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Review

Coupling receptor tyrosine kinases to Rho GTPases—GEFs what's the link

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Abstract

Rho GTPases are molecular switches involved in the regulation of many cellular processes. This review summarizes work examining how stimulation of receptor tyrosine kinases (RTKs) leads to the activation of Rho guanine nucleotide exchange factors (GEFs) and their Rho GTPase substrates. The collective findings strongly suggest that RTK signaling to Rho proteins is a general signal transduction mechanism, like RTK mediated activation of phosphatidyl inositol 3-kinase, phospholipase Cγ, and the mitogen activated protein kinase (MAPK) pathway. More than half of the 58 known human RTKs activate at least one Rho family member. Likewise, 16 Rho GEFs directly interact with and/or are phosphorylated by a RTK. The specificity of receptor tyrosine kinase/Rho GEF signaling seems to be somewhat promiscuous. There several cases where multiple RTKs activate the same Rho GEF and where a single RTK can activate multiple Rho GEFs. Expression analysis indicates that the average human tissue contains transcripts for 33 RTKs, 34 Rho GEFs, and 14 Rho GTPases with each tissue containing a unique complement of these proteins. Given the promiscuity of RTKs for Rho GEFs, Rho GEFs for Rho GTPases, and the large number of these proteins expressed in cells, a complex combinatorial network of proteins in these families may contribute to coding specific signals and cell responses from RTKs.

Keywords: Rho; Rho GEF; Rho GTPase; Receptor tyrosine kinase; Signal transduction; Pleckstrin homology domain

Contents

1. Introduction

Many of the pathways that transduce signals from cell surface receptors to the nucleus involve at least one G-protein.

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G-proteins act as molecular switches being inactive when bound to GDP and bind a variety of effector proteins when bound to GTP in their active conformation. G-proteins are controlled by guanine nucleotide exchange factors (GEFs) which destabilize the inactive GDP/G-protein complex inducing release of GDP, and binding of cytosolic GTP, activating the G-protein. GTPase activating proteins (GAPs) induce the hydrolysis of GTP bound to G-proteins deactivating the G-protein switch and guanine nucleotide dissociation inhibitors can sequester G-proteins bound to either GTP or GDP.

Many receptors are known to activate G-proteins. The majority of receptors in mammalian proteomes are serpentine G-protein coupled receptors (GPCRs) and the principal signaling mechanism for receptors in this family involves direct activation of heterotrimeric G-proteins and their downstream signaling pathways. Another superfamily of G-proteins (Ras) encompasses the Ras, Rab, Arf, Ran, and Rho families [1]. In general, Rabs and Arfs are involved in protein trafficking, Ras is involved in signal transduction, Ran is involved in nuclear export and Rho proteins are involved in modulation of the actin cytoskeleton. Rho proteins in their active GTP-bound form, bind to a rapidly expanding group of effector proteins that effect many cell processes [2]. Through binding these effectors, Rho family members play important roles as controllers of actin cytoskeleton, and related cell motility and chemotactic responses. In addition, Rho GTPases and the Rho GEFs that activate these Rho proteins play additional roles in cell adhesion, cytokinesis, cell-cycle progression, macropinocytosis, endocytosis, membrane trafficking, and signal transduction [3].

The Rho family GTPases are activated by Rho GEFs. Because Rho proteins affect so many different cellular processes, they are attractive candidates for processing incoming receptor signals similar to the activation of heterotrimeric G proteins by GPCRs. The general role of Rho GTPases in signal transduction was last reviewed in 2000 [4]. At the time of this review, several GPCRs were known to activate a Rho GTPase and p115, PDZ, or Lbc Rho GEFs were activated by G_{α} subunits of heterotrimeric G-proteins. The activation of Rho GTPases by GPCRs, was recently reviewed [5]. These reviews do not cover the now emerging connection between the receptor tyrosine kinase and Rho GTPase families. Over the past 5 years the coupling between receptor tyrosine kinases and activation of Rho GTPases has become evident. Activation of Rho GTPases, is probably a general property of receptor tyrosine kinase signaling and is the subject of this review.

2. Receptor tyrosine kinases that activate Rho proteins

About 35 years ago, through studies applying insulin, epidermal growth factor, and nerve growth factor to cells, the first cell-surface receptors were identified [6–10]. In the early 1980s, the Insulin receptor was shown to possess tyrosine autokinase activity and this family has become known as the receptor tyrosine kinase (RTK) family [11,12]. The human genome encodes 58 RTKs as recognized to date [13] (Fig. 1). Several years later the connection between growth factor stimulation and Ras activation paved the way for unraveling of the mitogen activated protein kinase pathway [14]. In addition

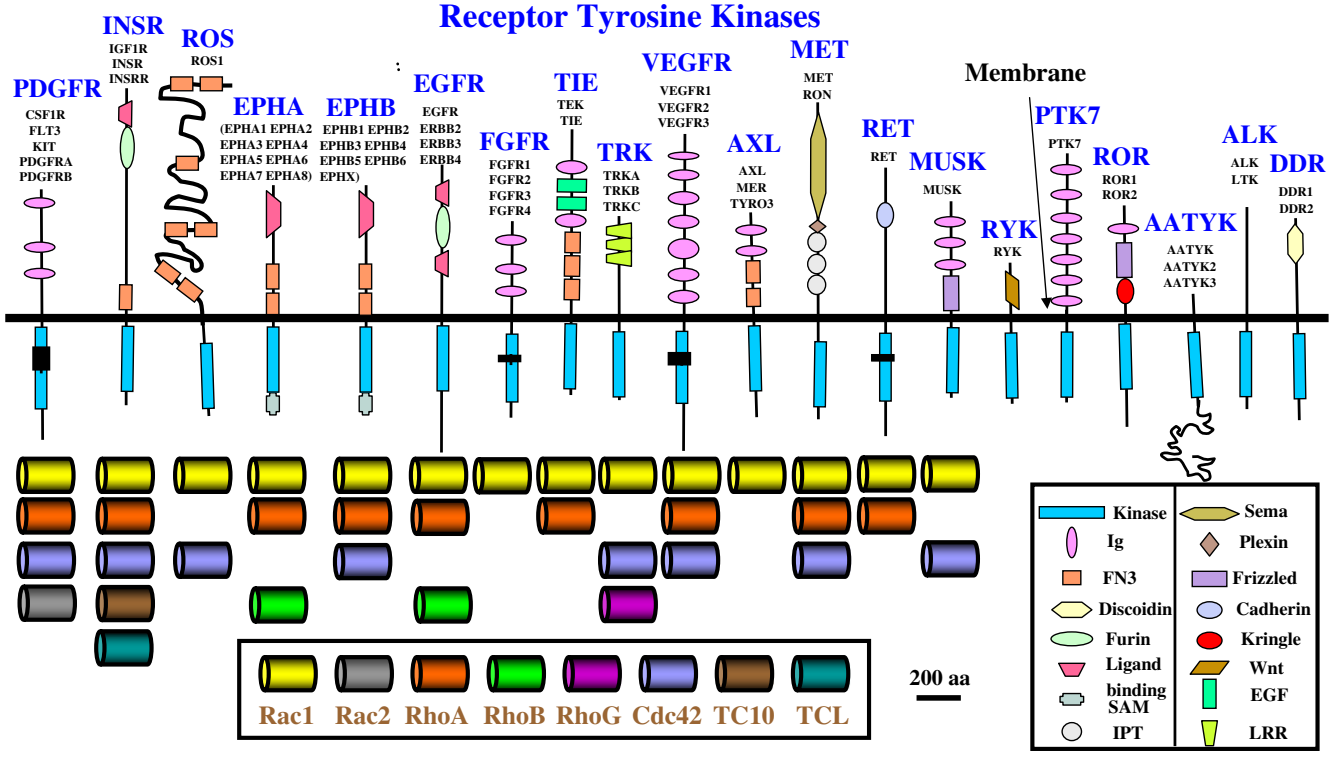

Fig. 1. Rho GTPases activated by different receptor tyrosine kinase subgroups. Schematic diagram shows Rho GTPases that are activated by RTK subgroups. Subgroups are as previously defined [13]. Specific Rho GTPases that are activated by RTKs are provided in Table 1. Key shows the domains of RTKs, and Rho GTPases are color coded. A scale for the RTKs is provided.