases the expression of integrin $\alpha5$ in glioma and colorectal cancer cells [51, 52]. Bon et al. reported that the expression of integrin $\beta4$ was decreased by either the ectopic expression of p53 or DNA damage in wild-type p53-expressing cells [56]. Conversely, the ectopic expression of transactivating p63 (TAp63) or transactivating p73 (TAp73), two p53 family members, increased the promoter activity of *ITGB4*, which encodes integrin $\beta4$. Importantly, depletion of p53 enhanced the TAp63- or TAp73-dependent activation of the *ITGB4* promoter. Not only DNA damage triggered by genotoxic drugs or activation of oncogenes but also other forms of stress, such as chromosomal aberrations, hypoxia, and telomere shortening, are associated with cancer progression [36]. Repression of integrin $\alpha5$ and $\beta4$ expression by p53 activated in response to these stresses is likely to prevent the progression of cancer stimulated by these stresses.

Vaillant et al. reported, using mammary tumors derived from p53-deficient mice lacking one allele ($p53^{+/-}$), that loss of p53 function promotes cancer cell invasion by upregulating integrin $\beta3$ expression at the cell surface [54]. We also reported that the depletion of p53 increased the expression of integrin $\beta3$, encoded by *ITGB3*, in a transcription factor NF-κB-dependent manner. This leads to an increase in integrin $\alpha v\beta3$ expression at the cell surface, which promotes the formation of lamellipodia. Lamellipodia formation mediated by integrin $\alpha v\beta3$ contributes to the constitutive activation of another transcription factor, STAT3, which plays an integral role in tumor cell invasion [55]. Conversely, Qui et al. showed that pifithrin-α, a p53 inhibitor, increases the expression of integrin $\beta1$ in endothelial cells when the expression of *ID1* (encoding inhibitor of DNA binding [ID] 1, which belongs to a family of basic helix-loop-helix transcription factors lacking DNA-binding domains and plays a critical role in angiogenesis) is depleted [53]. Pifithrin-α also enhances the formation of F-actin at the peripheral rim and promotes tubular formation. *ID1* expression is upregulated in angiogenic tumor vessels. These results suggest that the p53-dependent maintenance of the low expression levels of integrins $\beta1$ and $\beta3$ helps to attenuate both cancer cell invasion and angiogenesis, which would prevent cancer progression.

3. Regulation of Focal Adhesion-Rho Signaling Pathways by p53

FAK contains three distinct domains: a four-point-one, ezrin, radixin, moesin (FERM) domain; a kinase domain; and a focal adhesion targeting (FAT) domain [21]. The residues in the FERM domain are responsible for the autoinhibition of FAK by intramolecular interactions. External forces are believed to induce a conformational change of the FAT domain to disrupt these intramolecular interactions. However, since FAK does not bind directly to actin filaments, it is unclear whether FAK activity in cells is truly regulated by force such as actomyosin contraction.

Phosphorylation of p130Cas is also facilitated by external forces [57]. Src phosphorylates the substrate domain of p130Cas (CasSD), which is characterized by 15 YXXP motifs. Phosphorylated CasSD provides a binding site for the Crk-DOCK180 complex, a guanine nucleotide exchange factor (GEF) for Rac. External forces induce a conformational change of CasSD, which facilitates the phosphorylation of p130Cas. Like FAK, p130Cas does not bind directly to actin filaments [25]. Recently, we found that tensin 1 mediates the interaction of p130Cas with actin filaments [58]. However, given that the expression level of tensin 1 is generally low in metastatic cancers [59, 60], it may not be responsible for the enhanced phosphorylation of p130Cas and FAK in aggressive cancer cells.

Paxillin, an adaptor protein at focal adhesions, is known to be involved in the mechanical-cue-dependent regulation of Rho GTPases [22]. While the underlying mechanism remains unclear, the C-terminal LIM domains of paxillin are likely to be involved in the responses of paxillin against mechanical inputs [61]. Paxillin potentially promotes the invasion of cancer cells; however, its levels of expression and phosphorylation differ largely among cancer cell types [62].

It has been suggested that p53 regulates these mechanoresponsive proteins at focal adhesions (Figure 2). The ectopic expression of p53 suppresses the promoter activity of *FAK* either directly [63] or by inducing the expression of X-linked ectodermal dysplasia receptor (XEDAR), a member of the tumor necrosis factor receptor (TNFR) superfamily [64]. Recently, we reported that oncogenic Ras-induced transformation leads to the cleavage of β-actin and concomitant suppression of p130Cas phosphorylation in a p53-dependent manner [65]. We have further shown that both the oncogenic Ras-induced disruption of mitochondrial integrity and p53-mediated activation of the mitochondrial protease high temperature requirement A2 (HtrA2; also known as Omi) are involved in the cleavage of β-actin in Ras-transformed cells. The p130Cas-Rac1 axis is known to promote cell invasion by inducing lamellipodia formation [66]. Interestingly, the cytoplasmic localization of p53 was increased by Ras transformation, causing mitochondrial translocation of the mitogen-activated protein kinase p38. p38 translocated into mitochondria and then enhances activation of HtrA2/Omi [67]. While cytoplasmic p53 is known to have tumor suppressive functions via the suppression of centrosome duplication, induction of cell death, and inhibition of autophagy [68], our results revealed a novel mechanism underlying the tumor suppressive function of cytoplasmic p53.

The constitutively active form of Src and oncogenic Ras induce cellular transformation and invasion. Mukhopadhyay et al. reported that loss of p53 function enhances Src-driven cell invasion by promoting the formation of actin-rich structures, such as podosomes and invadopodia [14, 69–71]. They showed that the level of caldesmon, an actin binding protein that can suppress both podosome and invadopodia formation [72], was decreased by inhibition of p53 [70]. Further, there is a possibility that p53 diminishes Src-driven cell invasion via inhibition of p130Cas-mediated podosome and invadopodia activity. As described above, a decrease in p130Cas phosphorylation by impairment of actin filaments following Ras-induced transformation was suppressed by p53 knockdown, while the activity of Src, a kinase of p130Cas, was not affected. Indeed, knockdown of p53 decreases p130Cas phosphorylation in Src-transformed cells (personal communication).

p53 regulates the activity of Rho GTPases (Figure 2) [73–75]. p53 mediates the oncogenic-Ras-induced activation of p190 Rho GTPase-activating protein (RhoGAP) [76]. A deficiency in p53 expression increases RhoA activity and stimulates the formation of blebs via the activation of Rho-associated protein kinase (ROCK) [77]. While RhoA typically promotes stress fiber formation [9], RhoA can increase cell-exerted contractile forces even in Ras-transformed cells in which stress fiber formation is largely diminished [76]. The generation of cell-exerted contractile forces plays a crucial role in the invasion and intravasation/extravasation of cancer cell tissue and blood vessels.

p53 regulates the expression of several genes that encode effector proteins of RhoA/RhoC and Cdc42. For example, depletion of p53 increases the expression of *ROCK1/2* and *MRCK*α, which encodes myotonic dystrophy kinase-related Cdc42-binding kinase α (MRCKα). The ectopic expression of p53 in turn increases the expression of these genes [78]. Not only RhoA signaling but also Rac and Cdc42 signaling is affected by p53. Depletion of p53 increases phosphoinositide 3-kinase- (PI3-kinase-) mediated Rac activity [79]. Conversely, the ectopic expression of p53 decreases Cdc42 activity and concomitant filopodia formation [80].

F-actin formation is both negatively and positively regulated by p53 in response to DNA damage. Croft et al. reported that treatment with the antitumor drug doxorubicin reduces the activity of cofilin by increasing the expression of RhoC and LIM kinase 2 (LIMK2) in a p53-dependent manner [81]. While doxorubicin treatment promotes the formation of stress fibers, depletion of either RhoC or LIMK2 abrogates doxorubicin-induced stress fiber formation. Conversely, other antitumor drugs, including camptothecin and etoposide, attenuate the formation of stress fibers through the p53-dependent expression of RhoE [82]. Depletion of RhoE prevents the camptothecin-induced disassembly of stress fibers.

It has been suggested that, in response to DNA damage, p53 influences actin cytoskeleton remodeling by regulating the cytoskeleton adaptor protein ankyrin-1, which is encoded by *ANK1*. Hall et al. reported that the etoposide-induced activation of p53 increases the expression of *ANK1* [83]. Etoposide treatment promotes the formation of actin-rich long

protrusions, even though knockdown of ankyrin-1 attenuates this response. By contrast, stress fiber formation in etoposide-treated cells is enhanced by depleting ankyrin-1 expression. The ankyrin-1-mediated activation of cofilin may be involved in these actin remodeling processes. Furthermore, ankyrin-1 contributes to the association of the cortical spectrin-actin network with the plasma membrane by linking spectrin with membrane proteins including the anion exchanger and CD44 [84, 85]. Spectrin plays a crucial role in maintaining the structural integrity of the plasma membrane and has been suggested to be a potential mechanosensing protein [86]. Therefore, the p53-dependent regulation of ankyrin-1 may contribute not only to actin remodeling but also to mechanosensing/mechanoprotection of cells.

4. Regulation of Cadherin Expression by p53

It is well established that EMT promotes cell invasion and metastasis. It is important to note that EMT is associated with a decrease in E-cadherin expression and an increase in N-cadherin expression, which are major components of cell-cell adhesion complexes. They form homophilic adhesion bonds. Since the interactions of N-cadherin are much weaker than those of E-cadherin, the shift from E-cadherin to N-cadherin during EMT weakens cell-cell adhesions, which promotes the scattering and migration of cancer cells. Like focal adhesions, AJs are reportedly involved in sensing the mechanical microenvironments of cells [26, 87–90].

In cells undergoing EMT, the expression of E-cadherin, encoded by *CDH1*, is suppressed by Snail, zinc finger E-box binding homeobox 1/2 (ZEB1/2), and Slug. These proteins in turn increase the expression of N-cadherin, which is encoded by *CDH2* [91]. It has been revealed that p53 prevents EMT by regulating the expression of E- and N-cadherins. Siemens et al. showed that activated p53 suppresses Snail expression by inducing the expression of microRNA- (miR-) 34a/b/c [92]. The expression of miR-200 and miR-192 is also p53-dependent, and their expression is negatively correlated with *ZEB1/2* expression [93, 94]. Both p53 itself and its transcriptional targets (MDM2 and $p21^{WAF1}$) regulate Slug expression [95]. The ectopic expression of p53 induces the proteasomal degradation of Slug, which is mediated by the E3 ligase MDM2. A further study by Kim et al. showed that complex formation of Slug with $p21^{WAF1}$ and p53 is involved in MDM2-mediated Slug degradation [96].

5. p53 Gain-of-Function Mutants Regulate Cell Adhesion Molecules and Downstream Pathways

Mutations in *TP53* often result in a gain-of-function (GOF) of the protein [97]. Muller et al. showed that p53 GOF mutants increase the Rab-coupling protein- (RCP-) driven recycling of integrin $\alpha5\beta1$ by inhibiting TAp63-mediated transcription [98]. This would induce the formation of filopodia-like protrusions and thereby promotes the invasion of cancer cells. Furthermore, p53 GOF mutants promote the translocation of integrin $\beta1$ to the tips of filopodia by increasing the early growth response protein 1- (EGR1-) mediated expression of myosin-X (Myo10), an unconventional myosin [99]. The expression of integrin $\alpha5\beta1$ and its ligand fibronectin is also increased by p53 GOF mutants [100], which contributes to the survival of suspended cells.

Recently, Lee et al. showed that p53 GOF mutants increase the transcription of *ITGB4*, which encodes integrin $\beta4$ [101]. TAp63 and TAp73 also upregulate the expression of *ITGB4*, as described above [56]. Conversely, the transcriptional activity of TAp63 and TAp73 is reduced by their binding with a subset of p53 mutants [102]. Thus, additional studies are needed to reveal the actual relationship between p53 GOF mutants, p63, and p73 in terms of the regulation of *ITGB4* expression, which would provide a better understanding of the mechanisms underlying cancer progression.

p53 GOF mutants appear to contribute to cancer progression via the expression of the EMT-promoting factors Snail, Slug, and Twist [103, 104]. In addition, p53 GOF mutants upregulate the expression of paxillin and *ARHGDI*, which encodes Rho GDP-dissociation inhibitor alpha (Rho-GDIα) that typically downregulates Rho GTPases [105]. However, the role of paxillin and Rho-GDIs in metastasis is controversial, which may reflect the diversity of cancers.

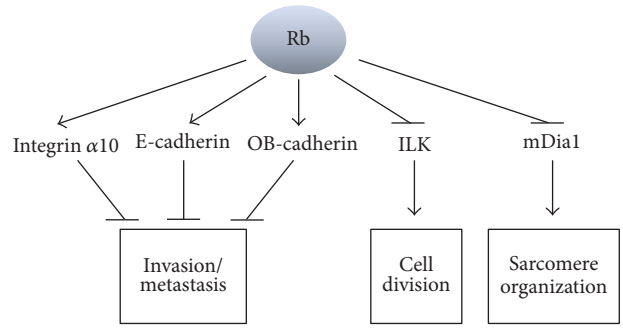

Figure 3: Rb-dependent regulation of the molecules involved in actin cytoskeleton remodeling. In cancer cells, Rb is inactivated either by Cdk4/6- and Cdk2-dependent hyperphosphorylation or by its mutation. Rb prevents cancer progression by suppressing both invasion and cell division via the alteration of actin cytoskeleton remodeling. Conversely, under inflammatory conditions, Rb is likely to have a promoting effect on cancer cachexia, which is associated with muscle atrophy characterized by disorganization of sarcomeres. TNFα upregulates the Cdk4/6-dependent phosphorylation of Rb, which causes disorganization of sarcomeres by inhibiting mDia1-mediated actin polymerization.

6. Rb Regulates Cell Adhesion Molecules and Downstream Pathways

Several studies have suggested a role for Rb in the regulation of the actin cytoskeleton and related pathways (Figure 3). Engel et al. showed, using Rb knockout cells and the ectopic expression of Rb mutants, that Rb promotes the expression of *ITGA10* (encoding integrin $\alpha10$) in osteoblasts independently of the canonical Rb-E2F pathway [106]. They used bioinformatic analysis to show that the expression of integrin $\alpha10$ is downregulated in several tumors compared with normal

tissues. Integrin $\alpha 10$ heterodimerizes with the integrin $\beta 1$ subunit [107]. While both loss-of-function and gain-of-function of p53 drive integrin $\beta 1$-mediated cancer cell progression as discussed above [53, 98–100], Rb might prevent cancer progression by increasing the heterodimerization of integrins $\alpha 10$ and $\beta 1$ and by suppressing the heterodimerization of integrins $\alpha 4$ or $\alpha 5$ with $\beta 1$.

It has been suggested that loss of Rb function causes the upregulation of ILK expression, which is required for cell division [108]. In retinoblastoma cells carrying mutations in the *Rb* gene, inhibition of ILK by the small molecule QLT-0267 induces the accumulation of multinucleated cells, which is associated with a decrease in cortical F-actin, alteration of mitotic spindle organization, and declustering of centrosomes. ILK upregulates actin polymerization by inactivating cofilin and by activating both Rac and Cdc42 [109]. Furthermore, ILK controls the complex formation of Aurora A kinase/chTOG/TACC3, which is essential for the assembly of mitotic spindles [110, 111]. Both microtubule-dependent forces and actin-dependent forces at the cell cortex contribute to centrosome clustering [112]. These findings suggest that loss of Rb function prevents mitotic defects, such as the arrest of and exit from mitosis, through upregulation of the ILK-mediated assembly of actin filaments and microtubules, which would ensure cell division.

We reported recently that Rb causes disruption of the sarcomeric structure of skeletal muscle myotubes via its interaction with the formin protein mDia1 [113], an effector of RhoA [114]. This pathway is stimulated by the inflammatory cytokine TNFα. TNFα increases the CDK4-dependent but CDK2-independent phosphorylation of Rb. Phosphorylated Rb subsequently translocates from the nucleus to the cytosol, where it binds to mDia1. The sarcomere, which consists of a highly ordered array of actin thin filaments and myosin thick filaments, provides a contractile unit in muscle cells and confers muscle strength. Our findings suggest that inflammation hampers the homeostasis of skeletal muscle via inhibition of mDia1-mediated actin polymerization by Rb. In advanced cancer patients, cachexia—the loss of body mass that is associated with muscle atrophy characterized by disorganization of sarcomeres—is often observed. Cytoplasmic Rb might contribute to cancer progression by promoting muscle atrophy. Indeed, cytoplasmic Rb was detected in atrophied tibialis anterior muscles, but not the normal muscles, of cancer patients [113].

Rb has also been implicated in the regulation of cadherin expression. Sosa-García et al. reported that, in Rb-deficient osteoblasts, the expression of E-cadherin and osteoblast-cadherin (OB-cadherin) is downregulated [115]. Associated with this, AJs are disrupted in these cells, which is mediated by the inactivation of merlin, a member of the ezrin, radixin, and moesin (ERM) family of proteins that links actin filaments to AJ complexes [116]. OB-cadherin (also known as cadherin-11), a cadherin isoform that is expressed in mesoderm-derived tissues, is known to be involved in cancer progression both positively and negatively. In prostate and brain cancers, OB-cadherin enhances the engagement between cancer cells and bone tissues by its hemophilic interactions, which promotes cancer metastasis [117–122]. By contrast, osteosarcoma formation is promoted by the disruption of OB-cadherin-mediated cell-cell interactions. These results imply that loss of Rb function might induce cancer progression preferentially in growing tissues.

7. Concluding Remarks

In this paper, we focused on the findings regarding the roles of the central tumor suppressors p53 and Rb in the regulation of the actin cytoskeleton and mechanoresponsive molecules. Intense studies have revealed that both these tumor suppressors and mechanical environments surrounding cells have significant effects on cancer progression. However, little is known about how these tumor suppressors influence the mechanical environment-dependent regulation of cancer progression.

Cancer cells sense various different mechanical environments during metastasis, leading to an alteration of cell behavior [123, 124]. The tumor stroma is composed of noncancerous cells, including cancer-associated fibroblasts (CAFs), as well as noncellular components, such as the ECM. The excess production of the ECM mainly by CAFs stiffens solid tumors [125, 126], which promotes the growth of cancer cells [127, 128]. In addition, along with the growth of tumor mass, cancer cells suffer high pressure caused by tissue compression and/or an increase in interstitial pressure [129]. Similar to ECM stiffening, this high pressure also promotes the metastasis of cancer cells. Following intravasation, cancer cells in blood vessels are exposed to shear forces exerted by blood flow, which facilitates the interaction of cancer cells with endothelial cells to permit extravasation [130]. Cell growth and sensitivity against chemotherapy and radiotherapy treatments are also affected by mechanical environments [131]. Furthermore, mechanical environments appear to be crucial for maintaining the properties of cancer stem cells, such as self-renewal and tumor formation abilities. Thus, mechanical environments affect cancer progression at multiple stages.

We have proposed the possibility that cancer cachexia with muscle atrophy is caused by Rb-mediated disruption of sarcomeric organization [113]. Currently there is no effective treatment for muscle atrophy, which makes it difficult to improve the quality of life (QOL) of patients with advanced cancers. Since CDK4 is responsible for the TNFα-induced phosphorylation of Rb and resultant disorganization of sarcomeres, disrupting the function of CDK4 may prevent cachexia in advanced cancers, which would improve QOL. p53 is known to be required for the promotion of muscle atrophy induced by inflammatory cytokines, including TNFα [132]. p53 may be involved in Rb-promoted muscle atrophy. It is well known that the p53 and Rb pathways cooperatively regulate cell proliferation and senescence; however, the relationship between p53 and Rb in actin cytoskeleton remodeling is totally unknown. As described above, we have shown that Rb appears to inhibit mDia1-mediated actin polymerization to disrupt sarcomeres. However, activation of RhoA, which promotes mDia1-induced actin polymerization [114], is prevented by p53 [77]. These observations support the notion that p53 synergistically enhances Rb-promoted

muscle atrophy. In addition to CDK4 inhibition, development of a drug that targets the pathway for p53-mediated inactivation of RhoA may enable the suppression of cancer-associated cachexia.

While accumulating evidence reveals that mechanical environments significantly affect the aggressiveness of cancer cells, it remains unclear how mechanical environments regulate the activities of p53 and Rb. Further studies into the mechanotransduction mechanisms responsible for mechanical cue-dependent regulation of these tumor suppressors would aid the development a definitive treatment for cancers and a treatment that improves the QOL of advanced cancer patients.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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