PERSPECTIVE

A G-protein signaling network mediated by an RGS protein

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A wide variety of extracellular stimuli induce signal transduction through receptors coupled to heterotrimeric G proteins, which consist of α , β , and γ subunits (Gilman 1987). The $G\alpha$ subunit has guanine nucleotide binding and GTP hydrolysis activities. Based on function and amino acid sequence homology, the $G\alpha$ subunits can be classified into four families, including $G\alpha_s$, $G\alpha_i/o$, $G\alpha_q$, and $G\alpha_{12}$ (Simon et al. 1991; Hepler and Gilman 1992). As exemplified by the responsiveness of our five senses to environmental stimuli, signaling mediated by trimeric G proteins is often extremely rapid and transient. A key step in achieving such a rapid response is the ability of the $G\alpha$ subunit to switch between its GDP- and GTP-bound forms. The nucleotide binding state of $G\alpha$ is regulated at both the GDP dissociation and GTP hydrolysis steps. Stimulation of receptors by agonists leads to a conformational change in the receptors which can function as a guanine nucleotide exchange factor to stimulate a rapid dissociation of GDP from the inactive $G\alpha$. The nucleotide-free $G\alpha$ is then available to bind GTP, leading to the dissociation of $G\alpha$ from the $G\beta\gamma$ heterodimer. Both the $G\alpha$ and $G\beta\gamma$ subunits can interact with and regulate downstream effectors that include adenylyl cyclase, phospholipase C, and ion channels (Gilman 1987; Birnbaumer 1992).

RGS proteins

Negative regulation of G proteins has an important role in controlling rapid and precise signaling responses. Because the $G\alpha$ -bound nucleotide has a very slow dissociation rate, termination of the signal depends on the hydrolysis of bound GTP. However, the intrinsic $G\alpha$ GTPase is too slow to account for the rapid physiological responses. Rapid termination of $G\alpha$ activity depends on a significant enhancement of the GTPase activity by other proteins similar to GTPase-activating proteins (GAP) for small GTPase Ras, which has an intrinsic GTPase even slower than that of $G\alpha$. RGS, regulators of G protein signaling, is a family of proteins recently identified

as GAPs for $G\alpha$. Whereas the first GAP protein for Ras was identified biochemically using frog extracts (Trahey and McCormick 1987), genetic studies in yeast, worms, and *Aspergillus* had key roles in the discovery of RGS proteins (Chan and Otte 1982; Koelle and Horvitz 1996; Yu et al. 1996). Sst2 RGS was first identified as a negative regulator of $G\alpha$ in the yeast mating pheromone response pathway (Chan and Otte 1982). *sst2* mutants are supersensitive to the pheromone signal and fail to desensitize upon prolonged stimulation. In *Caenorhabditis elegans*, the *egl-10* RGS gene was identified as a negative regulator of *goa-1*, which encodes the $G\alpha_o$ protein and regulates various behaviors (Koelle and Horvitz 1996).

Initial biochemical studies showed that RGS1, RGS4, RGS10, and GAIP were capable of stimulating the GTPase activity of $G\alpha$ (Berman et al. 1996; Chen et al. 1996; Hunt et al. 1996; Watson et al. 1996). Subsequently, the GAP activity of RGS proteins has been demonstrated for all $G\alpha$ subgroups except $G\alpha_s$. RGS proteins appear to enhance the GTPase activity of $G\alpha$ by binding to and stabilizing the transition state (Berman et al. 1996). The three-dimensional structure of an RGS and $G\alpha$ complex demonstrates that RGS stabilizes the flexible switch regions of $G\alpha$ to resemble the transition state, thereby, facilitating GTP hydrolysis (Tesmer et al. 1997).

Recent findings suggest that activities of RGS proteins are regulated, although much remains to be learned about how these processes are controlled. Analysis of the yeast mating pheromone response pathway indicate that *sst2* is induced at the transcriptional level by pheromone, suggesting a possible negative feedback mechanism of *sst2* in pheromone responses (Dietzel and Kurjan 1987). Several mammalian RGS proteins, including RGS1, RGS2, RGS3, and RGS16, have been shown to be regulated transcriptionally by mitogens, serum, inhibition of protein synthesis, and activation of the p53 tumor suppressor (Hong et al. 1993; Siderovski et al. 1994; Buckbinder et al. 1997). Interestingly, many RGS molecules contain additional protein sequence motifs, suggesting possible regulation at the post-translational level. For example, a DEP domain (Dishevelled/Egl-10/Pleckstrin) is found in the amino-terminal region of several RGS proteins (De Vries and Farquhar 1999). The

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DEP domain may function to regulate the membrane localization of RGS (Axelrod et al. 1998). In addition, these DEP domain-containing RGS proteins also have a GGL (G-protein gamma subunit-like) domain (Snow et al. 1998). The presence of GGL domains suggests that RGS proteins, in a complex with G β , may interact directly with the GDP-bound form of G α . Furthermore, axin/conductin are RGS domain-containing proteins that are involved in the Wnt signaling pathway and regulate a variety of developmental programs (Zeng et al. 1997; Behrens et al. 1998). Axin/conductin also contains several domains for interaction with glycogen synthase kinase 3, β -catenin, and adenomatous polyposis coli (APC) tumor suppressor. Possible regulation of axin/conductin by APC has been suggested by data showing that APC binds to the RGS domain of axin/conductin (Zeng et al. 1997; Behrens et al. 1998). These results strongly imply that regulation of RGS proteins has an important role in G protein signaling.

RGS proteins may also function as effectors of G protein signaling by linking the G protein to other pathways. RGS proteins interact with the switch regions of GTP-bound G α (Tesmer et al. 1997). Because the switch regions are involved in effector binding, it is possible that RGS proteins act as effectors or compete for effector binding. In fact, RGS4 has been shown to compete with phospholipase C for G α_q binding (Hepler et al. 1997). In another case, the RGS protein p115RhoGEF acts as an effector (Hart et al. 1998; Kozasa et al. 1998). p115RhoGEF is an exchange factor for Rho and also contains a RGS domain. The RGS domain of p115RhoGEF selectively stimulates the GTPase activity of G α_{12} and G α_{13} but not other G α family members. Interestingly, activated G α_{13} stimulates the exchange activity of p115RhoGEF on Rho (Hart et al. 1998). In contrast, activated G α_{12} inhibits the stimulation of p115RhoGEF by G α_{13} . The observations with p115RhoGEF establish a biochemical link between heterotrimeric G protein and the Rho small GTPase in regulation of cytoskeletal function. Certain G α effectors such as phospholipase C β can also function as a GAP for G α_q (Berstein et al. 1992; Ross 1995). The dual functions of these effector proteins may be of important physiological significance as they can facilitate a rapid turnover of G proteins after activation of downstream effectors.

The EAT-16 RGS protein mediates a G-protein network in *C. elegans*

In this issue Hajdu-Cronin and colleagues (1999) present elegant genetic studies that uncovered a likely novel function of RGS as a mediator of a G-protein signaling network. In this process, one G protein is regulated by an upstream G protein, whereas an RGS protein serves both as an effector and regulator between the two G proteins. The *C. elegans goa-1* gene encodes a G α_o protein that has been shown to have a key role in regulating a number of behaviors (Mendel et al. 1995; Segalat et al. 1995). Reduction-of-function mutations in *goa-1* caused behav-

ior defects, including hyperactive movement, premature egg laying, slow pharyngeal muscle pumping, and male impotence. In contrast, expression of an activated *goa-1* mutant in transgenic animals produced lethargic movement, delayed egg laying, active pharyngeal pumping in absence of food, and reduced mating efficiency. GOA-1 may mediate the functions of neurotransmitters such as serotonin, which regulates similar behaviors. *goa-1* appears to be negatively regulated by *egl-10* RGS (Koelle and Horvitz 1996). Through a genetic screen for suppressors of the lethargic phenotype of the activated *goa-1* mutant gene, Hajdu-Cronin et al. (1999) have identified two genes, *eat-16* and *sag-1*, that are likely to act downstream of *goa-1* in the signaling process. *eat-16* was cloned and shown to encode a RGS protein most similar to mammalian RGS7 and RGS9.

Genetic data indicates that EAT-16 RGS is unlikely to act as a GAP for GOA-1. Loss-of-function mutations in *eat-16* suppressed an activated *goa-1* mutation, whereas overexpression of *eat-16* suppressed *goa-1* loss-of-function mutant phenotypes such as premature egg laying, indicating that *eat-16* acts either downstream of or parallel to *goa-1*. However, these results do not formally rule out the possibility that EAT-16 acts both as an effector and a GAP for GOA-1.

Hajdu-Cronin et al. (1999) reported that EGL-30, a worm G α_q , is a likely target for the EAT-16 RGS. Reduction-of-function mutations of *egl-30* G α_q display defects such as slow body movement and delayed egg laying that are essentially opposite to those observed with *goa-1* loss-of-function mutations, suggesting that the two G α proteins have antagonistic physiological functions (Brundage et al. 1996; Hajdu-Cronin et al. 1999). Genetic interaction studies provide the key support for the idea that EAT-16 may act as a GAP for G α_q . *eat-16* mutations partially suppress the defects of a reduction-of-function mutant of *egl-30* but not the lethality of an *egl-30* null mutation. Overexpression of *eat-16* suppressed the phenotypes caused by overexpression of *egl-30* but not the phenotype caused by a constitutively active *egl-30* mutant that should be resistant to regulation by RGS. Moreover, negative regulation of *egl-30* G α_q activity by *eat-16* RGS is supported by the fact that reduction of *egl-30* gene activity suppressed the lethality that resulted from a synergistic effect of mutations in both *eat-16* and *sag-1*.

Analysis of *goa-1* and *egl-30* double mutants indicates that *egl-30* functions downstream of *goa-1*. Reduction-of-function mutations of *goa-1* and *egl-30* show essentially opposite phenotypes (Mendel et al. 1995; Segalat et al. 1995; Brundage et al. 1996). *goa-1 egl-30* double mutants display phenotypes similar to the *egl-30* single mutant. Similarly, overexpression of GOA-1 and EGL-30 has opposite effects. Interestingly, overexpression of EGL-30 suppressed the lethargic movement caused by active GOA-1. These data strongly support a G-protein network that *goa-1* G α_o functions upstream of and negatively regulates the activity of *egl-30* G α_q in *C. elegans*.

Cross talk among different G-protein signaling pathways is certainly of important biological significance.

G-protein receptors are the largest family of transmembrane receptors in mammalian cells. Agonists binding to G protein-coupled receptors have a wide range of biological activities, which may be synergistic, antagonistic, or partially antagonistic to each other. In higher eukaryotes, it is known that hormones with opposite physiological functions can induce their respective signaling by activation of receptors coupled to different G proteins. For example, activation of $G_{\alpha s}$ stimulates adenylyl cyclase, whereas activation of $G_{\alpha i}$ inhibits adenylyl cyclase (Gilman 1987). In this case, the antagonistic effects are achieved at the level of a common downstream effector, and cAMP levels are regulated by the relative strengths of the different signals transmitted through the two G proteins. The antagonist effects of $G_{\alpha o}$ and $G_{\alpha q}$ in *C. elegans*, however, can be explained by a hierarchy of G proteins (Fig. 1). In this situation, different agonists activate specific receptors, which then activate the two G protein complexes. Each G protein complex can interact with its specific downstream effectors to activate or inhibit specific functions. One of the effectors of the upstream G protein ($G_{\alpha o}$ in the model) is an RGS protein that functions as a GAP to inhibit the downstream G protein ($G_{\alpha q}$ in Fig. 1). Such a network may offer several advantages in regulation of G-protein functions. For example, when receptors for both G proteins are activated by different signals, the signals for the upstream $G_{\alpha o}$ (e.g., signals to inhibit locomotion in the worm) may have dominance over signals of the downstream $G_{\alpha q}$ (e.g., signals to stimulate locomotion in the worm). Such dominance may have a significant role in allowing the worms to cope with the environment. In a general sense, as the inhibition seems only unidirectional, it is also possible that signals acting on receptors coupled to upstream G protein may have broader physiological functions than signals acting on receptors coupled to downstream G protein. A G-protein network may also have

enough flexibility to allow these G proteins to be regulated differently in different cells. Antagonistic effect between the two G proteins may only occur in some cells for specific functions such as locomotion and egg laying. For example, only in the cells that expressed the RGS would such a negative regulation of one G protein by another be established.

Models for a G-protein cascade

The paper by Sternberg and colleagues in this issue indicates that one G protein can regulate the function of another G protein (Hajdu-Cronin et al. 1999). However, the genetic data cannot determine whether this regulation is direct or indirect. Although further biochemical studies are likely to answer this question, it is possible to speculate potential models of actions. It has been shown that Ras small GTPase can regulate other small GTPases such as Ral via direct regulation of a Ral-specific exchange factor activity (Urano et al. 1996). It is plausible that GOA-1 G_{α} could inhibit EGL-30 $G_{\alpha q}$ by a direct mechanism, particularly because EAT-16 RGS contains two domains, RGS and GGL, that are likely to interact directly with GOA-1 $G_{\alpha o}$ and EGL-30 $G_{\alpha q}$. The GGL domain displays a weak but significant level of sequence identity to the γ -subunit of G protein. The GGL domain of human RGS11 has been shown to form a complex with G β_5 (Cabrera et al. 1998; Snow et al. 1998) and could form a heterotrimeric complex with a GDP-bound G_{α} . The RGS11/ G β_5 complex also acts as a GAP selectively toward mammalian $G_{\alpha o}$. Human RGS11 has an overall structure very similar to EAT-16 RGS, with a DEP domain, a GGL domain, and a RGS domain (Snow et al. 1998).

One attractive model is that the GGL domain of EAT-16 RGS functions as a γ -subunit for GOA-1 $G_{\alpha o}$ (Fig. 2A). In the resting state, the GDP form of GOA-1 $G_{\alpha o}$ directly interacts with an EAT-16 RGS/ $G\beta$ heterodimer and prevents it from acting on EGL-30 $G_{\alpha q}$. Upon stimulation, GOA-1 $G_{\alpha o}$ becomes GTP-bound and dissociates from the EAT-16 RGS/ $G\beta$ heterodimer. EAT-16 RGS (with or without $G\beta$) is then free to interact with and inhibit the EGL-30 $G_{\alpha q}$ by promoting GTP hydrolysis. In addition, the GTP-bound GOA-1 may stimulate the GAP activity of EAT-16. This model predicts that EAT-16 RGS interacts stably with inactive GOA-1 $G_{\alpha o}$ via the GGL domain.

An alternative model is that the activated GOA-1 $G_{\alpha o}$ directly binds to and stimulates the GAP activity of EAT-16 RGS towards EGL-30 $G_{\alpha q}$ (Fig. 2B). This model predicts that the active form of GOA-1 $G_{\alpha o}$ interacts with EAT-16 RGS, which then functions as an effector of GOA-1. Both models require that all three proteins, GOA-1, EAT-16, and EGL-30, are expressed in the same cell. Similar expression patterns have been reported for GOA-1 and EAT-16 (Hajdu-Cronin et al. 1999).

The above models can be tested readily by biochemical experiments *in vitro* and *in vivo*. It is quite possible that these models may prove to be too simplistic. Contributions of other factors, such as *sag-1*, identified in the

Figure 1. RGS-mediated cross walk between two G proteins. In a specific cell, two G proteins may mediate opposite physiological effects. In *C. elegans*, $G_{\alpha o}$ and $G_{\alpha q}$ appear to function antagonistically on several behaviors such as locomotion, egg laying, and pharyngeal pumping. Each G protein can be activated by specific receptors and interact to specific effectors to generate downstream effects. RGS protein negatively links the two G proteins to coordinate the actions in response to extracellular signals (Hajdu-Cronin et al. 1999).

Figure 2. Models for EAT-16 RGS to directly mediate the inhibition of EGL-30 Gαq by GOA-1 Gαo. (A) Sequestration by the inactive GOA-1 Gαo via the GGL domain (yellow square) of EAT-16 RGS. The GGL domain of EAT-16 RGS functions as a γ subunit for GOA-1 Gαo. Activation of GOA-1 Gαo results in the release of EAT-16 RGS, which then is free to promote the GTP hydrolysis of EGL-30 Gαq. The GTP-bound GOA-1 Gαo may also directly stimulate the GAP activity of EAT-16 RGS. (B) Activation of EAT-16 RGS by GOA-1. In contrast to the model in A, this model predicts that EAT-16 RGS does not interact with the inactive GOA-1 Gαo. Instead, EAT-16 RGS is activated by interaction with the GTP-bound form of GOA-1 Gαo.

suppressor screen, may be critical for Gαo-to-Gαq networking. Nevertheless, the genetic work by Sternberg and colleagues has clearly established a signaling interaction between two G proteins and shown that an RGS protein may play a key role to mediate cross talk between two G protein-coupled receptors.

Mammalian cells contain several RGS proteins, including RGS6, RGS7, RGS9, and RGS11, which are highly related to EAT-16 RGS (De Vries and Farquhar 1999; Hajdu-Cronin et al. 1999). These proteins share a similar domain topology with an amino-terminal DEP domain, a central GGL domain, and a carboxy-terminal RGS domain. Given the conserved nature of many signal transduction pathways, and given that opposite effects of Gαo and Gαq through different effectors were reported in mammalian cells (Gollasch et al. 1991; Offermanns et al. 1991), it is conceivable that such a G-protein network

may also operate in mammalian cells. Such a network can provide a simple and direct mechanism for signal transduction cross talk among these classes of receptors.

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