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Review

Non-canonical functions of RGS proteins

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ABSTRACT

Regulators of G protein signalling (RGS) proteins are united into a family by the presence of the RGS domain which serves as a GTPase-activating protein (GAP) for various Galpha subunits of heterotrimeric G proteins. Through this mechanism, RGS proteins regulate signalling of numerous G protein-coupled receptors. In addition to the RGS domains, RGS proteins contain diverse regions of various lengths that regulate intracellular localization, GAP activity or receptor selectivity of RGS proteins, often through interaction with other partners. However, it is becoming increasingly appreciated that through these non-RGS regions, RGS proteins can serve non-canonical functions distinct from inactivation of Galpha subunits. This review summarizes the data implicating RGS proteins in the (i) regulation of G protein signalling by non-canonical mechanisms, (ii) regulation of non-G protein signalling, (iii) signal transduction from receptors not coupled to G proteins, (iv) activation of mitogen-activated protein kinases, and (v) non-canonical functions in the nucleus.

Contents

Abbreviations: AC, adenylyl cyclase; CHO, Chinese hamster ovary; CNK1, connector enhancer of KSR1; CREB, cAMP-response element binding protein; DH, dbl-homology; DMAP1, Dnmt1-associated protein 1; EGF, epidermal growth factor; eIF, eukaryotic initiation factor; ERK, extracellular signal regulated protein kinase; ERM, ezrin radixin moesin; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; GPCR, G protein-coupled receptor; Grb2, growth factor receptor-bound protein; GRK, G protein receptor kinase; GSK, glycogen synthase kinase; HEK, human embryonic kidney; IP_3, inositol trisphosphate; LARG, leukemia-associated RhoGEF; LPA, lysophosphatidic acid; LEF, lymphoid enhancer factor; MDCK, Madin–Darby canine kidney; MEK2, MAPK/ERK kinase; MH2, Mad homology 2; MKK, mitogen-activated kinase kinase; MLK, mixed-lineage kinase; NES, nuclear extraction signal; NGF, nerve growth factor; PDGF, platelet-derived growth factor; PDZ, PSD-95/Dlg/ZO-1 domain; PH, pleckstrin homology; PI3K, phosphoinositide (3) kinase; PIP_3, phosphatidylinositol (3,4,5) trisphosphate; PKA, protein kinase A; PLC, phospholipase C; PDGF, platelet-derived growth factor; PGE2, Prostaglandin E2; PTB, phosphotyrosine binding domain; RBD, Ras-binding domain; RGS, regulator of G protein signalling; RTK, receptor tyrosine kinase; S1P, sphingosine 1-phosphate; TCF, T-cell factor; TGF-β, transforming growth factor-β.

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1. Introduction

Seven-transmembrane G protein-coupled receptors signal through heterotrimeric G proteins by promoting GDP-to-GTP exchange on the Gα subunit, resulting in dissociation of Gα-GTP from Gβγ subunits and activation of their specific effectors. Gα subunits hydrolyze GTP through their intrinsic GTPase activity, which leads to inactivation of G proteins. This process is promoted by the regulators of G protein signalling (RGS) that function as GTPase-activating proteins (GAP) for Gα subunits [1,2]. RGS proteins are united into a family by the presence of the RGS domain which serves as a GAP with some degree of specificity for various Gα subunits and receptors [3]. In addition to the RGS domains, RGS proteins contain diverse regions of various lengths, often containing other defined domains. These unique regions may regulate intracellular localization, GAP activity or receptor selectivity of RGS proteins, often through interaction with other proteins (reviewed in [4–6]). However, it is becoming increasingly appreciated that the non-RGS regions of RGS proteins can serve non-canonical functions distinct from inactivation of Gα subunits, or even from G protein signalling entirely. This review summarizes the examples of five such novel types of RGS functions: (i) regulation of G protein signalling by RGS proteins through non-canonical mechanisms, (ii) regulation of non-G protein signalling by RGS proteins; (iii) RGS proteins as signal transducers, (iv) scaffolding function of RGS proteins in activation of mitogen-activated protein kinases, and (v) nuclear functions of RGS proteins.

2. Regulation of G protein signalling by RGS proteins through non-canonical mechanisms

2.1. Regulation of Gβγ signalling by RGS proteins (Fig. 1A, B)

Gβγ subunits mediate activation of a number of GPCR effectors, including phospholipase Cβ (PLCβ) and adenylyl cyclase (AC) [7,8]. G protein-coupled receptor kinase GRK2, also known as β-adrenergic receptor kinase, is the RGS family member that has been known for many years to interact with Gβγ subunits via its C-terminus [9]. In this manner, GRK2 acts as a Gβγ effector and functions to inhibit GPCR activity by either (i) phosphorylation of GPCRs, which leads to receptor desensitization [10], or (ii) inhibition of Gαq signalling by direct interaction via its RGS-homology domain [11,12]. At the same time, binding of GRK2 to Gβγ prevents activation of other Gβγ effectors; and thus the C-terminus of GRK2 is widely used to dissect Gβγ signalling [13]. Recently, it was found that the N-terminus of GRK2 could also interact with Gβγ and inhibit Gβγ-induced inositol trisphosphate (IP_3) production independently of its C-terminus or RGS domain [14] (Fig. 1A). In addition to GRK2, RGS3 can also bind Gβ1γ2, at least in part through a region N-terminal to the RGS domain [15] (Fig. 1B). Ectopic RGS3 inhibited Gβ1γ2-induced production of IP_3, activation of extracellular signal regulated protein kinase (ERK) and Akt [15], or activation of a small GTPase Rac [16]. Considering the requirement for Gβγ signalling in chemotaxis, Gβγ binding may account for the more potent inhibition of migration of lymphoid cells to interleukin-8 or monocyte chemoattractant protein (MCP-1) by RGS3 as compared to RGS1 or RGS2 [17].

2.2. Regulation of adenylyl cyclases by RGS proteins (Fig. 1C)

Adenylyl cyclases are commonly activated by Gαs [18] and inhibited by Gαi [19] subunits. However, many RGS proteins, such as RGS1, RGS2, RGS3, and RGS13, can also inhibit AC activation by Gαs [20–23]. This effect of RGS proteins is unlikely to be a result of GAP activity on Gαs, as (i) there is no evidence that these RGS proteins function as effective GAPs for Gαs, (ii) this inhibition (by RGS2) still occurs in the presence of the nonhydrolyzable analog GTPγS, and (iii) RGS proteins can inhibit forskolin stimulated AC in the absence of activated Gαs [23]. There is strong evidence that RGS proteins regulate AC activity through direct interaction with AC, at least in the case of RGS2 [22]. Deletion and alanine-scanning mutagenesis studies identified three critical amino acids in the N-terminus of RGS2 (outside of the RGS domain) that were required for its interaction with adenylyl cyclase V (ACV). Mutation of these residues or deletion of the N-terminus abrogated ACV interaction and suppression of cAMP production [24]. A recent study identified four different RGS2 protein products starting at methionines 1, 5, 16, and 33 of the full length RGS2, which were results of alternative translation initiation sites. Consistent with the RGS2-AC interaction data, only the longer fragments containing the N-terminus inhibited cAMP production by constitutively active Gαs, whereas all RGS2 isoforms equally suppressed Gαq-induced IP_3 generation and calcium flux [25]. Furthermore, the role of endogenous RGS2 in the regulation of AC was suggested by a study that showed that the increased expression of RGS2 in osteoblasts by ATP or forskolin accounted for the reduced

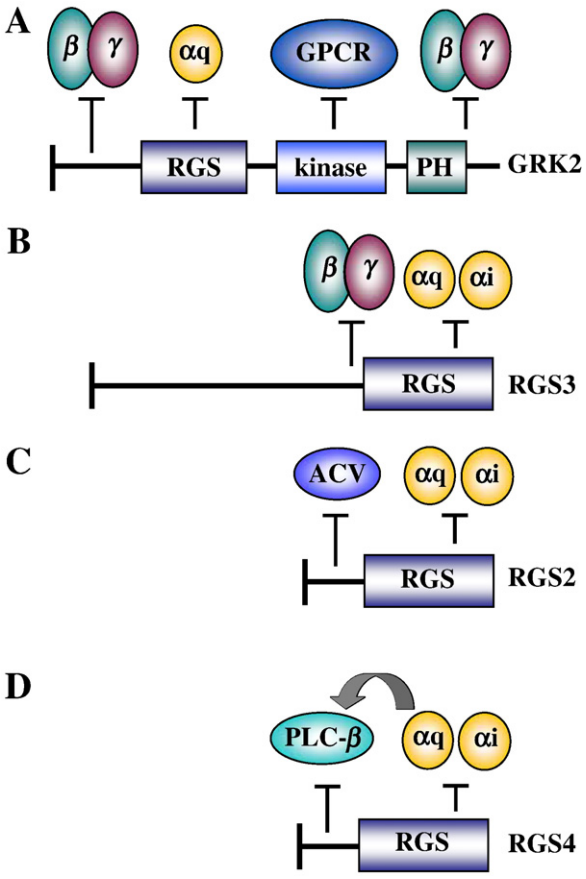

Fig. 1. Regulation of G protein signalling by RGS proteins through non-canonical mechanisms. A, B, regulation of Gβγ signalling by GRK2 and RGS3, respectively. C, regulation of ACV by RGS2. D, regulation of PLCβ by RGS4.