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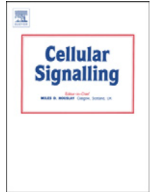

Review

Rac signaling in breast cancer: A tale of GEFs and GAPs

Eva Wertheimer, Alvaro Gutierrez-Uzquiza, Cinthia Rosemblit, Cynthia Lopez-Haber, Maria Soledad Sosa [1], Marcelo G. Kazanietz *

Department of Pharmacology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-6160, USA

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Rac GTPases, small G-proteins widely implicated in tumorigenesis and metastasis, transduce signals from tyrosine-kinase, G-protein-coupled receptors (GPCRs), and integrins, and control a number of essential cellular functions including motility, adhesion, and proliferation. Deregulation of Rac signaling in cancer is generally a consequence of enhanced upstream inputs from tyrosine-kinase receptors, PI3K or Guanine nucleotide Exchange Factors (GEFs), or reduced Rac inactivation by GTPase Activating Proteins (GAPs). In breast cancer cells Rac1 is a downstream effector of ErbB receptors and mediates migratory responses by ErbB1/EGFR ligands such as EGF or TGFα and ErbB3 ligands such as heregulins. Recent advances in the field led to the identification of the Rac-GEF P-Rex1 as an essential mediator of Rac1 responses in breast cancer cells. P-Rex1 is activated by the PI3K product PIP3 and Gβγ subunits, and integrates signals from ErbB receptors and GPCRs. Most notably, P-Rex1 is highly overexpressed in human luminal breast tumors, particularly those expressing ErbB2 and estrogen receptor (ER). The P-Rex1/Rac signaling pathway may represent an attractive target for breast cancer therapy.

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Abbreviations: DH, Dbl-homology; EGF, epidermal growth factor; ERα, estrogen receptor alpha; Erk, extracellular signal-regulated kinases; fMLP, N-formyl-methionine-leucine-phenylalanine; GAP, GTPase Activating Proteins; GBD, GTPase binding domain; GDI, GDP Dissociation Inhibitors; GDP, guanosine diphosphate; GEF, Guanine nucleotide Exchange Factors; GPCR, G-protein-coupled receptors; GTP, guanosine-5′-triphosphate; HDAC, histone deacetylase; HRG, heregulin; IGF-1R, insulin-like growth factor 1 receptor; IP4P, inositol polyphosphate 4-phosphatase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; Pak, p21-activated protein kinase; PH, pleckstrin-homology; PI3K, phosphoinositide 3-kinases; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; P-Rex, phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; TGFα, transforming growth factor alpha; TSA, Trichostatin A.

* Corresponding author at: Department of Pharmacology, Perelman School of Medicine, University of Pennsylvania, 1256 Biomedical Research Building II/III, 421 Curie Blvd., Philadelphia, PA 19104-6160, USA. Tel.: +1 215 898 0253; fax: +1 215 746 8941.

E-mail address: marcelog@upenn.edu (M.G. Kazanietz).

[1] Current address: Division of Hematology and Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA.

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1. Introduction

The Rho/Rac GTPases are a family of small G-proteins widely implicated in normal physiology and disease. They play an important role in cytoskeleton rearrangements and are key regulators of cellular adhesion, migration, proliferation, survival, differentiation and malignant transformation [1]. Members of this family in humans are divided into 6 classes: Rho (RhoA, RhoB and RhoC), Rac (Rac1, Rac2, Rac3 and RhoG), Cdc42 (Cdc42, Tc10, TCL, Chp/Wrch-2 and Wrch-1), RhoBTB, Rnd and RhoT [2]. The most studied members are RhoA, Rac1 and Cdc42. Like most GTPases, Rho, Rac and Cdc42 function as molecular switches that cycle between an inactive state that binds GDP and an active state that binds GTP. GTP is hydrolyzed to GDP through their intrinsic GTPase activity to render the G-protein inactive [3]. The switch between GDP and GTP is primarily regulated by two types of proteins: GEFs (Guanine nucleotide Exchange Factors) that facilitate GTP loading and thereby activate the small G-protein, and GAPs (GTPase Activating Proteins) that stimulate the hydrolysis of GTP by enhancing intrinsic GTPase activity, thus leading to G-protein inactivation. A third class of proteins known as Rho GDIs (GDP Dissociation Inhibitors) sequesters the inactive GTPases in the cytosol, preventing their translocation and subsequent activation. Dissociation from Rho GDI becomes essential for proper activation of the G proteins [4–6].

Rac isoforms have a very high degree of homology. The greatest divergence is in the C-terminal end, which is also the hypervariable region in Ras [7]. This domain is important for driving subcellular localization and binding to specific cellular regulators [8]. Rac2 shares significant nucleotide sequence identity (~88%) with the other Rac isoforms. At the nucleotide level Rac3 has 77% identity with Rac1, 83% identity with Rac2 and 69% identity with RhoG. At the amino acid level, Rac3 has 92% identity with Rac1 and 89% identity with Rac2.

The Rac1 gene localizes to chromosome 7 (7p22) and comprises 7 exons over a length of 29 kB [9]. Rac1, but not Rac2 or Rac3 genes, contains an additional exon 3b that is included by alternative splicing in the variant Rac1b, a constitutively active mutant that is expressed mainly in colon and breast cancer [10,11]. Rac1 is ubiquitously expressed, and it is involved in signal transduction pathways that control proliferation, adhesion, and migration. Its inactivation by gene targeting in mice leads to embryonic lethality caused by both gastrulation defects and apoptosis of mesodermal cells [12].

The Rac2 gene contains 7 exons in chromosome 22 (22q13.1) [13] and its expression is silenced in non-hematopoietic cells by DNA methylation [14]. Rac2-deficient mice show defects in neutrophil, macrophage, mast cell, lymphocyte B and lymphocyte T function [15,16]. Rac2 plays an important role in integrin-mediated hematopoietic stem-cell adhesion [17]. Patients with impaired Rac2 function display major alterations in hematopoiesis and an immunodeficiency syndrome [18,19].

The Rac3 gene encompasses 6 exons in chromosome 17 (17q25.3). Rac3 is primarily expressed in brain, although its expression has been reported in some human cell lines including GM04155 (lymphoblastic leukemia), K562 (chronic myelogenous leukemia), 5838 (Ewing sarcoma), HL60 (promyelocytic leukemia) and DU4475 (breast cancer) [8]. Rac3$^{-/-}$ mice display slight motor coordination problems and hyperactive behavior [20].

Rac proteins associate with membranes in order to carry out their biological functions. However, unlike other Ras superfamily proteins, this anchoring step is not achieved during biosynthesis but rather requires a combination of intrinsic and cooperative signaling. The first and most crucial signal is the post-translational modification of the "CAAX box" by incorporation of a geranyl–geranyl group or less frequently a farnesyl group. In cooperation with the CAAX box a closely located proline-rich domain contributes to the association of Rac with specific proteins in focal adhesion complexes [21,22].

2. Regulation of Rac activity by GEFs and GAPs

As mentioned above, Rac cycles between inactive and active states, two conformations that depend on the binding of GDP and GTP, respectively. Guanine nucleotides have picomolar affinities for Rac, and as a consequence their dissociation rate from the G-protein is slow. In order to lead to fast responses such as actin cytoskeleton reorganization, GEFs accelerate GDP/GTP exchange by several orders of magnitude [23]. GEFs catalyze the dissociation of the nucleotide from the G-protein by modifying the nucleotide-binding site. Rac has similar affinities for both nucleotides, and GEF binding does not favor binding of GTP over GDP. The resulting increase in GTP-bound over GDP-bound in Rac is rather due to the higher cellular concentrations of GTP relative to GDP. The mechanism by which GEFs weaken the binding of the nucleotide has been investigated in detail. According to the currently accepted model, the bound nucleotide in Rac is sandwiched between two loops called switches 1 and 2. These regions together with the phosphate-binding loop interact with the phosphates and a coordinating magnesium ion [23,24]. As the catalytic domains of GEFs display in many cases significant structural differences, it is possible to design drugs capable of interfering with their binding to Rac in a GEF-specific manner. One example is NSC23766, a compound that binds to a surface cleft between the switch 1 and switch 2 regions of Rac and prevents the binding of GEFs Tiam1 and Trio [25]. GEFs can be promiscuous in terms of small G-protein activation (for example Vav2 activates Rho, Cdc42 and Rac) or display selectivity, such as Tiam1 or P-Rex1 for Rac [26,27].

Rac can be activated by a variety of stimuli, including growth factors (such as EGF, PDGF, and HGF) and G-protein-coupled receptor ligands (such as SDF-1α, sphingosine-1-phosphate, and bombesin). Tyrosine-kinase receptors may convey signals to Rac-GEFs via intermediate molecules, as described for P-Rex1 (Fig. 1). As a consequence Rac-GEFs may change their subcellular localization, undergo conformational changes that disrupt autoinhibitory mechanisms, and/or go through allosteric changes in the catalytic domain. In several cases the activation of GEFs is mediated by phosphatidylinositol (3,4,5)-trisphosphate (PIP3), the product of the class I phosphoinositide 3-kinases (PI3K), which binds to the PH domain present in the Rac-GEFs [28]. PI3K-independent activation of GEFs may involve their direct binding to the tyrosine-kinase receptor, as described for Vav2 with EGFR [29]. GEFs can be also tightly regulated by tyrosine phosphorylation [30].

While the mechanisms by which Rac-GEFs promote Rac activation have been extensively studied, much less is known about the basis for Rac inactivation. Rac-GAPs accelerate the intrinsic GTPase activity of small G-proteins by several orders of magnitude. Biochemical and structural analyses revealed that GAPs stabilize important residues of the intrinsically mobile catalytic machinery of the G-protein. Some Rac-GAPs are stringently regulated by receptor stimulation. For example, the chimaerin Rac-GAPs are activated by the lipid second messenger diacylglycerol (DAG) generated in response to growth factor receptor stimulation (Fig. 1). DAG binds to the C1 domain present in chimaerins to promote their redistribution to the plasma

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