Cell. Mol. Life Sci. 66 (2009) 370 – 374
1420-682X/09/030370-5
DOI 10.1007/s00018-008-8552-x

Cellular and Molecular Life Sciences

Visions and Reflections (Minireview)

Rac1 GTPase: A "Rac" of All Trades

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Received 05 September 2008; received after revision 03 November 2008; accepted 18 November 2008
Online First 30 December 2008

Abstract. Rac1, a member of the Rho family of GTPases, is an intracellular transducer known to regulate multiple signaling pathways that control cytoskeleton organization, transcription, and cell proliferation. Deregulated expression or activation patterns of Rac1 can result in aberrant cell signaling and numerous pathological conditions. Here, we highlight the physiological functions and signaling mechanisms of Rac1 and their relevance to disease.

Keywords. Rac1, Rho GTPases, proliferation, cytoskeleton, survival.

Introduction

Discovery of Rac1. The Rho family of small guanosine triphosphatases (GTPases) are a subgroup of the Ras-superfamily of GTPases. Among this family, Rac1, one of the most extensively studied members, was initially discovered as Ras-related C3 botulinum toxin substrate 1 in 1989 [1]. Subsequently, it has been shown to play a fundamental role in a wide variety of cellular processes, including actin cytoskeletal reorganization, cell transformation, the induction of DNA synthesis, superoxide production, axonal guidance, and cell migration. New roles for Rac1, particularly in physiological settings and various primary cell types, are still emerging.

Upstream signaling to Rac1 and downstream effectors

Rac1 is ubiquitously expressed and exists in two conformational states, an inactive GDP-bound form and an active GTP-bound form. In response to extracellular signals, the interconversion of these states occurs via guanine nucleotide exchange factors (GEFs) which convert Rac1 to its active form, and GTPase-activating proteins (GAPs), which inactivate Rac1 (Fig. 1) [2, 3].

Rac1 interacts with specific effectors through domains that coordinate activation of a multitude of signaling cascades that influence diverse physiological outcomes. Among the first described Rac1 effector proteins was the family of p21 activating kinases (PAK). PAK binds Rac1 in a GTP-dependent manner, potently stimulating PAK kinase activity and leading to cytoskeletal dynamics, adhesion, and transcription [4, 5]. Rac1 signals through PAK to activate c-Jun N-terminal kinase (JNK) [6], placing Rac1 between Ha-Ras and MEKK in a signaling cascade from growth factor receptors and v-Src to JNK activation. In addition, Rac1, through PAK, can influence transmembrane guanylyl cyclase activity and the second messenger cGMP production [7] and mediates canonical JNK regulated Wnt-signaling to the TCF transcription factor [8]. Rac1 has also been shown to influence nuclear signaling through its effectors MLK2/3, which have been shown to activate the JNK pathway [9, 10].

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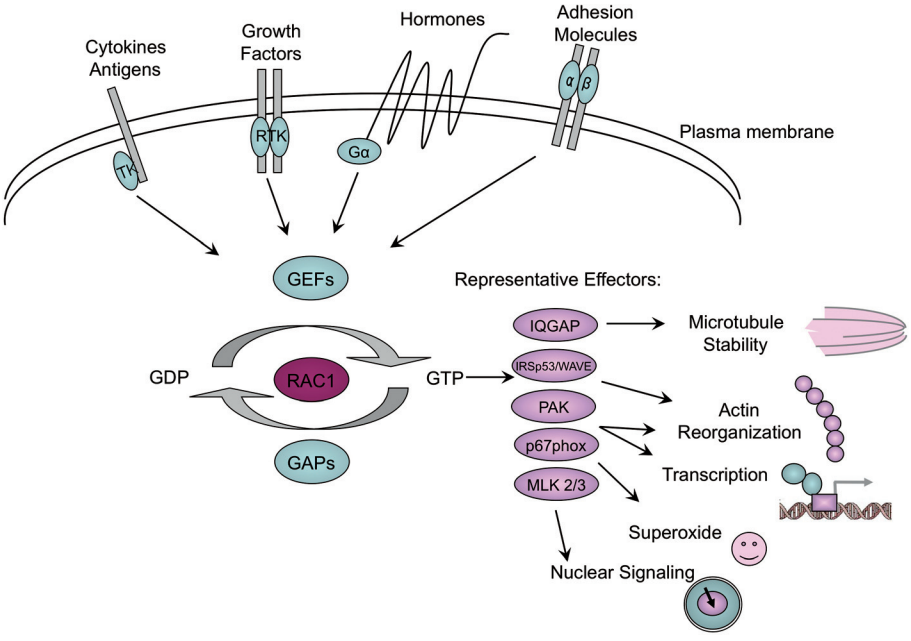

Figure 1. Rac1 signaling model. Rac1 acts as a signal transducer by receiving information via activated GEFs from a variety of extracellular stimuli such as receptor kinases, G protein-coupled receptors, or integrins. The GTP-bound Rac1 adopts an active conformation capable of binding effector molecules such as IQGAP, IRSp53/WAVE, PAK, MLK2/3, and p67phox. These effectors regulate diverse cellular functions, such as cytoskeleton remodeling, microtubule stability, gene transcription, and superoxide production.

Table 1. Cell-type specific roles of Rac1. Rac1 is a pleiotropic regulator of multiple cellular functions, some of which are unique in specific cellular contexts. Several recently characterized cell-type specific functions are listed [33, 54–63].

Cell type:	Functions:	References:
Mouse embryonic fibroblasts	ROS-mediated genomic instability	[33]
Hematopoietic stem cells	Retention of HSCs in bone marrow Regulation of HSC engraftment, proliferation, and differentiation	[54–57]
Epithelia	Hair follicle differentiation Maintainance of apico-basolateral cell polarity	[58–59]
Platelets	Agonist-induced expression of P-selectin and secretion of ADP from α and dense granules ADP-induced platelet aggregation	[60]
B and T lymphocytes	B and T cell development and signaling	[61–62]
Endothelial cells	Vascular development through cell migration, tubulogenesis, adhesion, and permeability	[63]

Rac1 signaling can be important for cellular transformation via modulation of anti-apoptotic and cell cycle machineries. Rac1 positively regulates transcription at NFkB transcription factor-dependent promoters [11] and facilitates phosphatidylinositol-3 kinase (PI3K)-dependent activation of AKT ser/thr kinase [12–15], thereby permitting the survival of transformed cells. Rac1 can also influence transformation through regulation of cyclin D1, a cell cycle protein that is frequently overexpressed in cancer [6, 16]. Thus, Rac1 is a critical component of a complex signaling network, given its ability to directly or indirectly impact a vast array of cellular signals.

Physiological Functions

The *in vitro* biochemical studies of Rac1 signaling and effector functions have paved the way for an examination of its physiological role in specific cell types *in vivo* using gene targeting in mice. Genetic studies have begun to elucidate the physiological functions specific to Rac1 that were difficult to discern using dominant negative or constitutively active mutants that could affect other Rho GTPase pathways (Table 1).

Actin dynamics. Historically, the first studies of Rac1 function were performed in the context of clonal cell lines. A body of work implicated Rac1 in reorganization of the actin cytoskeleton, specifically lamellipodia formation, which is thought to contribute to cell movement [17]. Rac1 was shown to reside at the leading edge of migrating cells, and microtubule growth can activate Rac1 to promote lamellipodial protrusion. Interestingly, Rac1-deficient primary MEFs are deprived of actin-stress fibers and focal adhesions, resulting in integrin-adhesion-mediated anoikis [18].

The studies in fibroblasts laid the groundwork for analogous studies in other eukaryotic cell types [19, 20]. As such, the actin-rich lamellae formed at the leading edge in fibroblasts are similar to the membrane dynamics at developing cell-cell contacts in epithelial cells, where actin is recruited to physically strengthen adherens junctions following E-cadherin activation of Rac1 [21, 22]. Elegant studies in neuroblastoma cells have revealed the importance of Rac1 in lamellipodia formation in the neural growth cone to promote neurite extensions [23]. Similarly, Rac1 has been shown to mediate actin polymerization in other cell types including stimulated blood platelets, lymphocytes, mast cells, and endothelial cells [24]. A more comprehensive discussion of the role of Rac1 in actin dynamics has been included in a recent review by A. J. Ridley [25].

Endocytosis/trafficking. Because actin cytoskeletal dynamics are intimately linked to vesicular trafficking, it is not surprising that Rac1 has been implicated in this process. In dendritic cells, Rac1 induces actin-rich membrane protrusions during pinocytosis [26], a process related to endocytosis which allows for antigen presentation, nutrient uptake, and sampling of the environment. Rac1 is involved in phagocytosis by mediating localized polymerization of actin at the membrane to promote the internalization of attached particles and microorganisms [2]. Together with $p47^{phox}$ and $p67^{phox}$, Rac1 is required for activation of NADPH oxidase of phagocytic cells to stimulate superoxide ions in order to kill bacteria [27, 28]. More specifically, Rac1 is critical for immunoglobulin-receptor mediated phagocytosis in macrophages, and its ability to activate MAPK and JNK pathways ensures activation of an inflammatory response [29].

ROS generation. Rac1 participates in reactive oxygen species (ROS) generation in primary cells [30] which can regulate diverse functions, including transcription factor activation, proliferation, transformation, apoptosis, and cellular innate immune responses. Rac1 is known to be essential for activation of NADPH oxidase in phagocytic cells, a defense against invading microbes [27], and generation of superoxide in fibroblasts, affecting cell mitogenesis [30]. Rac1 may also regulate ROS generation via Nox 1 [31]. Furthermore, constitutively active Rac1 is an efficient inducer of ROS, and dnRac1 inhibits ROS generation in Ras-transformed fibroblasts [32]. Other studies in primary cells have linked Rac1 activity to regulation of senescence through maintenance of cellular ROS levels, p53 activity, and genomic stability [33].

Cell Growth. In addition to its effects on the actin cytoskeleton, Rac1 signaling can affect cell growth through a variety of mechanisms. Rac1 can modulate gene transcription through the activation of NFkB, JNK, and p38 mitogen-activated protein kinase (MAPK), all of which induce activator protein-1 (AP1) transcription factors [29]. These transcription factors can upregulate the expression of proteins that control cell cycle progression, such as cyclin D1 and c-myc, to induce G1/S progression [34, 35]. In a specific cellular context, Vav, an exchange factor for Rac1, can upregulate AP1 through a Rac1/JNK signaling pathway, inducing proliferation in Jurkat cells [36]. Similarly, Rac1 is also involved in nuclear factor of activated T cells (NFAT) binding to the AP1 transcription factor which is critical for cell cycle progression and clonal expansion of the correct antigen-specific lymphocytes [37].

Pathologic effects of Rac1 malfunction

Recent studies have implicated aberrant Rac1 activity not only in tumorigenesis, but also in neurodegenerative disorders, mental retardation syndromes, cirrhosis of the liver, and cardio-remodeling/hypertension [38–40]. Although Rac1 mutations in tumors have not been reported, its overexpression occurs in many tumor types including cancers of the breast, lung, and colon [41–43]. In breast cancer, this increased pool of Rac1 is localized to the plasma membrane and is not a result of gene amplification, indicating that it is a consequence of transcriptional deregulation or increased RNA stability [41]. Further, a fast cycling splice variant of Rac1, Rac1b, has also been found to be highly expressed in breast and colon cancers rendering Rac1 predominantly in the GTP-bound form [41, 44]. Studies using constitutively active mutants have assigned a role for Rac1 in cellular transformation and tumorigenesis. Specifically, expression of constitutively active Rac1 (e. g. Q61L Rac1 or Rac1 V12), Rac1b, or many Rac GEF's (Tiam1 and Vav) promoted all of the hallmarks of oncogenesis in fibroblasts, including tumor induction in mice [6, 44–46]. Additionally, activated Rac1 is necessary for transformation and tumorigenesis induced by several oncogenes, including Ras and Tiam1 [45, 47, 48], and is able to collaborate with p53 loss of function to promote transformation in primary fibroblasts [49]. The specific mechanisms by which Rac1 influences transformation and tumor progression are still emerging, yet clear evidence exists that deregulated Rac1 can lead to loss of adhesion to the extracellular matrix [50] and increased invasiveness [51], not only through modulation of actin, but also by

altering the transcriptional activity of matrix metalloproteinases or their inhibitors (Fig. 1) [52, 53].

Summary

The intracellular signaling roles of Rac1 GTPase have come to light by a body of work carried out in the past two decades. It is now established that Rac1, together with other Rho proteins, control the organization of actin cytoskeleton and microtubule dynamics through direct interaction with multiple effector proteins. It has also been revealed that Rac1 plays critical roles in integrating signals from extracellular stimuli to the cell nucleus, mediating serum response factor-, β-catenin-, and NFkB-dependent transcription, and is required during G1 and G2/M cell cycle progression. Additional cell biological studies have unveiled an intimate relationship between Rac1 activity and intracellular membrane trafficking, ROS production, cell-cell and cell-extracellular matrix adhesion, and survival. With these critical roles in cell regulation, it is not surprising that malfunction of Rac1 GTPase-controlled signaling pathways has begun to be associated with many aspects of human pathologies including cancer. Thus, understanding and applying the physiological functions and mechanisms of Rac1 signaling to future therapeutic principles represents an important aspect of biomedical research.

Acknowledgements. This work was supported by grants from National Institutes of Health, USA, and E.E.B is funded by an NIH Training Program in Cancer Therapeutics Grant.

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