Children with positive DHT responses to tuberculin had serum cytokine concentrations suggestive of predominant T_H1 responses, in contrast to the T_H2 profiles seen in children with negative DHTs.

These results are an important extension of observations in the 1960s and 1970s that there is a reciprocal relation between inflammatory and humoral responses to vaccination regimes (*7*, *8*). This reciprocal relation has also been attributed to preferential activation of T_H1 or T_H2 subsets of T cells and is consistent with the genetic predisposition to T_H1 or T_H2 responses of different strains of mice.

Central to the relevance of the results is the hypothesis that the immune system can be manipulated to manifest a persistent T_H1 or T_H2 response. If this is the case, vaccination to induce T_H1 responses may be effective against asthma and other allergic disorders (*9*). In mice, overwhelming *Schistosoma mansoni* infection induces T_H2 responses. The infection concomitantly down-regulates the T_H1 response to other antigens and delays the clearance of vaccinia virus (*10*). However, in humans with filariasis, who show T_H2-biased cytokine profiles, the ability to respond to Mtb proteins is not lost (*11*). Children with eczema, another atopic condition, occasionally undergo spontaneous remission after severe bacterial or viral infections (*12*), although usually temporarily. Both of these observations suggest that alterations in the T_H2/T_H1 balance may become important only in the presence of continued overwhelming infection.

Also confusing the T_H1/T_H2 theory of asthma are the findings that helminth and other parasite infection may protect against allergic diseases, despite up-regulation of T_H2 responses. This type of infestation is invoked to explain the low prevalence of asthma in rural Africa and the Venezuelan slums (*13*, *14*). Helminth infection produces high levels of polyclonal IgE that, possibly by saturating the number of binding sites for IgE on mast and other effector cells of allergy, prevent activation of these cells by the relatively trivial exposures to allergens.

Thus, the results of Shirakawa *et al.* invite the speculation that the decline in childhood tuberculosis infection in Japan is causal in the recent asthma epidemic. However, the incidence of other infections may also be declining, so the case for tuberculosis requires further study. Nevertheless, the new results emphasize the complexity of the environmental contribution to asthma and remind us that identification of the relevant factors may ultimately resolve this epidemic.

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SIGNAL TRANSDUCTION

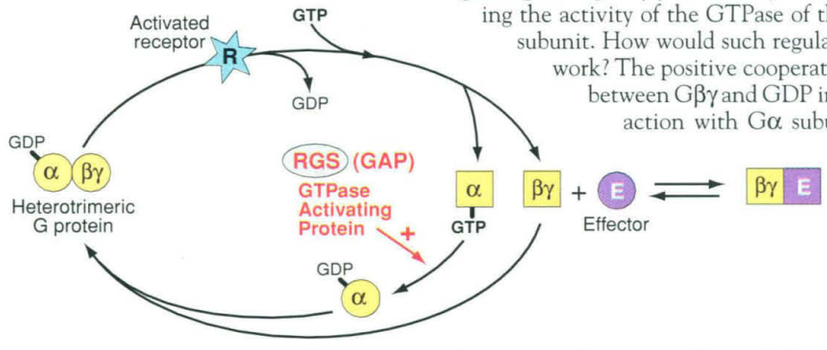
There Are GAPS and There Are GAPS

Ravi Iyengar

Although their main function is to regulate other proteins, guanine nucleotide–binding proteins (G proteins) are also guanosine triphosphatases (GTPases), cleaving guanosine triphosphate (GTP) to form guanosine diphosphate (GDP). Because of this activity, they oscillate between GTP- and GDP-bound states, and thus regulate diverse processes such as protein synthesis, cytoskeleton assembly, vesicle transport, and signal transduction. The superfamily comprises both small monomeric and large multimeric G proteins, but for all members, the release of bound GDP and the binding of GTP are highly regulated processes (*1*). The GTPase activity of small G proteins, such as EF-Tu and Ras, is stimulated by associated proteins called GAPs (GTPase activating proteins) (*2*). But GAPs for most large G proteins had not been described until recent work identified members of the regulators of G protein–signaling (RGS) family as GAPs for this subfamily.

The large heterotrimeric G proteins involved in signal transduction have α subunits, which are related to small G proteins, and $\beta\gamma$ subunits that exist as a single complex. Both $G\alpha$ and $G\beta\gamma$ can independently transmit signals (*3*). Signal termination for both $G\alpha$ and $G\beta\gamma$ subunits likely occurs through GTP hydrolysis. How the GTPase terminates signaling through $G\alpha$ subunits is easily understood given the observation that GDP-$G\alpha$ subunits have much lower affinities for effectors than do GTP-$G\alpha$ complexes (*4*). But how signaling through $G\beta\gamma$ is terminated has not been as clear. A report in *Cell* by Gilman and co-workers (*5*) and two others in *Nature* (*6*) identifying two members of the RGS family, GAIP and RGS4, as GAPs for members of the $G\alpha_i$ family and other recent papers shed light on this issue.

Members of the RGS family have been identified in yeast, *Caenorhabditis elegans*, and mammals (*7*). Sst2p in yeast and EGL-10 in *C. elegans*, homologs of RGS, suppress signal transmission by acting on the G protein–α subunit (*8*). Mammalian RGS can substitute for yeast Sst2p in regulating pheromone signaling (*9*), which is transmitted through $G\beta\gamma$ subunits (*10*). Taken together, these data suggest that RGS can regulate signaling through $G\beta\gamma$ subunits by modulating the activity of the GTPase of the α subunit. How would such regulation work? The positive cooperativity between $G\beta\gamma$ and GDP interaction with $G\alpha$ subunits



A four-component heterotrimeric G protein–signaling system. The resting G protein is an $\alpha\beta\gamma$ heterotrimer with GDP bound to it. Activated receptor promotes the release of GDP, the binding of GTP, and dissociation of GTP-$G\alpha$ from the $G\beta\gamma$ complex. GTP-$G\alpha$ and $G\beta\gamma$ can now interact with their effectors and propagate the signal. RGS stimulates (+) the GTPase activity of the $G\alpha$ subunit, resulting in the accumulation of GDP-$G\alpha$, which re-forms the stable heterotrimer. Free $G\beta\gamma$ leads to dissociation of $G\beta\gamma$ from effector, thus terminating signal propagation. R, receptor; E, effector; $\alpha\beta\gamma$, the heterotrimeric G protein; and RGS (GAP), stimulator of the GTPase of the $G\alpha$ subunit.

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(*11*) indicates that Gβγ has a higher affinity for GDP-Gα than for GTP-Gα. If Gβγ also has a higher affinity for GDP-Gα than for effectors such as K^+ channels, adenylyl cyclase, and phospholipase C, then RGS, by stimulating the GTPase catalytic activity and the accumulation of GDP-Gα, could shift the steady-state level toward the inactive heterotrimeric state. Alternatively, if the affinity of Gβγ for GDP-Gα and effectors is in the same range, a much greater concentration of Gα in comparison to the effector could push Gβγ to the heterotrimeric state. Either way, RGS would be essential to build up the concentration of GDP-Gα after activation of the G protein, and the relative stoichiometry of effectors to Gα is likely to be important for Gβγ-mediated signaling.

This mechanism may be operative for G_i. Here the Gα subunit would define the specificity of receptor interaction and in conjunction with RGS define the lifetime of the active Gβγ complex. Different $G\alpha_i$ isoforms have different rates of GDP release (*12*), and if the different RGS isoforms stimulate the GTPase rates to different extents, then a wide range of timing can easily be obtained. Such facile temporal regulation would be particularly valuable for Gβγ regulation of K^+ and Ca^{2+} channels. RGS stimulation of $G\alpha_{i1}$ GTPase could explain the discrepancy between the 20-fold faster deactivation rate of the muscarinic K^+ channel upon removal of the agonist, as compared to the basal GTP hydrolysis rate of purified G_i (*13*). The type of regulation described above presumes that activation results in subunit dissociation and that all of the free Gβγ can regulate effector, although this has not been proven.

Experiments in E. Ross's laboratory have shown that Gβγ inhibits GAP stimulation of the GTPase-Gα (*14*), suggesting that Gβγ and RGS may interact with overlapping regions of Gα. Additionally, the RGS (GAP) proteins interact with GDP-Gα with much lower affinity than they do with the transition-state complex (*15*). These properties would facilitate GTP hydrolysis on Gα followed by dissociation of RGS from Gα and the reassociation of Gα and Gβγ, further supporting the notion that RGS regulated GTPase is the major mechanism for turning off Gβγ signaling. Clearly, for G_i/G_o coupled systems we have moved from a three- to a four-component system (see figure).

In contrast, GAPs for monomeric G proteins function as On-Off switches because the basal GTPase activity of the monomeric G proteins is very low. RGS is poised to be an effective modulator of transmembrane signaling through G protein pathways and can serve as a putative locus for interactions between signaling pathways.

Comparison of the work by Gilman and co-workers (*5*, *15*) with that from the Wittinghofer group (*6*, *17*) suggests that GAPs regulate the activity of small and large G proteins by different mechanisms. GDP-Gα can bind AlF_4—small G proteins, such as Ras, cannot, but GDP-Ras protein can bind AlF_4 when associated with its GAP protein (*16*). Crystallographic studies on Gα subunits indicate that the AlF_4^-·GDP–Gα complex represents the transition state of the S_N2 reaction that occurs during GTP hydrolysis (*18*). Thus for Ras, GAP is thought to contribute residues crucial for formation of the transition state (*16*). Prominent in this context is an Arg (Arg^{178} in $G\alpha_{i1}$) present in Gα subunits but not in Ras or other small G proteins. The crystal structure of the active domain of the p120GAP and a manual docking model of Ras and the GAP active domain suggest that an Arg from GAP could be used for GTP hydrolysis by Ras (*17*). Thus, for small G proteins the main function of GAP would be to move the Ras-GTP complex to a transition state for nucleotide hydrolysis. It is unlikely that this is the primary mechanism by which RGS stimulates the GTPase activity of Gα, since Gα by itself can form a transition-state complex (*18*). However, RGS has the highest affinity for AlF_4^-·GDP-Gα (*15*) indicating that it preferentially binds to the transition-state complex and thus promotes hydrolysis. The precise mechanism by which RGS promotes GTP hydrolysis by Gα remains to be determined.

Just when we thought that the basic G protein–signaling system had been well defined, nature has provided us with a surprise. There are probably more surprises to come.

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Galaxy gallery

http://imagelib.ncsa.uiuc.edu/imagelib.html

One of the strengths of the World Wide Web is its capability for disseminating graphics, and few sciences are as rich in images as astronomy. The National Center for Supercomputing Applications at the University of Illinois now has 4000 astronomical images in its Digital Image Library. The Web page allows searching of the database by sky position, name of object, waveband, or bibliographic reference. The images are presented in a variety of formats, including some in the Virtual Reality Markup Language (VRML), which allows rotation and manipulation of data.

The body visible

http://www.npac.syr.edu/projects/vishuman/VisibleHuman.html

The Visible Human Project of the National Library of Medicine has been widely noted as a breakthrough in providing anatomical data over the Internet. Several data sets are available: magnetic resonance, computed tomography, and cryosection images of male and female human cadavers at 1-mm resolution. In the early stages of the project, viewing the raw data was not straightforward. Now a variety of image browsers are becoming available. One group at Syracuse University has a Web site that offers a way to quickly view selected data with a browser capable of running the Java programming language.

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