(*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.

References

1. H. R. Bourne *et al.*, *Nature* **349**, 117 (1991).
2. Y. Kaziro, *Biochem. Biophys. Acta* **505**, 95 (1978); M. Trahey and F. McCormick, *Science* **238**, 542 (1987).
3. D. E. Clapham and E. J. Neer, *Nature* **365**, 403 (1993).
4. M. Kutuzov and C. Pfister, *Eur. J. Biochem.* **220**, 963 (1994); W.-J. Tang, M. Stanzel, A. G. Gilman, *Biochemistry* **34**, 14563 (1995); R. Taussig *et al.*, *J. Biol. Chem.* **269**, 6039 (1994).
5. D. Berman, T. M. Wilke, A. G. Gilman, *Cell* **86**, 445 (1996).
6. N. Watson *et al.*, *Nature* **383**, 175 (1996); T. W. Hunt *et al.*, *ibid.*, p. 178.
7. W. Roush, *Science* **271**, 1056 (1996).
8. H. G. Dohlman *et al.*, *Mol. Cell. Biol.* **15**, 3635 (1995); M. R. Koelle and H. R. Horvitz, *Cell* **84**, 115 (1996).
9. K. M. Druey *et al.*, *Nature* **379**, 742 (1996).
10. J. Kurjan, *Annu. Rev. Genetics* **27**, 147 (1993).
11. T. Higashijima *et al.*, *J. Biol. Chem.* **262**, 762 (1987).
12. D. J. Carty *et al.*, *ibid.* **265**, 6268 (1987); M. E. Linder *et al.*, *ibid.*, p. 8283.
13. G. E. Breitwieser and G. Szabo, *J. Gen. Physiol.* **91**, 469 (1988).
14. J. Wang *et al.*, *J. Biol. Chem.*, in press.
15. D. M. Berman *et al.*, *ibid.* **271**, 27209 (1996).
16. R. Mittal, M. R. Ahmadian, R. S. Goody, A. Wittinghofer, *Science* **273**, 115 (1996).
17. K. Scheffzek *et al.*, *Nature* **384**, 591 (1996).
18. D. E. Coleman *et al.*, *Science* **265**, 1405 (1994); J. Sondek *et al.*, *Nature* **372**, 276 (1994).

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.

Academy reports

http://www.nap.edu/readingroom/

The U.S. National Academy of Sciences (NAS), which includes the National Research Council and the Institute of Medicine, issues books and reports on a wide range of topics, from agriculture to urban development. Approximately 1000 of the NAS titles are now available on the Web from the National Academy Press at no cost, and there are plans to add 4000 more titles to the collection over the next year.

Edited by David Voss

Readers are invited to suggest excellent scientific Web sites by e-mail to science_editors@aaas.org.