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Rho GTPases modulate malignant transformation of tumor cells

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Rho GTPases are involved in the acquisition of all the hallmarks of cancer, which comprise 6 biological capabilities acquired during the development of human tumors. The hallmarks include proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis programs, as defined by Hanahan and Weinberg.[1] Controlling these hallmarks are genome instability and inflammation. Emerging hallmarks are reprogramming of energy metabolism and evading immune destruction. To give a different view to the readers, we will not be focusing on invasion, metastasis or cytoskeletal remodelling, but we will review here how Rho GTPases contribute to other hallmarks of cancer with a special emphasis on malignant transformation.

Introduction

Rho GTPases are a family of small G proteins that regulate the cytoskeleton dynamics, as well as other key cell functions such as cell cycle progression, cell migration, malignant transformation, cell polarity, invasion and metastasis.[2] Rho GTPases are molecular switches that cycle between a GDP-bound inactive form and a GTP-bound active form. Upon activation, Rho GTPases interact with downstream effectors that lead a signaling cascade to direct cellular responses.[2]

Tremendous efforts have been dedicated in the last years to elucidate and decipher the role of Rho GTPases on cytoskeletal remodelling.[2,3] In this review, we will not address the contribution of Rho GTPases to cell migration. Instead, we will focus on how this family of proteins regulate other hallmarks of cancer, including cell cycle progression, oncogenic transformation, tumor suppression, cancer cell survival, senescence, inflammation, angiogenesis and altered metabolism.

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Aberrant Expression of Rho GTPases in Tumorigenesis

Several Rho GTPases have been found overexpressed in human tumors and, in some cases, this correlates with cancer progression[4] (see **Table 1** summarizing aberrant regulation of Rho GTPases). RhoA overexpression has been associated with progression in testicular cancer[5] and breast cancer.[6,7] Overexpression of RhoA has also been described in colon and lung cancers[7] and in head and neck squamous cell carcinoma.[8] RhoA expression and activity has also been found to be increased in liver cancer.[9] RhoB has been shown to be overexpressed in breast cancer and correlate with progression of the disease,[6] while other studies report a downregulation of RhoB expression in squamous cell carcinoma[10] and loss of expression in lung cancer progression,[11] suggesting a tumor suppressor role for RhoB (see "Rho GTPases regulating tumor suppressors" subheading below). Overexpression of RhoC has been identified in inflammatory breast cancer[12] and colorectal carcinoma;[13] and it correlates with progression and poor prognosis in melanoma[14] and pancreatic adenocarcinoma.[15] Rac1 is overexpressed in testicular cancer,[5] breast cancer[7] and various leukemias.[16] A self-activating splice variant of Rac1, Rac1b, was reported to be highly expressed in colon,[17] breast,[16] and non-small cell lung[19] carcinomas; and it is thought to mediate the epithelial–mesenchymal transition in lung epithelial cells by upregulating the transcription factor Snail.[17,20,21] Cdc42 has been shown to be overexpressed in several human cancers, such as non-small cell lung cancer,[22] colorectal adenocarcinoma,[23] melanoma,[24] breast cancer[6,7] and testicular cancer.[5] Overall, the frequent overexpression of Rho GTPases in cancer highlights the important role of Rho proteins in the different steps of tumorigenesis and the value of analyzing Rho protein levels as prognostic markers of cancer progression.

Rho GTPases Mutated in Cancer

Unlike the Ras family of GTPases, which are mutated in 30% of human tumors,[25,26] Rho GTPases had rarely been identified to be mutated in human cancers until recent advances on genome sequencing.[27-29] Several studies in recent years have started

Table 1. Aberrant Rho GTPase expression in cancer

Rho GTPase	Deregulation	Tumor type
RhoA	Overexpression	Testicular cancer,[5] breast,[6,7] colon,[7] lung,[7] liver,[9] head and neck squamous cell carcinoma,[8] hepatocellular carcinoma,[231] bladder,[232] esophageal squamous cell carcinoma,[233] ovarian carcinoma,[234] gastric carcinoma[235]
RhoB	Overexpression	Breast cancer[6,7]
	Downregulation	Squamous cell carcinoma[10]
	Loss of expression	Lung cancer[11]
RhoC	Overexpression	Melanoma,[14] inflammatory breast cancer,[12] breast cancer,[6,7,236] colorectal carcinoma,[13] pancreatic ductal adenocarcinoma,[15] non-small cell lung carcinoma,[237] gastric cancer,[238] hepatocellular carcinoma,[239] prostate cancer,[240] head and neck squamous cell carcinoma,[241] squamous cell carcinoma of the skin,[242] bladder cancer,[232] esophageal squamous cell carcinoma,[233] ovarian carcinoma[234]
Rac1	Overexpression	Testicular cancer,[5] breast cancer,[7] leukemia,[16] gastric carcinoma,[235] prostate cancer[243]
	Alternative splicing, Rac1b	Breast,[18] colon carcinoma,[17] non-small cell lung cancer[19]
Cdc42	Overexpression	Non-small cell lung cancer,[22] colorectal adenocarcinoma,[23] melanoma,[24] breast,[6,7] testicular cancer[5]

to challenge the concept that Rho GTPases are not mutated in cancer[30] (**Table 2**). Rac1 mutations located in the effector domain of the protein have been found in human brain tumors, which enhanced the activity of Rac1 and increased the survival of brain tumors.[31] Recently, a human exome sequencing analysis allowed for the identification of a Rac1 mutation, $Rac1^{P29S}$. This mutation was found in 5% of sun-exposed melanomas, making Rac1 the fourth most commonly mutated gene in melanoma after BRAF, NRAS and p53, and one of the most common mutations discovered in a Rho family GTPase.[27-29] A mutation in a homologous residue in $Rac2^{P29L}$ has also been found in melanoma, along with a mutation in $Cdc42^{G12D}$.[27] $Rac1^{P29S}$ is a recurrent somatic missense mutation at codon 29 that results in substitution of a proline to a serine residue. This location is distinct from the commonly found oncogenic mutations in the Ras oncogenes and $Rac1^{P29S}$ has been reported to be a spontaneously activating cancer-associated GTPase.[32] In contrast to Ras mutations, which affect the GTPase activity, $Rac1^{P29S}$ conserves intrinsic GTP hydrolysis and is activated by a fast-cycling GDP/GTP nucleotide exchange. Activated $Rac1^{P29S}$ has increased binding activity toward Rac1 effectors and mutated Rac1 induces increased cell proliferation, altered cell migration, and stimulates membrane ruffling and MAPK signaling.[28] Other transforming Rac mutations ($Rac1^{N92I}$, $Rac1^{C157Y}$, $Rac2^{P29L}$, $Rac2^{P29Q}$) have also been found in human cancer cell lines.[33]

Despite the oncogenic potential of RhoA in several human cancers (**Table 1**), very recent studies have unexpectedly identified a loss-of-function mutation on RhoA ($RhoA^{G17V}$) in 50–68% of angioimmunoblastic T cell lymphomas.[34,35] Whether activating mutations or aberrant expression of the other Rho GTPases contribute to the malignant progression of T-cell derived tumors remains to be elucidated.

RhoH gene is altered in tumors of myeloid origin. RhoH has been reported to be frequently rearranged in non-Hodgkin's lymphomas and multiple myeloma, and the 5' untranslated region of RhoH gene is mutated in diffuse large cell lymphomas.[36,37]

These studies might just highlight the important advances that next-generation sequencing analysis will be able to provide in the near future. Identification of genetic alterations in Rho GTPases will help to understand the biological relevance of such mutations in cancer progression.

Rho GTPases and the Cell Cycle

In addition to their important role in regulating cytoskeletal dynamics,[2,3] Rho GTPases are also important regulators of cell cycle progression and proliferation (**Fig. 1**). During cell proliferation, the accurate transition from G1 phase of the cell cycle to S phase is a critical step, which is controlled by the cyclin-dependent kinases (CDKs) as well as the cyclin regulatory subunits. Type D cyclins (cyclin D1, cyclin D2 and cyclin D3) associate with CDK4 or CDK6, whereas type E cyclins (cyclins E1 and cyclin E2) associate with CDK2. The activity of cyclin-CDK complexes is negatively regulated by CDK inhibitors (CDKIs), either by direct inhibition of CDK activity (the INK4 CDKI family of proteins) or by binding to the cyclin-CDK complexes (the Cip/Kip family of CDKIs). The Rho proteins have been reported to modulate G1 progression.[38]

RhoA is required for G1 to S progression in mammary epithelial cells, in response to normal or oncogenic signaling, by repression of p21 (Waf1/ Cip1)[39] and the induction of cyclin D1.[40] RhoA also downregulates CDK inhibitor p27 (Kip1) during the G1 phase of the cell cycle[41] and contributes to maintaining the correct timing of cyclin D1 expression in G1 phase by sustaining ERK signaling.[42] In the same lines, RhoA-mediated activation of ROCK and mDia promotes G1 progression via Skp2-mediated degradation of p27 (Kip1).[43]

RhoC has been shown to promote proliferation of gastric cells by recruitment of IQ-domain GTPase-activating protein 1 (IQGAP1) and increased expression of cyclin E and cyclin D1.[44] In normal hepatocytes, RhoC overexpression induced proliferation and anchorage-independent growth by increasing the expression

of cell cycle-related genes, such as cyclin G1, cyclin A, cyclin D1 and CDK4, and downregulating the mRNA expression of G1 cyclin-CDK inhibitor p27 (Kip1) and the formation of tumors in nude mice.[45]

Rac1 and p21-activated kinase (PAK) have been shown to induce cyclin D1 expression primarily through activation of nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF-κB) to activate the cyclin D1 promoter.[46] Rac1 can also directly activate cyclin D1 expression[47] and mediate integrin-induced cyclin D1 translation.[48] Rac1 and ERK are required for the mid-G1 phase induction of cyclin D1 and S phase entry in both epithelial and mesenchymal cells.[49] On the other hand, in mouse embryonic fibroblasts, cyclin D1 expression is induced by Rac1 independently of NF-κB signaling pathway.[50] The Rac effector WAVE3 (Wiskott-Aldrich syndrome protein) has also been shown to promote tumor growth in orthotopic breast cancer mouse models.[51] Adenocarcinoma cells overexpressing or lacking Rac1 and orthotopically injected into mice showed that Rac1 is important for tumor progression.[52] Cdc42 induces cyclin E expression and promotes G1 progression through p70 S6 kinase[53] and regulates cyclin D1 expression in bovine tracheal myocytes.[54] Therefore, inhibition of Rac1 and Cdc42, using a novel small molecule inhibitor targeting both Rho GTPases, caused a decrease in tumor growth of primary human prostate cancer xenografts and prolonged survival in mice. Treatment with this inhibitor downregulated cyclin D1 expression and PAK and Akt activity in prostate cancer cells.[55]

Other less characterized Rho GTPases, such as RhoD, can extert a positive regulation of G1/S-phase progression and increased proliferation via its novel effector Diaph1.[56] Among the atypical Rho GTPases, the putative tumor suppressor RhoBTB2 might also negatively regulate cell cycle progression and induce apoptosis.[57] On the other hand, RhoE overexpression inhibits cell cycle progression by decreasing cyclin D1 expression.[58]

Further to their role in cell cycle regulation as mediators of G1 progression, Rho GTPases can also contribute to mitosis and/or cytokinesis. These processes need to be carefully regulated in order to maintain genomic stability and to prevent tumorigenesis.[59] RhoA regulates centrosome duplication and positioning.[60] The Rho effector Citron-K has been shown to have a role in G2/M progression of hepatocytes.[61] A dominant negative Rac1 expressed in Rat2 fibroblasts resulted in accumulation of the G2/M phase.[62] In late G2 phase, expression of a mutant of Rac1 that is localized in the nucleus increased the mitotic rate.[63] During metaphase, Cdc42 and mDia3 regulate spindle microtubule attachment to kinetochores and control mitosis, while RhoJ/TCL and RhoQ/TC10 enhance this effect when suppressed in conjunction with Cdc42.[64] Cdc42 and Ect2 have been reported to regulate spindle assembly in mitosis in *Xenopus* embryogenesis.[65,66]

The process of the cytoplasmic division or cytokinesis, which terminates cell division, requires the formation and contraction of a cortical ring containing actin and myosin, resulting in cell body cleavage.[67] RhoA and its downstream effectors, such as ROCK and Citron-K, contribute to different aspects of this process.[67] Active RhoA promotes cytokinesis by coordinating the diaphanous-related formins (DRF)-mediated formation of linear filamentous actin with contractile force driven by myosin-II motor activity to promote the assembly and constriction of a contractile ring.[68-70] ROCK contributes to the progression of cytokinesis through the phosphorylation of myosin light chain at the cleavage furrow,[71] whereas Citron-K associates with the central spindle kinesin family member 14 (KIF14), and these 2 proteins depend on each other for proper localization during cytokinesis.[72,73] Further roles of Rho GTPases in mitosis and/or cytokinesis have been reviewed in detail elsewhere.[59,74]

These studies reveal that Rho proteins are key players in promoting uncontrolled cell proliferation by stimulating positive regulators and decreasing negative regulators of cell cycle progression.

Rho GTPases Mediate Oncogenic Transformation

Rho GTPases are required for Ras GTPase-mediated oncogenesis and also for aberrant growth induced by other oncoproteins that will be discussed below, such as polyomavirus middle T antigen;[75,76] tyrosine kinases such as Abl, Met, Fps, BCR-Abl, RET, epidermal growth factor receptor and insulin-like growth factor receptor; G protein-coupled receptors (Mas, G2A, M1-muscarinic receptor, and PAR-1), and Dbl family proteins (**Fig. 1**).[77-88]

1. Ras-promoted oncogenic transformation

Ras GTPase family of proteins are the most frequently mutated genes in cancer.[25,26] Several studies reported that Ras transformation of rodent fibroblasts is prevented by inhibitory mutants of RhoA,[79,82,85,86,89] RhoB,[80] RhoG,[86] Rac1,[79,84,86] TC10,[81] and Cdc42;[83] whereas constitutively activated mutants of these proteins can lead to cellular transformation of rodent fibroblasts. Rac1 has also been shown to suppress Ras-induced apoptosis by a mechanism linked with NF-κB activation contributing to Ras oncogenic transformation.[90]

Activated Rac1 can cooperate with activated membrane-targeted Raf-1 (Raf-CAAX)[84] to promote malignant transformation, while Rac1 and Raf induce E1A-dependent transformation of primary BRK rat epithelial cells.[91] Activated Rac1 also cooperates with MEK1 to promote growth transformation of FRTL-5 rat thyroid epithelial cells.[92] In many cells, PAK signaling downstream of Ras and PI3 kinase sustains cell transformation.[93-95] Furthermore, the less characterized Rho GTPase Wrch1/RhoU is able to induce transformation of fibroblasts when overexpressed.[96,97]

Several lines of evidence suggest that each GTPase alone can confer an advantage in the growth-promoting actions of Ras-mediated oncogenesis. Activated RhoA or Rac1 stably expressed in NIH-3T3 cells or constitutively active Cdc42 expressed in Rat-1 fibroblasts promote anchorage-independent growth and the formation of tumors in nude mice.[79,83,98] Nevertheless, the oncogenic potential of Rho GTPases is not comparable to the morphologic transformation induced by activated Ras, as measured by formation of foci or growth in soft agar.[83-85,99]

More recent studies using in vivo models have shown that Rac1 contributes to tumorigenesis in K-Ras^{G12D}-driven lung

Figure 1. (Opposite page.) Roles of Rho GTPases during malignant transformation and tumor progression. Diagram showing different roles of Rho GTPases during cell transformation and tumor progression. Upon cell transformation, Rho GTPases contribute -alone or in cooperation with oncogenes- to aberrant proliferation, altered metabolism, increased survival and evasion of senescence and apoptosis, which will sustain tumor proliferation. Later on, Rho GTPases also contribute to the development of an inflammatory environment, which increases cell survival and tumor progression; and to the induction of tumor angiogenesis, which will sustain tumor growth further and may also serve as an escape route for cancer cells to colonize distant organs. Rho GTPases are also essential for the cytoskeletal changes underlying cell motility and invasion, which allow cancer cells to migrate away from the primary tumor and invade surrounding and later distant tissues, ultimately developing metastasis.

tumors[100] and oral papillomas.[101] Rac1 also cooperates with N-Ras^{Q61K} to promote dermal melanocyte survival in vivo and to increase invasiveness on primary melanocytes in vitro and in vivo.[102] Inhibition of Rac1 in melanoma tumors harboring the mutation N-Ras^{Q61K} suppresses tumor growth and lymph node spread.[102] In a colorectal carcinoma model, Rac1-overexpressing adenocarcinoma cells orthotopically injected into mice accelerated tumor formation.[52] The alternative splice variant of Rac1, Rac1b, has been found to be upregulated in a significant fraction of lung tumors, correlating with mutational status of K-Ras. Moreover, expression of Rac1b promotes K-Ras-induced lung adenocarcinoma in vivo.[19]

These studies infer that Ras oncogenes in different cancers will take advantage of specific Rho GTPase signaling cascades to further promote tumorigenesis.

2. Tyrosine kinase oncoprotein transformation

Epidermal growth factor receptor (EGFR)

EGFR is an oncoprotein that is overexpressed, mutated and/or aberrantly activated in several human cancers.[103] Inappropriate EGFR signaling contributes to tumor progression through activation of mitogenic signaling pathways.[104] Therefore, EGFR activity must be tightly regulated by different mechanisms, such as ligand-mediated receptor activation and through endocytosis and recycling/degradation.[105] Both active RhoA[106] and/or Rac1[107] are required for EGFR-induced mitogenesis and cell transformation. In addition, Rho GTPases also contribute to the disruption of the normal EGFR endocytosis and degradation cycles, which leads to aberrant and sustained mitogenic signal. RhoA and ROCK negatively regulate EGFR endocytosis through activation and recruitment of endophilin A1 to the EGFR-c-Cbl-CIN85 complex, which reduces EGFR endocytosis.[108,109] Activated RhoB[110] and Cdc42[111] can also delay EGFR endocytic trafficking. On the other hand, activation of Cdc42 prevents EGFR degradation through sequestering the ubiquitin ligase c-Cbl, which contributes to the initiation of EGFR degradation.[112,113]

Met/Hepatocyte growth factor (HGF) receptor

Met is a receptor tyrosine kinase involved in cell transformation and which is overexpressed and mutated in a variety of tumors.[114] Several studies using dominant negative mutants of Rho GTPases have shown the implication of Rac1 and Cdc42 in mediating the transforming ability of Met in fibroblasts and epithelial cells.[115,116]

Insulin-like growth factor-I receptor (IGFR)

IGFR is a tyrosine kinase receptor that plays an important role in the maintenance of the transformed phenotype. Upon activation with several ligands, IGFR leads to cell type-dependent proliferation, differentiation or inhibition of apoptosis.[117] Transformation by IGFR requires Rho GTPase activity, since dominant negative mutants of RhoA, Rac1, and Cdc42 inhibited IGFR-induced fibroblast transformation, as measured by focus and colony forming ability. In particular RhoA was suggested to promote escape of contact inhibition, whereas Cdc42 seems to be more important for anchorage-independent growth.[87]

Src

The cytoplasmic tyrosine kinase Src was initially identified as the protein product of the viral oncogene v-Src, responsible for the transforming ability of the Rous sarcoma virus.[118-120] Its normal cellular counterpart, the product of the proto-oncogene c-Src, plays a key role in signal transduction processes by acting downstream from several cell surface receptors, such as EGFR, and it is amplified in a variety of cancers.[120] RhoA, Rac1 and Cdc42 play roles in cellular transformation mediated by Src.[121] Rac1 activation by the GEFs Vav2 and Tiam1 was shown to be required for Src-induced cell transformation.[122] The Rac1 effector WAVE was found to be activated in v-Src-transformed cells through phosphorylation downstream of MAPK signaling, suggesting its potential role in cell transformation.[123] The Rho effector mDia1 is also essential for v-Src-induced cellular transformation, since this process is inhibited in mDia1-deficient cells.[124] Src kinases, both v-Src and c-Src, need to be directed to a specific subcellular structure(s) to induce transformation. Deficiency of mDia decreases the levels of several tyrosine-phosphorylated proteins in v-Src-transformed cells, which impairs the translocation of v-Src from the perinuclear region to the cell periphery. Such impairment leads to the downregulation of downstream signaling pathways and suppression of v-Src-induced cell transformation.[124] Likewise, RhoB also regulates the peripheral translocation of Src and ultimately its activity via endosomal transport.[125,126]

Abl and BCR

The viral oncogene v-Abl of the Abelson murine lymphosarcoma virus[127] has been shown to require Rac1 to induce mitogenesis.[128] The human ortholog of Abl was identified as part of a fusion oncoprotein with breakpoint cluster region (BCR), BCR-ABL, common in chronic myeloid leukemia (CML) patients,[129] and which can be found as the p190- and p210-BCR-ABL isoforms. The p210-BCR-ABL isoform displays GEF activity through the double homology (DH) domain and can activate Rac1, RhoA and Cdc42.[130] Rac1 and Rac2 deficiency was described to impair myeloid leukemogenesis induced by p210-BCR-ABL expression in hematopoietic stem and progenitor cells.[131,132] It has been proposed that Rac2-induced reactive oxygen species (ROS) generation[133] could lead to DNA damage and genetic instability in BCR-ABL leukemias.[134] The

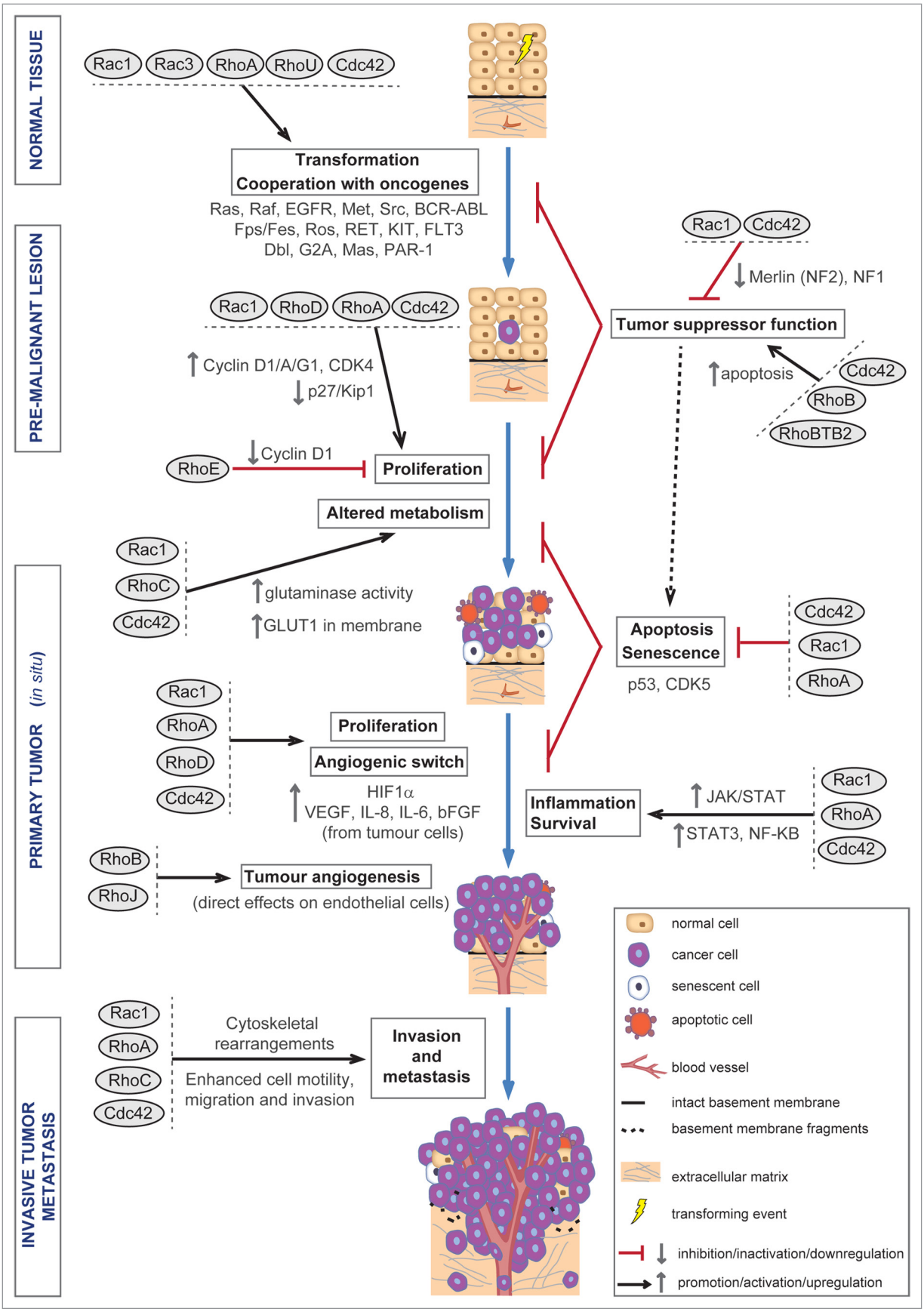

Figure 1. For figure legend, see previous page.

p190-BCR-ABL lacks a DH domain but can activate Rac1,[130] suggesting activation of alternative GEFs. For example, Vav3 Dbl family protein (see below) was required for p190-BCR-ABL-induced leukemogenesis, since Vav3 deficiency decreased p190-BCR-ABL-induced Rac activation and cell proliferation.[135] In vivo studies of Rac3-null mice have reported that Rac3, but not Rac1 or Rac2, specifically contributes to the development of BCR-ABL-induced lymphomas.[136]

Rho GTPases have also been implicated in other tyrosine kinase oncogenic pathways.[137] Cell transformation by Fps/Fes tyrosine kinases requires Rac and Cdc42 (along with Ras), which then in turn activate c-Jun N-terminal kinases (JNKs) to sustain proliferation.[138] Rac, Cdc42 and RhoA were shown to be necessary for anchorage-independent growth after Ros receptor tyrosine kinase-induced transformation.[139] RhoA was also found to facilitate evasion of apoptosis upon transformation with oncogenic RET tyrosine kinase.[140] The Vav/Rac/PAK pathway plays an essential role in regulating transformation via an oncogenic form of KIT (KIT^{D814V}) associated with myeloproliferative neoplasms and acute myeloid leukemia.[141] It has also been reported that the Rac/PAK pathway is vital to ErbB2-mediated transformation of human breast epithelial cancer cells.[142] Finally, RhoA-ROCK signaling regulates the survival and transformation of cells harboring oncogenic forms of KIT, FLT3, and BCR-ABL.[143]

3. G-protein coupled receptor (GPCR) transformation

GPCR are the largest family of cell surface receptors, and some of them, when aberrantly activated, can lead to oncogenic transformation through Rho GTPase.[88] Mas transformation appears to be mediated by Rac activation,[144] whereas transformation by G2A,[145,146] PAR-1,[147] and m1 muscarinic acetylcholine receptor[148,149] involves the activation of RhoA.

4. Dbl family oncoproteins

Many Dbl family proteins were initially identified as oncoproteins before being characterized as Rho GEFs, such as Dbl, Vav, Ect2, Tim, Net1, Lfc, Lsc or Tiam1.[150,151] Fast cycling mutants of RhoA, Cdc42 and Rac1 can mediate cell transformation induced by the Dbl oncoprotein.[152,153] Some Dbl family members were initially identified as rearranged in human leukemias, and these fusion proteins also require Rho GTPase activity for promoting tumorigenesis.[137] For example, the oncogenic fusion protein BCR-ABL (see above *Abl and BCR* subheading) activates Rac1 through the Vav Dbl family protein.[135,154,155] In addition, leukemia-associated RhoGEF (LARG) is also rearranged in mixed lineage leukemia (MLL), encoding a chimeric fusion protein with MLL.[156] LARG has been shown to cause cell transformation via activation of RhoA.[157,158]

In summary, Rho GTPases play a crucial role in transformation mediated by a variety of oncogenic pathways (**Fig. 1**), suggesting their potential use as therapeutic targets in cancers driven by those oncogenes. Targeting specific GEFs or GTPase effectors (ROCKs, PAKs), alone or in combination with drugs against certain oncogenes (i.e., Ras, Raf, Src), might provide effective therapeutic opportunities.

Rho GTPases Regulating Tumor Suppressors

In addition to their cooperation with oncogenic signaling pathways, Rho GTPases have also been associated with either promotion or inhibition of tumor suppressor function, which could depend on cell type, stage of tumor progression and differentiation status (**Fig. 1**).

Overexpression of the tumor suppressor Merlin (Nf2) was described to block Rac1-induced transformation, whereas Merlin deficiency enhances Rac1 activity and aberrant cell growth. In addition, Rac1 promoted Merlin phosphorylation, rendering it inactive.[159,160] Moreover, the hematopoietic-specific Rac2 was described to cooperate with Ras to promote the proliferation of mast cells deficient for the tumor suppressor neurofibromin (NF1).[161] Therefore, Rac impairs tumor suppressor function, and unsurprisingly its activity is negatively regulated by tumor suppressors.

On the other hand, RhoB has been proposed as a tumor suppressor, since it is activated in response to several stress stimuli such as DNA damage or hypoxia, and it was shown to promote apoptosis and inhibit tumor growth, cell migration and invasion.[162-164] In addition, RhoB knockout mice have enhanced carcinogen-induced skin tumor formation,[164] also in agreement with its putative role as a tumor suppressor.

The association between Cdc42 and tumor suppression appears to be more complex and context-dependent. In agreement with its oncogenic abilities described in previous sections, Cdc42 can control cell transformation upon loss of tumor suppressor function signal (e.g., loss of p53, PTEN or NF1). In fact, increased cell growth in p53- or p19ARF-deficient fibroblasts was partially dependent on regulation of NF-κB and cyclin D1 by Cdc42.[165] Cdc42 and Rho can cooperate to regulate PTEN localization and activity at the cell membrane, ultimately controlling PTEN-mediated tumor suppression activity.[166] Cdc42 was also shown to inactivate the tumor suppressor merlin;[159] and the Cdc42 effector PAK was required for transformation upon loss of NF1.[94] A possible oncogenic role on human liver tumors has also been suggested for Cdc42, as a study on liver regeneration showed elevated Cdc42 levels correlating with hepatocyte proliferation after partial hepatectomy,[167] and Cdc42 upregulation was described in human hepatocellular carcinoma (HCC).[168,169]

However, other lines of evidence suggest a tumor suppressor function for Cdc42. Contrary to the aforementioned studies on liver tumors; loss of Cdc42 in the liver was reported to lead to development of HCC,[170] which warrant further studies to elucidate the complex role Cdc42 has on hepatocellular carcinoma. Further evidence on the putative tumor suppressor function of Cdc42 comes from studies on hematopoietic and neuroblastoma models. Specific deletion of Cdc42 in murine bone marrow hematopoietic progenitor cells caused loss of hematopoietic stem cell quiescence, skewed differentiation from erythroid to a myeloid fate and hyperproliferation of blood progenitors, leading to lethality in mice due to myeloproliferative disease.[171] Most neuroblastomas with N-myc amplifications harbor deletions in the chromosomal region encompassing the

Table 2. Rho GTPase mutations in cancer

Rho GTPase	Mutation	Tumor type
Rac1	Deletions, frame shift and point mutations	Brain cancer[31]
	P29S	Melanoma[27,28]
	N92I	HT1080 fibrosarcoma cell line[33]
	C157Y	Lung adenocarcinoma[33]
Rac2	P29L	Melanoma[27] HCC1143 breast cancer cell line[33]
	P29Q	KCL-22 chronic myeloid leukemia cell line[33]
Cdc42	G12D	Melanoma[27]
RhoA	G17V	Angioimmunoblastic T-cell lymphomas[34,35]
RhoH	Rearrangement	Non-Hodgkin's lymphomas, multiple myeloma[37]
	Point mutation	Diffuse large B-cell lymphoma[36]

Cdc42 gene, leading to loss of one gene copy in these cancers.[172] N-myc overexpression in neuroblastoma cells was also shown to decrease Cdc42 expression, while exogenous activated Cdc42 promoted neuroblastoma cell differentiation. Therefore, these studies taken together suggest that Cdc42 could be suppressing tumor development by promoting cell differentiation and tightly controlling progenitor differentiation.[173]

An additional mechanism of tumor suppression mediated by Cdc42 could be through maintenance of cell polarity, which is critical to the correct function of cells in multicellular environments such as epithelia, but also in cell migration, directional cell growth and asymmetrical cell division, among other cell functions.[173,174] Cdc42 can regulate the establishment of cell polarity through modulation of intracellular vesicle trafficking to the apical surface;[175] orientation of the cell division spindle;[176] and through strengthening of cell-cell junctions.[177] Therefore, absence of Cdc42 could result in disruption of cell junctions and loss of epithelial cell polarity associated with cell transformation and tumorigenicity.[173,178]

These observations support the notion that the effect of Cdc42 signaling in tumor progression is complex, displaying pro-tumorigenic or tumor suppressive functions that seem to depend on cell type, differentiation status and stage in malignant progression.

Rho GTPases and Tumor Senescence

Normal cells, unlike cancer cells, have a finite proliferative capacity in vitro that leads to a stable and long-term cell cycle arrest, termed senescence, which is characterized by lack of response to growth factors, sustained metabolic activity and morphological changes.[179] Interestingly, aberrant oncogene signaling can trigger senescence and, in fact, senescence is prevalent in pre-malignant lesions but absent in malignant tumors. Therefore, senescence has been proposed as a barrier that tumor cells need to evade in order to sustaining aberrant proliferation.[180] The characteristic morphologic changes that senescent cells undergo —flattening and enlarged cell shapes—hint toward a role of Rho GTPases in this cytoskeletal reorganization. Nevertheless, Rho GTPases could either be drivers of the process or activated as a consequence of senescence. For example, cyclin-dependent kinase 5 (CDK5) activation in senescing cells reduced Rac1 activity and PAK activation, leading to actin polymerization and change in cell shape.[181] In line with this, the membrane linker ezrin was shown to be phosphorylated by CDK5 in senescing cells after retinoblastoma protein transfection, causing the dissociation of Rho GDI from an ezrin/Rho-GDI complex. The release of Rho-GDI resulted in increased interaction with Rac1 and posterior inhibition of Rac1 activity, contributing to the flattened cell morphology.[182]

However, several studies favor a direct role of Rho GTPases in the regulation of cell senescence (**Fig. 1**). Rac1-deficient embryonic fibroblasts display decreased cell growth, increased apoptosis and higher ROS levels due to Rac3 upregulation, which leads to increased DNA damage and subsequent cell senescence through augmented p53 activity.[183] Therefore, Rac1 could serve as a regulator of cell senescence through modulation of ROS, genomic stability and p53 activity. A role in bypassing senescence has been suggested for RhoA. Interestingly, enhanced expression of LPA2 or Dbs bypassed senescence in a Rho-dependent fashion, since dominant negative mutant RhoA blocked proliferation in LPA2- or Dbs-immortalized cells.[184] Cdc42 has been implicated in p53-induced changes in cell morphology and increased apoptosis.[185] In addition, activation of Cdc42 upon loss of Cdc42GAP was shown to be sufficient to promote a premature p53-dependent cell senescent phenotype.[186]

Further investigations are warranted in order to elucidate if Rho GTPases could have also a direct role in senescence in the context of aging.

Rho GTPases, Cancer Cell Survival, and Inflammation

Proinflammatory cytokines are frequently observed in the tumor microenvironment, and chronic inflammation is

involved in cancer initiation and progression. The inflammatory tumor microenvironment includes leukocytes, cytokines and complement components; and are orchestrated by transcription factors, such as signal transducer of activator of transcription 3 (STAT3) and NF-κB. Inflammation in the tumor microenvironment promotes proliferation and survival of malignant cells, angiogenesis, metastasis, subversion of adaptive immunity, response to hormones and chemotherapeutic agents.[187]

The JAK-STAT pathway is an important oncogenic signaling cascade that consists of the Janus kinase (JAK) family of non-receptor tyrosine kinases and the STAT family of transcription factors.[188] However, in most malignancies, STAT proteins and particularly STAT3, are aberrantly activated (tyrosine phosphorylation).[189,190] Some of the tumor-intrinsic functions of activated STAT3 include: inhibition of differentiation, cancer stem cell expansion/survival (WNT5A, CD44 and jagged), proliferation (stimulation of transcription of cyclin D1, cdc2, c-myc, cyclin B1, c-jun, c-fos and greb1), evasion of apoptosis (upregulation of the expression of the pro-survival Bcl-2, Bcl-xL, Mcl-1, Bcl-w and Survivin transcripts) and response to hypoxia and cellular metabolism (HIF1α, Glut1, Hsp70, Hsp90, p21 and Cdc2).[190-192] The JAK-STAT3 pathway also regulates tumor-extrinsic aspects of tumorigenesis including: angiogenesis (regulates transcription of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1 α (HIF1α), endothelial cell survival and neo-vascularization, immune cell infiltration, mesenchymal cell activation and finally progression to metastasis.[193,194] Therefore JAK-STAT3 signaling is crucial for tumor initiation and progression, and cross-talk with Rho GTPase signaling has now started to be evident[195]

Rac1, acting in a complex with the MgcRacGAP (male germ cell RacGAP), promotes tyrosine phosphorylation of STAT3 by the interleukin-6 (IL6)-receptor family/Jak kinase complex, as well as its translocation to the nucleus.[196] Interestingly, evidence also shows that the engagement of cadherins, cell to cell adhesion-molecules, specifically induces a striking increase in Rac1 and Cdc42 protein levels and activity, which in turn results in STAT3 activation.[197] Furthermore, JAK1/2 and Rho-ROCK signaling have been placed upstream and downstream of each other; therefore JAKs and ROCKs may mutually enhance each other in tumor cells to propagate pro-tumorigenic signals.[198,199] In addition, NF-κB is a transcription factor which functions as a master regulator of genes implicated in inflammation, immune response, cell proliferation, apoptosis and invasion. There is evidence that NF-κB regulates STAT3 activation through control of IL-6.[200] Connections between Rho-GTPase signaling and NF-κB activity have also been reported, that could further amplify STAT3 mediated protumorigenic functions. All 3 GTPases, Rho, Rac and Cdc42 are strong activators of transcription factor NF-κB,[201] but specific functions for each of them have been reported. For example, Rhotekin (RTKN), the gene coding for the Rho effector, RTKN, was shown to be overexpressed in human gastric cancer and reducing RTKN expression by small interfering RNAs greatly sensitized cells to apoptosis and this was dependent on NF-κB regulation of antiapoptotic genes.[202] Rac1/PAK1 activation downstream of α6β4 integrin leads to NF-κB-mediated resistance of mammary epithelial cells to apoptosis in 3-dimensional cultures.[203]

Therefore Rho GTPase-regulated signaling pathways can impinge on transcriptional regulators that promote tumorigenesis through cytokine mediated inflammatory signals allowing cancer cells to evade apoptosis, bypass senescence and induce malignant transformation (**Fig. 1**). These inflammatory mediators and their regulated pathways emerge as very attractive therapeutic targets for cancers of inflammatory origin.

Rho GTPases and Tumor Cell Metabolism

Bioenergetics and cellular metabolism are known to play an essential role in cancer development. After the seminal observations that tumor cells display elevated glycolytic activity (the Warburg effect),[204] recent studies are providing insights into how tumor cells establish this altered metabolic phenotype and its role in tumorigenesis.[205-207] The tricarboxylic acid cycle (TCA, also citric acid cycle) is essential in proliferating cells since it provides key precursors needed for macromolecule biosynthesis. Recently, a mutant version of the tumor suppressor protein p53 has been described to contribute to the Warburg effect.[208] Using human cancer cells and mouse models, the authors showed that mutant p53 stimulates aerobic glycolysis by promoting the translocation of the glucose transporter GLUT1 to the plasma membrane, which is mediated by active RhoA and ROCK. Importantly, disruption of glycolysis in tumor cells impaired promotion of tumorigenesis by mutant p53.[208] Therefore, targeting altered glucose metabolism driven by Rho-ROCK could be a feasible therapeutic strategy for mutant p53-bearing tumors. The Rac and Cdc42 effector PAK1 affects the glycolytic pathway by inhibition of phosphoglycerate mutase (PGAM)-B, an important regulatory enzyme in cellular glucose utilization and energy homeostasis.[209,210]

Apart from increased glycolytic activity, tumor cells also sustain enhanced glutamine consumption, which fosters proliferation by replenishing TCA cycle intermediates, allowing a sustained biogenesis of lipids, aminoacids/proteins and nucleic acids.[211] A novel mechanism was provided by which Rho GTPases could contribute to cell transformation by means of alteration of glutamine metabolism.[212] Wang and coworkers showed that the transforming capability of Cdc42, Rac1 and RhoC requires glutaminase activity, which is elevated in transformed/cancer cells.[207] Glutaminase is critical for sustained glutamine metabolism, since it hydrolyzes glutamine to glutamate and ammonia.[213] Suppression of glutaminase activity by small molecule inhibitors diminished cell growth and transformation induced by the 3 GTPases fast cycling mutants ($Cdc42^{F28L}$, Rac^{F28L} and $RhoC^{F30L}$)[212] (**Fig. 1**). Whether wild type Rho GTPases cooperate with glutaminase remains to be determined.

Therefore, the ability of Rho GTPases to induce cell transformation could be associated not only with their ability to impinge on the cell cycle, but also with their ability to enhance metabolic activity of cancer cells to fulfill fast growing

demands. Targeting Rho GTPase signaling could provide novel therapeutic avenues to halt tumor growth facilitated by high metabolic rate.

Rho GTPases and Tumor Angiogenesis

In order to grow beyond a certain size, solid tumors need to induce the formation of new blood vessels, or angiogenesis, which will maintain a supply of oxygen and nutrients, and eventually may also serve as an escape route to colonize distant organs.[1] Tumor angiogenesis is controlled by a balance of pro- and anti-angiogenic factors, and during tumor progression cancer cells need to shift the balance toward increased pro-angiogenic factors (angiogenic switch),[214,215] which in turn activate endothelial cells. In response to pro-angiogenic factors Rho GTPases regulate different processes in endothelial cells during angiogenesis, including proliferation, survival, and migration.[216] In particular, Rho GTPase actions on endothelial cell survival and sprouting during angiogenesis require low ROCK activity and high ERK-MAPK signaling.[217] In addition, RhoJ has been recently shown to promote tumor angiogenesis. Using mouse models, Kim and coworkers described how RhoJ blockade inhibits tumor angiogenesis and disrupts the preformed tumor vessels through activation of RhoA-ROCK signaling pathway in tumor endothelial cells, eventually resulting in a functional failure of tumor vasculature.[218] RhoB has also been implicated in the regulation of angiogenesis through direct actions on endothelial cells. After the angiogenic switch in a breast cancer model, RhoB promotes tumor angiogenesis through enhanced Akt signaling, growth and survival of endothelial cells.[219] In a mouse model of ischemia the loss of RhoB decreased pathological angiogenesis in the ischemic retina and reduced angiogenesis in response to cutaneous wounding.[220]

PAKs are also important in controlling key cellular events required for angiogenesis, including endothelial cell proliferation, survival, attachment and migration.[221] In endothelial cells, the ERK pathway regulates cellular proliferation and migration downstream the activation of Rac/PAK pathway.[222] PAK1 and PAK4 also protect endothelial cells against apoptotic stimuli by phosphorylation of Bad and CRAF, which induces the translocation of CRAF to mitochondria and the displacement of Bad/Bcl-2 complexes.[221,223]

Regarding Rho GTPase actions on cancer cells, some Rho GTPases have been shown to contribute to angiogenesis by regulating the hypoxia-triggered induction of HIF1α[224] or the production of angiogenic factors,[225] which would lead to increased tumor vascularization. Hypoxia increases the expression and activity of Cdc42, Rac1 and RhoA in cancer cells.[224] Then, RhoA,[224] Rac1,[226, 227, 228] and Cdc42[228] have been shown to be required for the accumulation of HIF-1α under hypoxic conditions (**Fig. 1**). RhoC-mediated transformation of mammary epithelial cells increases expression and/or secretion of proangiogenic factors such as VEGF, basic fibroblast growth factor (bFGF), IL-6 and interleukin-8 (IL-8).[229] Rac1 has also been shown to promote angiogenesis through augmented expression and secretion of VEGF via HIF1α stabilization in hepatocellular carcinoma cells (**Fig. 1**).[227] The Rac effector WAVE3 has been described to modulate tumor angiogenesis. As such, WAVE3-knockdown in breast cancer cells reduces microvessel density in orthothopic tumors in mice, possibly due to reduced VEGF levels from WAVE3-knockdown cells.[51]

Therefore, Rho GTPases are essential for tumor angiogenesis since they play key roles in both the endothelial and tumor cell compartments, which make them appealing targets to improve current antitumor and antiangiogenic therapies (**Fig. 1**). Apart from targeting Rho GTPase effectors (PAK, N-WASP) or GEFs (Trio) with small molecule inhibitors to impair tumor angiogenesis, other approaches are being considered such as the use post-translational modification inhibitors (statins) in combination with conventional anticancer therapies.[230]

Concluding Remarks

Rho GTPases emerge as key molecular machinery involved in every single step during cancer progression (**Fig. 1**). Strong efforts have recently focused on studying the role of RhoGTPases in the later stages of tumor progression such as invasion and metastatic dissemination. We have reviewed here evidence supporting the role of Rho GTPase signaling in the initial steps leading to malignant transformation, providing a rationale for targeting Rho signaling to block not only tumor dissemination, but initial tumor growth as well.

Rho GTPase functions are in many cases redundant for tumor development (**Fig. 1**). It appears that cancer cells manage to direct Rho GTPase signaling to achieve full transformation potential driven by oncogenes, and even in some cases, Rho GTPases act as oncogenes themselves. Therefore even when some Rho GTPase activity is lost, cancer cells will overexpress or activate another family member to compensate. In some other cases, the role of individual Rho GTPases is completely different or even opposed between members of the family. How specificity and selection is achieved in different tumor contexts, either through engagement of GEFs, GAPs or effectors, remains a matter of active study in the field.

On the other hand, the recent findings regarding Rho GTPases mutated in cancer may change current views on Rho GTPase regulation of tumor progression. Future studies dissecting the biological meaning of these mutations will be of the utmost importance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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