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THE ROLE OF RAC IN TUMOUR SUSCEPTIBILITY AND DISEASE PROGRESSION: FROM BIOCHEMISTRY TO THE CLINIC

Victoria Casado-Medrano[1], **Martin J. Baker**[1], **Cynthia Lopez-Haber**[1], **Mariana Cooke**[1], **Shaofei Wang**[1], **Maria J. Caloca**[2], and **Marcelo G. Kazanietz**[1,*]

[1]Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.

[2]Instituto de Biología y Genética Molecular, Consejo Superior de Investigaciones Científicas, Universidad de Valladolid, 47003 Valladolid, Spain

Abstract

The family of Rho GTPases are involved in the dynamic control of cytoskeleton reorganization and other fundamental cellular functions, including growth, motility, and survival. Rac1, one of the best characterized Rho GTPases, is an established effector of receptors and an important node in signaling networks crucial for tumorigenesis and metastasis. Rac1 hyperactivation is common in human cancer, and could be the consequence of overexpression, abnormal upstream inputs, deregulated degradation, and/or anomalous intracellular localization. More recently, cancer associated gain-of-function mutations in Rac1 have been identified which contribute to tumor phenotypes and confer resistance to targeted therapies. Deregulated expression/activity of Rac Guanine nucleotide Exchange Factors (GEFs) responsible for Rac activation has been largely associated to a metastatic phenotype and drug resistance. Translating our extensive knowledge in Rac pathway biochemistry into a clinical setting still remains a major challenge, nonetheless remarkable opportunities for cancer therapeutics arise from promising lead compounds targeting Rac and its effectors.

Keywords

Rac; Rho GTPases; Rac-GEF; Pak; cancer signaling; tumour susceptibility; cancer therapeutics

Introduction

Rho GTPases play central roles in the regulation of actin cytoskeleton and thereby control a number of cellular functions such as motility, polarity, adhesion, and mitogenesis. This family of small G-proteins comprises 20 members divided into Rac, Cdc42 and Rho

*Correspondence and reprint requests should be addressed to M.G.K. (marcelog@upenn.edu, Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, 1256 Biomedical Research Building II/III, 421 Curie Blvd., Philadelphia, PA 19104-6160, USA).

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subfamilies, and also includes other less characterized GTPases. Individual Rho family members play distinctive roles in normal physiological processes and development, and have been widely associated with a number of diseases. In particular, Rac GTPases (Rac1, Rac2, and Rac3) have been recognized as important nodes in signaling networks that control malignant transformation and the metastatic dissemination of cancer cells (1–5). Dissecting the molecular mechanisms controlling the activity of Rac and other related GTPases, identifying their regulators and effectors, and establishing their alterations in cancer cells have become a significant goal in the field of cancer research. The expectation is that pharmacological interventions designed to interfere with this pathway will ultimately translate into benefits for patients in a clinical setting.

Regulation of Rac activity: nucleotide binding, post-translational modifications and scaffolding

Like most GTPases, Rac is a molecular switch that cycles between active (GTP-bound) and inactive (GDP-bound) states. This process is tightly regulated by three types of proteins: Guanine nucleotide Exchange Factors (GEFs), GTPase Activating Proteins (GAPs), and Guanine Dissociation Inhibitors (GDIs). In the inactive state, Rac-GDP is stabilized through binding to GDIs. The crucial step in Rac activation is the displacement of GDP by the action of GEFs, followed by binding of GTP that is normally present at high cytosolic concentrations. This last step leads to a conformational change in Rac that favors its interaction with downstream effectors at specific intracellular compartments. Conversely, GAPs are responsible for Rac inactivation by stimulating the intrinsic GTPase activity and accelerating the rate of GTP hydrolysis (1–5).

Several other regulatory mechanisms control Rac activation (Figure 1), primarily post-translational modifications. For example, a well-described mechanism for Rac membrane targeting is the prenylation of the carboxy-terminal region (6). Phosphorylation of Rac1 in Ser71 and Tyr64 have also been shown to modulate Rac function by influencing the selection of downstream effector proteins (2, 7, 8). Ubiquitination of Rac1 at Lys147 by the E3 ligase HACE1 (a tumor suppressor) is another described post-translational modification that is required for proteasomal degradation of the GTP-bound protein. It is remarkable that loss of HACE1 function as seen in a clinical cancer setting leads to a drastic reduction in Rac1 ubiquitination, ensuing protein up-regulation and hyperactivation (9, 10).

Rac1 can be located at various intracellular compartments, and abnormal shuttling towards the nucleus has been detected in tumor cells. In the nucleus, Rac1 is involved in actin polymerization required for the nuclear plasticity in invasiveness (11). Accumulation of Rac1 in the nucleolus has been recently described. This Rac pool participates in the synthesis of ribosomal RNA (rRNA), and thus influences the metabolically demanding requirements of protein biosynthesis in cancer cells (12, 13). The localization and activity of Rac GTPases are greatly influenced via scaffolding mechanisms. The dynamics of Rac1 temporal and spatial localization is fine-tuned by tightly regulated protein-protein interactions (1, 14, 15). As an example, IQGAP proteins have been described as a scaffolding platform that assemble small GTPases, GEFs, and effectors. This association is a

multi-step process that involves a high affinity binding of IQGAP1 to the switch regions of the small G-protein (a GTP-dependent event), and low affinity binding to an adjacent region (16). The described direct association of IQGAP1 with the Rac-GEF Tiam1 and Rac1 exemplifies the relevance of multiprotein complexes in Rac1 activation (17).

Aberrant Rac expression and activity in human cancer

Like many other small GTPases, Rac isoforms have been linked to cancer progression. Early studies reported the requirement of Rac1 for cancer cell growth, including the inhibition by dominant-negative mutants and positive growth effects by constitutively active mutants (18, 19). The pro-tumorigenic role of Rac1 in solid tumors has been validated *in vivo* using Rac1-deficient mouse models. Most notably, Rac1 knockout mice are resistant to KRas-driven skin, lung, and pancreatic cancer (20–22). Similarly, deletion of the *Rac2* and *Rac3* genes in mice significantly delays the initiation of acute myeloid and acute lymphoblastic leukemias, respectively (23, 24).

Rac1 overexpression and/or hyperactivation have been reported in various cancers, including prostate, testicular, ovarian, lung, and gastric cancer (5, 25–29). In some cases, high expression of Rac1 has been associated with the expression epithelial-to-mesenchymal transition (EMT) markers and correlates with poor patient prognosis. For example, elevated expression of Rac1 and mesenchymal markers (Twist, Snail, vimentin, and N-cadherin) with a concomitant E-cadherin down-regulation has been described in lung cancer patients resistant to radiotherapy (29). The specific up-regulation of Rac1 in cancer-associated fibroblasts, both from primary tumors and lymph nodes, supports a potential pro-tumorigenic role for stromal Rac-mediated signaling and underscores the existence of yet unidentified Rac-driven interactions in the tumor microenvironment (30).

Rac1b, a Rac isoform generated by alternative splicing from the *RAC1* gene, contains an in-frame insertion of 19 amino acids that results in enhanced nucleotide exchange activity, impaired GTP hydrolysis activity and reduced affinity for GDIs (31). In several human cancers, the expression of this hyperactive Rac1 splice variant associates with poor prognosis. For example, Rac1b overexpression in metastatic colorectal cancer patients is a negative factor for overall survival and progression-free survival (32). Likewise, Rac1b overexpression is linked to the presence of distant metastasis and poor clinical outcome in patients with follicular thyroid cancer (33). Despite the reported ability of Rac1b to promote cellular transformation *in vitro*, studies in mice suggest that Rac1b alone is insufficient to promote tumor initiation, however it synergizes with other oncogenic inputs, such as the described synergistic interaction with mutant K-ras for promoting lung tumorigenesis (34). Rac1b displays distinctive signaling properties in the context of EMT, where it emerged as an endogenous inhibitor of Rac1 in TGF-β signaling in pancreatic cancer (35, 36).

Only in recent years have cancer-associated Rac mutations been identified through massive efforts in genome sequencing (Figure 1). Nonetheless, mutations in Rac1 and other members of the Rho GTPase family are much less frequent than those in Ras GTPases. The most prominent example has been reported for *RAC1* gene mutations in melanoma, particularly a missense mutation in Pro29 present in up to 9% of cronically sun-exposed melanomas.

Mutation of Pro29 to Ser makes Rac1 spontaneously active by increasing GDP/GTP exchange while still maintaining its ability to hydrolyze GTP (37–39). Ectopic expression of this “fast cycling” mutant in normal melanocytes increases proliferative and motile rates, although paradoxically excessive Rac1 activity by this mutant can negatively regulate invadopodia formation and matrix degradation in melanoma cells (40). The Rac-GEF DOCK1 has recently been demonstrated as a critical regulator of the malignant phenotypes induced by $Rac1^{P29S}$ (41). From a pharmacological standpoint, the $Rac1^{P29S}$ mutation is associated with resistance to Raf inhibitors and PD-L1 up-regulation, thus contributing to evading immune surveillance and potentially serving as a predictive biomarker for therapy resistance in melanoma (42, 43). A recent interesting study revealed that Rac1 mutant melanoma cells are highly sensitive to Pak inhibition, a result consistent with the augmented engagement of Rac effectors by the $Rac1^{P29S}$ mutant (44). Other described gain-of-function mutants in human tumors include $Rac1^{Q61R}$ (prostate cancer) and $Rac1^{A159V}$ (head and neck cancer) (45). Oncogenic mutations in *RAC1* and *RAC2* genes have also been identified in breast cancer, fibrosarcoma, and chronic myeloid leukemia cell lines (46). The most common mechanisms leading to Rac hyperactivation in cancer are depicted in Figure 2.

Aberrant Rac inputs and outputs in human cancer

Rac-GEFs have been largely linked to pro-oncogenic and pro-metastatic phenotypes. In cancer, Rac-GEF deregulation occurs as a consequence of overexpression, activating mutations/deletions, and/or excessive upstream inputs (1, 3, 5). There are more than 80 Rho-family GEFs in the genome that can be structurally divided into two classes. The first is the the Dbl family, composed of >70 members, which has a characteristic Dbl homology (DH) catalytic domain responsible for GDP/GTP exchange which in most cases has an adjacent regulatory pleckstrin homology (PH) domain. Representative Dbl-family GEFs with activity towards Rac are shown in Table 1. The second class comprises the DOCKs (DOCK1 to 11) which lack the thypical DH-PH domain tandem, and instead Rac activation is displayed through DOCK-homology regions DHR2 (responsible for GDP/GTP exchange) and DHR1 (involved in membrane localization). The complexity of GEF regulation and the intricate mechanisms governing their activation in cancer models have been extensively reviewed (1, 47–50).

A paradigmatic example of abnormal Rac-GEF deregulation in cancer is P-Rex1. Originally identified in neutrophils, this exchange factor is synergistically activated by the PI3K product PIP_3 and $G\beta\gamma$ subunits released upon activation of G-protein-coupled receptors (GPCRs), thus integrating signals emanating from multiple pathways (51, 52). The DH domain in P-Rex1 is the main point of contact with Rac1, whilst the PH domain is required for PIP_3 binding and for the interaction with norbin, an adaptor protein that facilitates P-Rex1 membrane recruitment (51, 53). P-Rex1 is also regulated by phosphorylations by protein kinase C (PKC), protein kinase A (PKA), and Pak, which in all cases negatively regulate its activation. P-Rex1 and protein kinase A (PKA) are reciprocally regulated, since P-Rex1 contributes to the spatiotemporal localization of this kinase, hence highlighting potential scaffolding functions of this GEF (54–57).

P-Rex1 mutations rarely occur in disease, however abnormal up-regulation has been described in specific cancer types. Our laboratory initially found that P-Rex1 is overexpressed in luminal breast cancer cells relative to non-transformed cells, whereas normal levels were observed in “triple-negative” basal breast cancer cells. Elevated P-Rex1 levels in estrogen-receptor positive luminal breast cancer were confirmed by immunohistochemistry and database analysis (58). P-Rex1 expression associates with metastatic progression and poor prognosis in breast cancer patients (58–60). Luminal breast cancer specific P-Rex1 overexpression is associated with promoter hypomethylation, unlike other pro-metastatic GEFs such as Vav3. This epigenetic modification in the *PREX1* promoter turned out to be a prognostic marker of poor patient survival (61). In melanoma cells, P-Rex1 amplification is primarily driven by augmented gene transcription and protein stability, and it causally associates with invasiveness rather than proliferative capacity, as also described in prostate and glioblastoma models (62–64).

Unlike P-Rex1, the related isoform P-Rex2 is mutated in cancer, particularly in melanoma, and less frequently mutated in other cancers. Mutations are distributed throughout the protein, and confer in some cases a hyperactive status, as also observed with truncated P-Rex2 mutants. Notably, *PREX2* is the third most prevalently mutated gene in melanoma after *BRAF* and *NRAS* (65–68). In the TCGA database, *PREX2* mutations show co-occurrence with *BRAF*, *NRAS*, and *RAC1* mutations. A remarkable difference between P-Rex isoforms is the selective interaction of P-Rex2 with Pten, a lipid phosphatase that negatively regulates PI3K signaling, leading to Pten inhibition and augmented Akt activity. Pten binding inhibits P-Rex2 GEF activity, however cancer-derived P-Rex2 mutants escape Pten-mediated inhibition (69, 70).

Among the multiple factors impacting Rac activation, the coordinated influence of signaling pathways converging on GEFs stands as a prominent mechanism. One of these key pathways is PKC. In hairy cell leukemia cells, for example, the pro-oncogenic PKCε isozyme contributes to maintaining a persistent Vav1-Rac1 activation that drives cell survival (71). Along the same line, activation of PKCε in non-small lung cancer (NSCLC) cells by growth factors or selective PKC activators (phorbol esters, diacyglycerol mimetics) stimulates a Rac response. Indeed, RNAi-mediated knockdown of PKCε or its pharmacological inhibition impairs the ability of NSCLC cells to form membrane ruffles and migrate in response to various stimuli (72, 73). Whereas the specific Rac-GEF(s) involved in this effect remain(s) to be identified, one attractive hypothesis is that PKCε, which is overexpressed in NSCLC and other cancer types, activates relevant Rac-GEF(s) and/or other key Rac regulatory proteins. In this regard, Tiam1 is an attractive candidate GEF based on the proposed role for this Rac-GEF in EGFR-driven lung tumorigenesis (74). Nuclear activation of Rac1 in lung cancer cells involves another PKC isozyme, the atypical PKCι. This effect is mediated by the GEF Ect2, arguing for an exquisite compartmentalization of Rac1 activation by discrete GEFs and PKCs (13).

Regardless of the nature of the hyperactive upstream signal, or potentially Rac-GAP down-regulation (5, 75), hyperactive Rac1 leads to enhanced downstream tumorigenic and metastatic signaling effector activation. Among the Rac1 effectors, Pak Ser/Thr kinases emerged as important drivers of motility, proliferation, survival, and drug resistance in

multiple cancers. Notably, Pak1 and Pak4, the best characterized member of the Pak family, were found to be hyperactivated or overexpressed in human tumors, and thus became attractive therapeutic targets (76, 77). Pak kinases are involved in cytoskeletal remodeling through complex regulation of the actin polymerization process, and they also control cell-cell contact and metalloprotease secretion (78–80). Pak-dependent phenotypic responses in tumor cells rely upon complex phosphorylation events involving Ras-Raf-MEK-ERK, β-catenin-APC, and PI3K-Akt cascades (76, 81–83). Targeting Pak isoforms using knock-out mouse models or pharmacological inhibitors successfully demonstrated the relevance of these kinases in tumor formation and progression, particularly as an effector of KRas and other oncogenes (84–86).

Concluding remarks - Rac and tumor susceptibility: from biochemistry to the clinic

Based on the prominent involvement of Rac1 in cancer progression, widespread efforts to target this GTPase have been pursued by academic laboratories and pharmaceutical companies in the last two decades. Although still in an experimental stage, Rac1 inhibitors have remarkable anti-tumorigenic and anti-metastatic effects in preclinical models, as originally demonstrated with the small molecule NSC23766 in blood cancer and solid tumor models (49, 87, 88). This drug, and others like EHop-016, ZINC69391, and 1A-116, represent prototypical blockers of the Rac-GEF/Rac association (49, 89). Considering the large number of Rac-GEFs, the actual specificity of these agents still needs to be biochemically and functionally determined. Another interesting prototype drug is EHT1864, a small molecule originally described to interfere with nucleotide binding to Rac and makes the GTPase uncapable of engaging downtream effectors (49, 90). This unique mechanism underscores its potential usefulness for inhibiting the “fast cycling” Rac1 mutants as those present in melanoma.

Rac isoforms have been shown to mediate resistance to radiation, and thus drugs that inhibit the Rac pathway could be efficient radiosensitizing agents. Rac1 activity is required for G2/M checkpoint activation and cell survival in response to ionizing radiation, as demonstrated with the sensitization of breast cancer cells to radiation exposure by treatemnet with NSC23766, leading to the induction of apoptosis. Interestingly, radioresistant breast cancer cells display elevated Rac1 expression with a concomintant increase in pro-survival NF-kB activity (91–93). The Rac effector Pak1 also plays crucial roles in the DNA damage response and thus influences cellular sensitivity to ionizing radiation and PARP inhibitors (94).

There is also extensive evidence linking the Rac pathway to chemoresistance, including resistance to genotoxic agents, anti-hormones and targeted therapies (5). Remarkably, the Vav3/Rac1/Pak1 axis mediates resistance to breast cancer endocrine therapy and contributes to estrogen receptor-mediated transcriptional activity, an effect that is reversed by EHT1864 (95, 96). Also in breast cancer models, Tiam1 RNAi depletion or NSC23766 treatment reduce resistance to the anti-HER2 monoclonal antibody trastuzumab (Herceptin) (97, 98). The recent suggestion that P-Rex1 dictates the sensitivity of breast cancer cells to PI3K

inhibitors also highlights the potential of the Rac pathway to influence tumor susceptibility to targeted therapeutic agents (99).

Interesting examples of Rac-dependent drug sensitivity have also been reported in prostate cancer. Rac signaling is activated in castrate-resistant human tumors, and forced expression of active Rac1 in prostate cancer cells promotes both androgen-independent cell growth and a survival response (27). More recently, the Rac pathway was identified as a critical player in resistance to anti-VEGF (bevacizumab) and anti-VEGFR (sunitinib) therapy. In this context, resistance to this targeted therapy in prostate cancer cells associates with elevated P-Rex1/Rac signaling. Notably, inhibition of the P-Rex1/Rac pathway overcomes bevacizumab/sunitinib resistance and reduces prostate cancer stem cell properties (100).

As indicated above, $Rac1^{P29S}$ mutated melanoma cells are resistant to clinical BRAF inhibitors but highly sensitive to Pak inhibition (42, 44), and they exhibit elevated expression of PD-L1, a ligand of the checkpoint protein PD-1 that plays a fundamental role in immune evasion (43). Conceivably, pharmacological inhibition of Rac could be beneficial in combination with anti-PD-L1 monoclonal antibodies or other immune checkpoint inhibitors. Nonetheless, additional studies would be required to establish the effectiveness of Rac inhibitors for cancer immunotherapy.

In summary, the overwhelming *in vitro* and *in vivo* evidence argues for important roles of the Rac signaling pathway in virtually every aspect of cancer progression. The aberrant activity of Rac, Rac-GEFs and Rac effectors in cancer, together with their involvement in tumor susceptibility and therapy resistance, emphasize the rich therapeutic opportunities afforded by inhibition of the Rac pathway.

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ABBREVIATIONS

APC	adenomatous polyposis coli
DH domain	Dbl homology domain
DHR1	DOCK homology region 1
DHR2	DOCK homology region 2
DOCK	dedicator of cytokinesis
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
ERK	extracellular signal-regulated kinase

GAP	GTPase activating protein
GDI	guanine nucleotide dissociation inhibitor
GDP	guanosine diphosphate
GEF	guanine-nucleotide exchange factor
GTP	guanosine triphosphate
HACE1	HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1
IQGAP	IQ motif containing GTPase activating protein
MEK	mitogen-activated protein kinase kinase
NSCLC	non-small cell lung cancer
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
Pak	p21-activated kinase
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PH domain	plekstrin homology domain
PI3K	phosphoinositide 3-kinase
PKC	protein kinase C
P-Rex	phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor
rRNA	ribosomal RNA
TGF-β	transforming growth factor-beta

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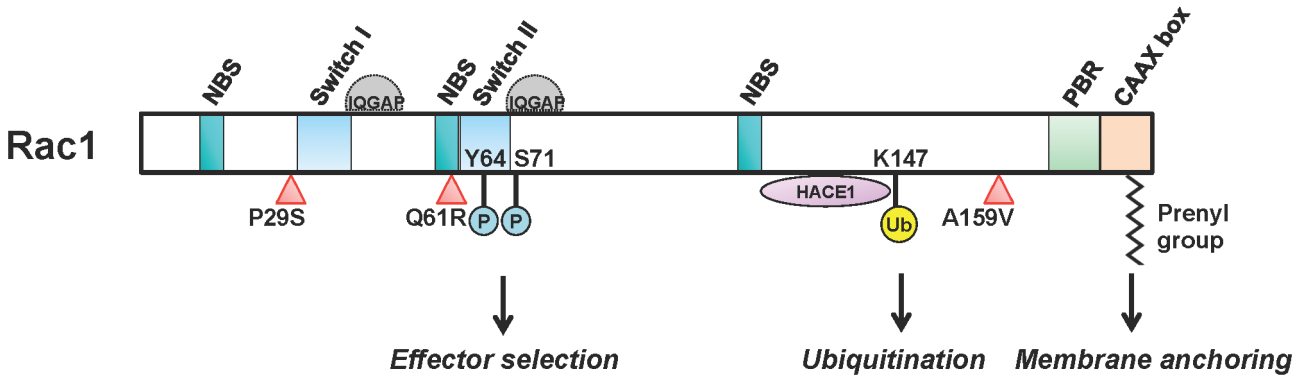

Figure 1. Rac1 domains, post-translational modifications and mutations.

The different domains in Rac1 include the nucleotide binding sites (*NBS*), switch I, switch II, polybasic region (*PRB*), and the *CAAX* box. The binding regions for IQGAP are indicated. The figure also shows sites of phosphorylation (Y64 and S71) and ubiquitination (K147) by the ubiquitinase ligase HACE1. Cancer-associated mutations (P29S, Q61R, and A159V) are represented as triangles.

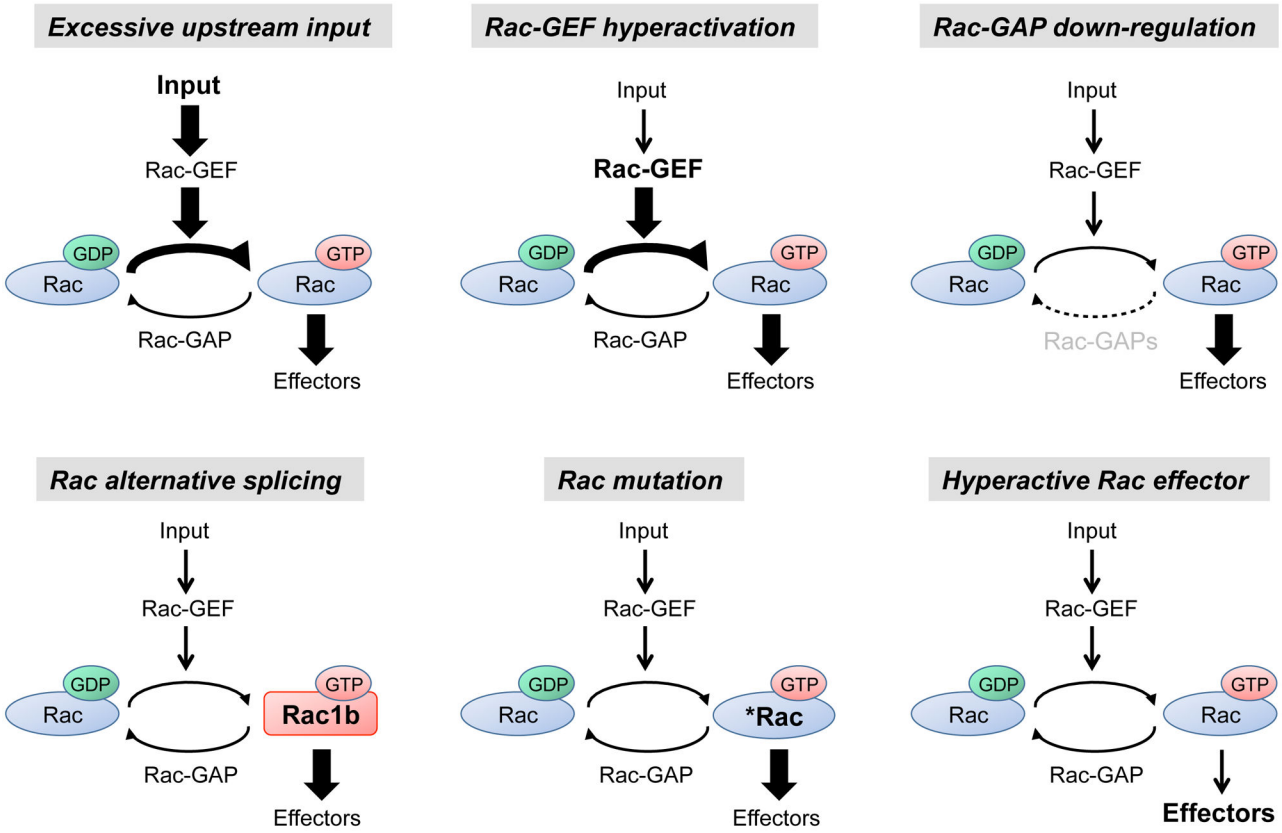

Figure 2. Rac hyperactivation in cancer.

Rac cycles between GDP-bound (inactive) and GTP-bound (active) states. Different mechanisms can lead to hyperactivation of the Rac signaling pathway in cancer. Other potential mechanisms for Rac signaling deregulation include the reduced degradation via HACE1, altered Rac localization, mutations in Rho GDIs, and oxydation/reduction (not depicted here).

Table 1.

Rho GEFs with activity towards Rac.

This table includes GEFs with demonstrated Rac exchange activity.

	Specificity		
DBL GEFs	**Rac**	**Cdc42**	**Rho**
ABR	X	X	X
ALS2	X		
ARHGEF6 / ARHGEF7 / ARHGEF16	X	X	
ARHGEF15 / ARHGEF19	X	X	X
ARHGEF18	X		X
ARHGEF39	X		
Def6	X		
ECT2	X	X	X
FARP1	X	X	
FARP2	X		
KALRN	X		X
MCF2	X	X	X
NGEF	X	X	X
PLEKHG1 / PLEKHG2 / PLEKHG3	X	X	
PLEKHG4	X	X	X
PREX1 / PREX2	X		
RasGRF1 / RasGRF2	X		
SOS1	X		
SPATA13	X	X	
TIAM1 / TIAM2	X		
TRIO	X		X
VAV1 / VAV2 / VAV3	X		X
DOCK GEFs			
DOCK1	X		
DOCK2	X		
DOCK3	X		
DOCK4	X		
DOCK5	X		
DOCK6	X	X	
DOCK7	X	X	
DOCK8	X	X	
DOCK10	X	X	