Minireview

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The Many Faces of G Protein Signaling*

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A large number of hormones, neurotransmitters, chemokines, local mediators, and sensory stimuli exert their effects on cells and organisms by binding to G protein-coupled receptors. More than a thousand such receptors are known, and more are being discovered all the time. Heterotrimeric G proteins transduce ligand binding to these receptors into intracellular responses, which underlie physiological responses of tissues and organisms. G proteins play important roles in determining the specificity and temporal characteristics of the cellular responses to signals. They are made up of α, β, and γ subunits, and although there are many gene products encoding each subunit (20 α, 6 β, and 12 γ gene products are known), four main classes of G proteins can be distinguished: G_s, which activates adenylyl cyclase; G_i, which inhibits adenylyl cyclase; G_q, which activates phospholipase C; and G_{12} and G_{13}, of unknown function.

G proteins are inactive in the GDP-bound, heterotrimeric state and are activated by receptor-catalyzed guanine nucleotide exchange resulting in GTP binding to the α subunit. GTP binding leads to dissociation of Gα·GTP from G$\beta\gamma$ subunits and activation of downstream effectors by both Gα·GTP and free G$\beta\gamma$ subunits. G protein deactivation is rate-limiting for turnoff of the cellular response and occurs when the Gα subunit hydrolyzes GTP to GDP. The recent resolution of crystal structures of heterotrimeric G proteins in inactive and active conformations provides a structural framework for understanding their role as conformational switches in signaling pathways. As more and more novel pathways that use G proteins emerge, recognition of the diversity of regulatory mechanisms of G protein signaling is also increasing. The recent progress in the structure, mechanisms, and regulation of G protein signaling pathways is the subject of this review. Because of space considerations, I will concentrate mainly on recent studies; readers are directed to a number of excellent reviews that cover earlier studies.

G Protein Structure

Gα subunits contain two domains, a domain involved in binding and hydrolyzing GTP (the G domain) that is structurally identical to the superfamily of GTPases including small G proteins and elongation factors (1) and a unique helical domain that buries the GTP in the core of the protein (2, 3) (Fig. 1). The β subunit of heterotrimeric G proteins has a 7-membered β-propeller structure based on its 7 WD-40 repeats (4–6). The γ subunit interacts with β through an N-terminal coiled coil and then all along the base of β, making extensive contacts (Fig. 1). The β and γ subunits form a functional unit that is not dissociable except by denaturation. G protein activation by receptors leads to GTP binding on the Gα subunit. The structural nature of the GTP-mediated switch on the Gα subunit is a change in conformation of three flexible regions designated Switches I, II, and III to a well ordered, GTP-bound activated conformation with lowered affinity for G$\beta\gamma$ (7) (Fig. 1). This leads to increased affinity of Gα·GTP for effectors, subunit dissociation, and generation of free G$\beta\gamma$ that can activate a number of effectors.

Mechanism of Activation of G Proteins by Receptors

G protein-coupled receptors have a common body plan with seven transmembrane helices; the intracellular loops that connect these helices form the G protein-binding domain (Fig. 2). Although no high resolution structure of a G protein-coupled receptor has yet been determined, recently a low resolution electron diffraction structure of rhodopsin, a model G protein-coupled receptor, shows the position and orientation of the seven transmembrane α-helices (8, 9). Both mutagenesis and biochemical experiments with a variety of G protein-coupled receptors suggest that receptor activation by ligand binding causes changes in the relative orientations of transmembrane helices 3 and 6. These changes then affect the conformation of G protein-interacting intracellular loops of the receptor and thus uncover previously masked G protein-binding sites (10, 11) (reviewed in Ref. 12). When an activated receptor interacts with a heterotrimeric G protein, it induces GDP release from the G protein. It is thought that the receptor contact sites on the G protein are distant from the GDP-binding pocket, so the receptor must work "at a distance" to change the conformation of the protein (13). Because GDP is buried within the protein between the two domains of Gα, this must necessarily involve changing some interdomain interactions. Upon GDP release and in the absence of GTP a stable complex between the activated receptor and the heterotrimer is formed. This so-called "empty pocket" conformation is of great interest, but its structure is as yet unknown.

What are the regions on G proteins that contact receptors, and how does G protein activation occur? The conformation of the GDP-bound heterotrimeric G proteins G_t and G_i (5, 6) shows the overall shape of the GDP-bound heterotrimer and the residues on the surface that can interact with other proteins and provides the structural context for understanding a variety of biochemical and mutagenesis studies of receptor-interacting regions on G proteins. The N-terminal region of the α subunit and the C-terminal region of the γ subunit are both sites of lipid modification (reviewed in Ref. 14). These lipidated regions are relatively close together in the heterotrimer, suggesting a site of membrane attachment. There is good evidence for receptor contact surfaces on all three subunits.

On the α subunit, the best characterized receptor contact region is at the C terminus (reviewed in Refs. 13 and 15). The last 7 amino acids of the α subunit are disordered in the heterotrimer crystal structures, and analysis of receptor-binding peptides selected from a combinatorial peptide library shows that these 7 residues are the most critical (16). Studies using chimeric Gα subunits confirm that in fact the last 5 residues contribute importantly to specificity of receptor G protein interaction. Elegant mutagenesis studies have shown that the C terminus of the third intracellular loop of receptors binds to this C-terminal region on Gα subunits. In the case of M_2 muscarinic receptor coupling to G_i, the exact residues of the receptor that are critical for recognizing the C terminus of $G\alpha_{i/o}$ have been elucidated (Val-385, Thr-386, Ile-389, and Leu-390) (17).

A larger region of the C-terminal region of Gα subunits, as well as the N-terminal helix, has been implicated in receptor contact. Alanine-scanning mutagenesis of $G\alpha_t$ (18) and analysis of residues conserved in subclasses of G protein α subunits (19) both identify a number of residues in the C-terminal 50 amino acids of $G\alpha_t$ that contact rhodopsin. Arg-310 located at the α4-β6 loop of $G\alpha_t$ is completely blocked from tryptic proteolysis in the presence of light-activated rhodopsin, suggesting that the α4-β6 loop region contributes to receptor contact (20). The α4-β6 loop has also been implicated in specific interaction of the $5HT_{1B}$ serotonin receptor with $G\alpha_{i1}$ as well as in receptor-catalyzed G_i activation (21).

It is clear that the $\beta\gamma$ subunits of heterotrimeric G proteins enhance receptor interaction with α subunits (reviewed in Ref. 15). Single Ala mutations in residues of the β subunit that contact the

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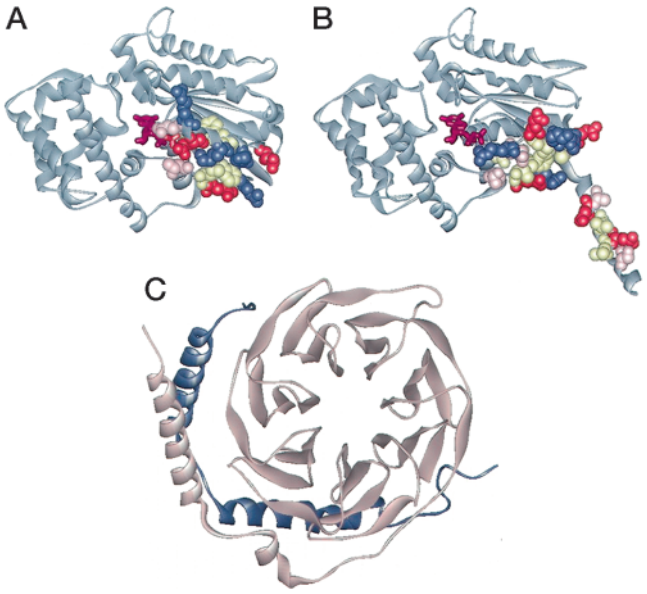

FIG. 1. **Upon GTP binding to Gα, the Gβ-binding site is rearranged and the subunits dissociate.** Ribbon diagrams of G protein subunits shown are the activated GTPγS-bound $G\alpha_t$ subunit (*A*) and the inactive GDP-bound chimeric $G\alpha_t/G\alpha_i$ subunit (*B*) (2, 5). Notice the N-terminal helix is visible only in the GDP-bound structure. The Gα subunit is *silver*, and the bound nucleotides are *magenta*. The Gβ contact sites on Gα are indicated by space-filled residues. Polar residues are *pink*, hydrophobic residues are *yellow*, basic residues are *blue*, and acidic residues are *red*. The relative orientations of the β contact sites in the switch interface of $G\alpha_t$·GTPγS are very different from the Gα·GDP and result in decreased βγ binding. *C*, the $G\beta_1\gamma_1$ dimer (4). The Gβ subunit, in *metallic pink*, forms a seven-bladed propeller structure that contains a water-filled pore. The Gγ subunit, in *blue*, is an α-helical structure that lies along the bottom of Gβ. The N termini of Gβ and Gγ form a parallel coiled coil. When the subunits dissociate, Gβγ is free to activate a number of effectors as discussed in the text.

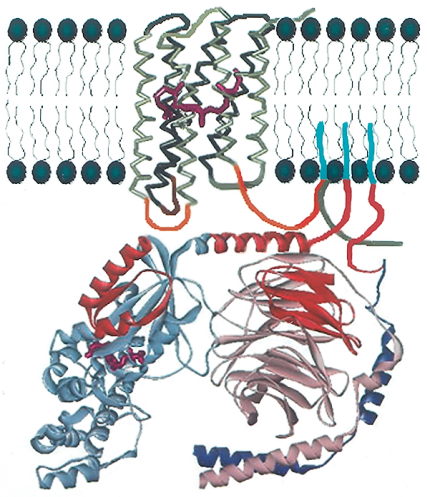

FIG. 2. **Heterotrimeric G protein interactions with rhodopsin and the membrane lipid bilayer.** The configuration of the α helices of rhodopsin are from Schertler and Baldwin *et al.* (8, 9). Transmembrane helices 1, 5, 6, and 7 at the front of the rhodopsin form are *light green* whereas transmembrane helices 2, 3, 4 at the back are *dark green*. The 11-*cis*-retinal prosthetic group that forms a Schiff base linkage with Lys-296 is *magenta*, and the membrane bilayer is *green*. The structures of the intracellular and extracellular loops are not known and are hand drawn to show helix connectivity. The intracellular loops that interact with heterotrimeric G protein are *orange* (intracellular loop 3 and putative fourth intracellular loop connecting transmembrane α helix 7 with the palmitoylation site) and *brown* (intracellular loop 2). The Gα subunit is *medium blue*, the Gβ subunit is *pink*, and the Gγ is *blue*. The bound guanine nucleotide (GDP) is *magenta*. The receptor-binding surface of the G protein is rotated 20° toward the viewer. The receptor contacts on the heterotrimeric G protein discussed in the text are *red* and include amino acids 1–23 and 299–350 of Gα, a contact site within amino acids 280–340 of Gβ, and amino acids 60–71 of Gγ. Rhodopsin is palmitylated at its C terminus, Gα is myristoylated and/or palmitoylated at its N terminus, and Gγ is farnesylated at its C terminus. The acyl groups on rhodopsin, Gα, and Gγ (*cyan*) are shown interacting with the membrane.

α subunit block receptor-mediated GTP/GDP exchange.[1] This suggests that the β subunit must hold the α subunit rigidly in place for GDP release to occur. Direct binding interactions between receptor and βγ subunit have been reported (24–26). A cross-linking study demonstrated that the C-terminal 60-amino acid region of Gβ can be cross-linked to an α_2-adrenergic receptor peptide corresponding to the intracellular third loop of the receptor (24). In addition, the C-terminal region of the γ subunit of G proteins has been shown to be involved in receptor coupling and specificity (25, 26).

Mechanisms of Effector Activation

Upon GTP binding to the α subunit, the α·GTP (a*) and βγ subunits dissociate (5, 7). In the GTP-bound, active conformation, a new surface is formed on Gα* subunits (27), and they interact with effectors with 20–100-fold higher affinity than in their GDP-bound state. The various Gα*s interact in a highly specific manner with the well studied, classical effector enzymes through this surface. $G\alpha^*_s$ activates (and $G\alpha^*_i$ inhibits) adenylyl cyclase, $G\alpha^*_t$ activates photoreceptor cGMP phosphodiesterase, and $G\alpha^*_q$ activates phospholipase C-β. However, this conserved switch surface on Gα subunits does not explain the exquisite specificity of G protein α subunit effector interaction. A chimeric $G\alpha_t/G\alpha_i$ approach identified two other regions that underlie the specific interaction of $G\alpha_t$ with phosphodiesterase γ (27). Similar regions are involved in effector interaction of $G\alpha_q$ with PLC[2] (80) and $G\alpha_s$ with adenylyl cyclase (AC) (reviewed in Ref. 15).

Novel α Targets

The major classes of Gαs, the G_s, G_i, and G_q families of α subunits, have well known cellular targets. More recently yeast two-hybrid screening has uncovered new targets. GAIP, a Gα-interacting protein and a member of the RGS family of GTPase-activating proteins (reviewed in Ref. 28), was first identified in this way; and recently two more putative α targets, nucleobindin (29) and a novel LGN repeat protein (30), were described by Insel and co-workers. So far, no physiological role of the latter two Gα targets has been determined.

Other effectors of G protein α subunits are being discovered. For example, $G\alpha_q$ directly stimulates the activity of Bruton's tyrosine kinase *in vitro* as well as *in vivo* in lymphoma cells (31). Two Gα subunits without known effectors are $G\alpha_{12}$ and $G\alpha_{13}$. They are reported to couple to thrombin, thromboxane, and angiotensin receptors (32). The cellular effects of mutant constitutively activated forms of these G proteins have been studied, and it is well established that they can regulate Na^+/H^+ exchange (33). They are involved in bradykinin activation of voltage-dependent Ca^{2+} channels via activation of Rac and Cdc42 (34). To understand the biological roles of $G\alpha_{13}$, knockout mice were produced (35). Homozygous $G\alpha_{13}$ (−/−) mice were never found, and although embryos were normal at embryonic day 8.5, they were resorbed before embryonic day 10.5. It appeared that lack of $G\alpha_{13}$ led to an impaired angiogenesis of endothelial cells and caused inability to develop an organized vascular system. In addition, $G\alpha_{13}$ (−/−) embryonic fibroblasts showed greatly impaired migratory responses to thrombin, suggesting that chemotaxis was impaired. Interestingly, although $G\alpha_{12}$ shares 67% amino acid identity to $G\alpha_{13}$, it cannot substitute for $G\alpha_{13}$.

βγ Targets

Once Gα·GTP has dissociated from Gβγ, free βγ is an activator of a dizzying array of proteins, and the list continues to increase (see Ref. 36 for review). Significantly, the conformation of free Gβγ is identical to Gβγ in the heterotrimer (4), suggesting that Gα inhibits Gβγ interactions with its effectors through the Gα-binding site on Gβ.[1] Evidence for this comes from the laboratory of Iyengar and co-workers (37), who found a peptide from ACII that bound to Gβγ and blocked its activation of various effectors, suggesting that part of the effector binding site is shared between ACII, G protein-activated inward rectifier K^+ channel (GIRK), and PLCβ. Cross-linking and docking experiments localized the binding site to a part of the Gα-binding region (38). Besides the Gα-binding region, other

[1] C. E. Ford, N. P. Skiba, H. Bae, Y. Daaka, E. Reuveny, L. R. Shekter, R. Rosal, G. Weng, C. S. Yang, R. Iyengar, R. J. Miller, L. Y. Jan, R. J. Lefkowitz, and H. E. Hamm, submitted for publication.

[2] The abbreviations used are: PLC, phospholipase C; AC, adenylyl cyclase; GIRK, G protein-activated inward rectifier K^+ channel; MAP, mitogen-activated protein; GTPγS, guanosine 5′-3-*O*-(thio)triphosphate.

regions of Gβγ subunits that have been implicated in effector interaction include the N-terminal coiled coil (39, 40) and blades 1 and 7 of the β-propeller of Gβ (41, 42).

Gβγ has well defined effects on some isoforms of the classical second messenger enzymes, PLCβ2 and -β3 (reviewed by Ref. 43) and AC (Gβγ stimulates $G\alpha_s$-activated ACII, -IV, and -VII whereas it inhibits ACI (44)). It also recruits the β-adrenergic receptor kinase to the membrane where the kinase phosphorylates activated β-adrenergic receptors. It binds to the phosphoprotein phosducin, which is thought to sequester βγ and thereby regulate its availability via a cAMP-dependent protein kinase-regulated mechanism. Phosducin-like proteins have also been shown to bind to Gβγ (45). Elucidation of the crystal structure of the phosducin-Gβγ complex showed that there is a shared surface on the top of Gβγ for interaction with Gα and phosducin but that a second site of interaction occurs between phosducin's C terminus and β-propeller blades 1 and 7 at the side of Gβγ (46). Interestingly, the phosphorylation site on phosducin, which regulates its affinity with Gβγ, is far from the protein-protein interface.

In addition, Gβγ serves as the direct activator of certain G protein-responsive K^+, Ca^{2+}, and perhaps also Na^+ channels (for reviews, see Refs. 36, 47, and 48). I_{KACh} is the inwardly rectifying K^+ channel responsible for slowing heart beat in response to the parasympathetic transmitter acetylcholine. It is a homo- or heteromultimer of GIRK (49) monomers found in the heart and brain. Gβγ subunits bind the N- and C-terminal intracellular domains of GIRKs and directly activate them (49–51). The Gβγ subunit similarly plays an important modulatory role in certain presynaptic Ca^{2+} channels (52, 53), especially α1A, α1B, and to a lesser extent α1E but not α1C, α1D, or α1S isoforms (47). It has been shown that Gβγ inhibits Ca^{2+} channel current by directly contacting two regions on Ca^{2+} channel α1 subunits: the intracellular I–II loop (55, 56) and the C terminus (57, 58).

Gβγ also directly activates more than one phosphatidylinositol 3-kinase isoform (59). There is a unique Gβγ-responsive phosphatidylinositol 3-kinase, P110γ, that does not have a p85 subunit or the N-terminal p85-binding region on the catalytic subunit (60, 61). Gβγ has also been reported to activate a number of kinases as well, for example, the Raf1 protein kinase (62) and Bruton and Tsk tyrosine kinases (63).

In yeast, Gβγ is the activator of a pheromone-stimulated MAP kinase pathway. It is known to bind to the N-terminal region of the scaffold protein Ste5 in yeast (64). Recently, Thorner and co-workers (65) showed that Ste5 contains a homodimerization domain, which is required for β binding. They demonstrated that Gβγ interaction leads to oligomerization of this domain on Ste5. Most interestingly, dimerization of this domain by making a glutathione *S*-transferase fusion protein of Ste5 leads to Gβγ-independent activation of the MAP kinase cascade. Recently, yeast Gβγ was also shown to activate Cdc24, the exchange factor for the Rho-type GTPase Cdc42 (66). Gβγ has also been reported to bind to other members of the Rho family of GTPases, Rho and Rac (67), as well as to the small G protein Arf (ADP-ribosylation factor), which is involved in coat formation and vesicular trafficking (68).

Given this very rich and expanding list of Gβγ effectors and effector activation mechanisms, a number of key questions are posed for future investigation. Under what physiological situations are the various effectors activated, and what are the constraints that keep all of these effectors from being activated at the same time? Does more than one G protein-coupled signaling pathway need to be activated for enough Gβγ to be generated to cause activation of these effectors? What is the specificity of Gβγ effector interactions and what is the mechanism by which effector activation occurs? And finally what is the turnoff mechanism?

Determinants for Gβγ Effector Interaction

There are multiple genes for Gβ and Gγ, and most Gβγ pairs can form functional Gβγs (reviewed in Ref. 36). One of the first questions that was posed was whether different Gβγs regulated different effectors. The answer from a large number of biochemical experiments was: not much. $G\beta_1\gamma_1$ is better than the others at interacting with rhodopsin and phosducin in photoreceptor cells and somewhat worse than all the other Gβγ pairs at interacting with other effectors. One series of studies that showed selectivity of Gβγ pairs at interacting with receptors and effectors was done using antisense oligonucleotides to suppress the translation of particular proteins, and these studies showed a very high degree of selectivity (see below). Other evidence of specificity, using different techniques, is slowly emerging. $G\beta_5$, a recently discovered Gβ subunit found in the central nervous system (69), differentially couples to two MAP kinase pathways (54).

Because Gα can inhibit all the actions of Gβγ, the Gα-binding residues are candidate effector activation determinants. We have tested this idea by singly mutating the 15 Gα-binding residues of Gβ to alanines, and in all effectors that have been examined, some of the mutants no longer activate the effector.[2] In each effector interaction, however, different residues clustered on the surface of Gβ are critical, suggesting a mechanism whereby a unique contact surface of Gβ can make specific interactions with a number of different effectors. Interestingly, in some cases, removing the side chain increases the potency of the mutant Gβγ to activate an effector.

Specificity of Signaling Defined by Molecular Interactions

The complexity of signal transduction events in cells that are receiving and processing multiple signals is the subject of intense research. Some of the key questions are: 1) how much specificity is encoded in the direct protein-protein interactions; 2) are there other levels of cellular organization that impart specificity; and 3) what are the mechanisms of cross-regulation resulting in the final integrated cellular response?

It is well known that multiple receptors can converge on a single G protein, and in many cases a single receptor can activate more than one G protein and thereby modulate multiple intracellular signals. In other cases, it seems that interaction of a single receptor with a given G protein is regulated by a high degree of selectivity imparted by specific heterotrimers. A number of excellent reviews describing the determinants of specific receptor-G protein interaction have recently appeared (12, 13, 70–72). Earlier *in vitro* studies of receptor-G protein interaction were often characterized by high promiscuity of receptor-G protein interaction, but a number of recent studies demonstrate that some receptors discriminate even between related G proteins within the same family.

In situ there can sometimes be high specificity. How is it achieved? The most exquisite specificity of receptor coupling to intracellular pathways by G proteins *in vivo* has been demonstrated using antisense oligonucleotides to suppress translation of specific G protein subunits. This technique allows suppression of distinct components involved in the signal transduction pathway and examination of any subsequent impaired cellular responses. Kleuss *et al.* (73) showed that inhibition of calcium channels by somatostatin receptors in the GH_3 cell is mediated by $G\alpha_{o2}\beta_1\gamma_3$, whereas inhibition by M_4 muscarinic receptors is mediated by $G\alpha_{o1}\beta_1\gamma_4$. The elimination of $G\alpha_o$ by antisense technique abolishes somatostatin, M_4 muscarinic, or D_2 dopamine receptor-mediated inhibition of calcium entry in rat pituitary GH_4C_1 cells (74). By contrast, depletion of $G\alpha_{i2}$ selectively impairs receptor-mediated inhibition of cAMP accumulation in the same system. Another antisense study indicates that the M_1 muscarinic receptor utilizes a specific G protein complex composed of $G\alpha_{q/11}\beta_{1/4}\gamma_4$ to activate phospholipase C (75). A recent study showed coupling of angiotensin II AT1A receptors to regulation of Ca^{2+} channels, calcium-induced calcium release channels, and Na^+/H^+ exchange is via $\alpha_{13}\beta_1\gamma_3$ (76). This level of specificity is not seen *in vitro* or in transfection studies using overexpressed proteins. This raises the question of how targeting proteins or other cellular mechanisms can achieve high specificity.

Limiting the Repertoire of Signaling Outcomes

A number of organizing and targeting proteins and cellular structures are candidates for a role in specifying protein interactions in G protein signaling cascades. Another potential regulator of G protein specificity is targeted inactivation of a G protein by a GTPase-activating protein (discussed in Ref. 28). In yeast, Ste5 is a scaffold protein that organizes the MAP kinase sequential enzyme cascade and contributes to specificity and fidelity of signaling (77). No mammalian homolog of Ste5 has been found. A particularly interesting possible scaffold for G protein-coupled signal transduction molecules is the growing family of PDZ domain-containing proteins, so named

for the three proteins that contain them, postsynaptic density protein 95 (P), *Drosophila* discs large tumor suppressor (D), and zona occludens protein (Z) (for review see Ref. 23). An unusual PDZ domain containing protein in *Drosophila* photoreceptors called InaD has 5 PDZ domains, each of which bind different signaling molecules of the G_q-regulated visual cascade including rhodopsin, PLCβ, protein kinase C, and the transient receptor potential protein (Trp), a homologue of the calcium-induced calcium release channel (23, 78, 79). Notably, G_q was missing from the complex. Another unusual PDZ domain-containing protein, Homer, contains a single PDZ domain, which binds to certain G protein-coupled metabotropic glutamate receptors in the brain (22). Other scaffold proteins are characterized by having multiple conserved domains such as phosphotyrosine-recognizing Src homology 2 (SH2) domains, SH3 domains, pleckstrin homology domains, Dbl homology domains, and domains with enzymatic activities, particularly activity controlling the GTP binding state of small G proteins such as guanine nucleotide exchange and GTPase-activating protein activity. Future studies may reveal more scaffolding or clustering mechanisms that may greatly increase the specificity of *in vivo* signal transduction by heterotrimeric G proteins.

Summary

Progress in areas of research that once might have seemed distant from the field of G protein signaling now shows that G proteins are involved in a broad range of cellular regulatory activities. The understanding of how the proteins interact (receptors, G proteins, and effectors, as well as other regulatory proteins) thus has enormous implications for physiology. The rapid progress in determining three-dimensional structures of G proteins, and more recently their regulators and effectors, has illuminated the search for mechanisms of activation and regulation and has allowed structure-based mutagenesis to test these ideas. The structural and mechanistic studies will in the future also hopefully provide opportunities to alter those interactions in pathological situations.

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REFERENCES

1. Kjeldgaard, M., Nyborg, J., and Clark, B. F. (1996) *FASEB J.* **10,** 1347–1368
2. Noel, J. P., Hamm, H. E., and Sigler, P. B. (1993) *Nature* **366,** 654–663
3. Coleman, D. E., Berghuis, A. M., Lee, E., Linder, M. E., Gilman, A. G., and Sprang, S. R. (1994) *Science* **269,** 1405–1412
4. Sondek, J., Bohm, A., Lambright, D., Hamm, H., and Sigler, P. (1996) *Nature* **379,** 369–374
5. Lambright, D., Sondek, J., Bohm, A., Skiba, N., Hamm, H., and Sigler, P. (1996) *Nature* **379,** 311–319
6. Wall, M., Coleman, D., Lee, E., Iniguez-Lluhi, J., Posner, B., Gilman, A., and Sprang, S. (1995) *Cell* **83,** 1047–1058
7. Lambright, D. G., Noel, J. P., Hamm, H. E., and Sigler, P. B. (1994) *Nature* **369,** 621–628
8. Unger, V., Hargrave, P., Baldwin, J., and Schertler, G. (1997) *Nature* **389,** 203–206
9. Baldwin, J., Schertler, G., and Unger, V. (1997) *J. Mol. Biol.* **272,** 144–164
10. Altenbach, C., Yang, K., Farrens, D., Farahbakhsh, Z., Khorana, H., and Hubbell, W. (1996) *Biochemistry* **35,** 12470–12478
11. Farrens, D., Altenbach, C., Yang, K., Hubbell, W., and Khorana, H. (1996) *Science* **274,** 768–770
12. Wess, J. (1997) *FASEB J.* **11,** 346–354
13. Bourne, H. (1997) *Curr. Opin. Cell Biol.* **9,** 134–142
14. Resh, M. (1996) *Cell Signal* **8,** 403–412
15. Sprang, S. R. (1997) *Annu. Rev. Biochem.* **66,** 639–678
16. Martin, E. L., Rens-Domiano, S., Schatz, P. J., and Hamm, H. E. (1996) *J. Biol. Chem.* **271,** 361–366
17. Kostenis, E., Conklin, B. R., and Wess, J. (1997) *Biochemistry* **36,** 1487–1495
18. Onrust, R., Herzmark, P., Chi, P., Garcia, P., Lichtarge, O., Kingsley, C., and Bourne, H. (1997) *Science* **275,** 381–384
19. Lichtarge, O., Bourne, H., and Cohen, F. (1996) *Proc. Natl. Acad. Sci. U. S. A.* **93,** 7507–7511
20. Mazzoni, M., and Hamm, H. (1996) *J. Biol. Chem.* **271,** 30034–30040
21. Bae, H., Anderson, K., Flood, L. A., Skiba, N. P., Hamm, H. E., and Graber, S. G. (1997) *J. Biol. Chem.* **272,** 32071–32077
22. Brakeman, P., Lanahan, A., O'Brien, R., Roche, K., Barnes, C., Huganir, R., and Worley, P. (1997) *Nature* **386,** 284–288
23. Tsunoda, S., Sierralta, J., Sun, Y., Bodner, R., Suzuki, E., Becker, A., Socolich, M., and Zuker, C. (1997) *Nature* **388,** 243–249
24. Taylor, J., Jacob-Mosier, G., Lawton, R., VanDort, M., and Neubig, R. (1996) *J. Biol. Chem.* **271,** 3336–3339
25. Kisselev, O., Pronin, A., Ermolaeva, M., and Gautam, N. (1995) *Proc. Natl. Acad. Sci. U. S. A.* **92,** 9102–9106
26. Yasuda, H., Lindorfer, M., Woodfork, K., Fletcher, J., and Garrison, J. (1996) *J. Biol. Chem.* **271,** 18588–18595
27. Skiba, N. P., Bae, H., and Hamm, H. E. (1996) *J. Biol. Chem.* **271,** 413–424
28. Berman, D., and Gilman, A. (1998) *J. Biol. Chem.* **273,** 1269–1272
29. Mochizuki, N., Hibi, M., Kanai, Y., and Insel, P. (1995) *FEBS Lett.* **373,** 155–158
30. Mochizuki, N., Cho, G., Wen, B., and Insel, P. (1996) *Gene (Amst.)* **181,** 39–43
31. Bence, K., Ma, W., Kozasa, T., and Huang, X. (1997) *Nature* **389,** 296–299
32. Barr, A., Brass, L., and Manning, D. (1997) *J. Biol. Chem.* **272,** 2223–2229
33. Hooley, R., Yu, C., Symons, M., and Barber, D. (1996) *J. Biol. Chem.* **271,** 6152–6158
34. Wilk-Blaszczak, M., Singer, W., Quill, T., Miller, B., Frost, J., Sternweis, P., and Belardetti, F. (1997) *J. Neurosci.* **17,** 4094–4100
35. Offermanns, S., Mancino, V., Revel, J., and Simon, M. (1997) *Science* **275,** 533–536
36. Clapham, D., and Neer, E. (1997) *Annu. Rev. Pharmacol. Toxicol.* **37,** 167–203
37. Chen, J., DeVivo, M., Dingus, J., Harry, A., Li, J., Sui, J., Carty, D., Blank, J., Exton, J., Stoffel, R., Inglese, J., Lefkowitz, R., Logothetis, D., Hildebrandt, J., and Iyengar, R. (1995) *Science* **268,** 1166–1169
38. Chen, Y., Weng, G., Li, J., Harry, A., Pieroni, J., Dingus, J., Hildebrandt, J., Guarnieri, F., Weinstein, H., and Iyengar, R. (1997) *Proc. Natl. Acad. Sci. U. S. A.* **94,** 2711–2714
39. Yan, K., and Gautam, N. (1997) *J. Biol. Chem.* **272,** 2056–2059
40. Pellegrino, S., Zhang, S., Garritsen, A., and Simonds, W. F. (1997) *J. Biol. Chem.* **272,** 25360–25366
41. Yamauchi, J., Kaziro, Y., and Itoh, H. (1997) *J. Biol. Chem.* **272,** 7602–7607
42. Blüml, K., Schnepp, W., Schröder, S., Beyermann, M., Macias, M., Oschkinat, H., and Lohse, M. (1997) *EMBO J.* **16,** 4908–4915
43. Morris, A., and Scarlata, S. (1997) *Biochem. Pharmacol.* **54,** 429–435
44. Sunahara, R., Dessauer, C., and Gilman, A. (1996) *Annu. Rev. Pharmacol. Toxicol.* **36,** 461–480
45. Thibault, C., Sganga, M., and Miles, M. (1997) *J. Biol. Chem.* **272,** 12253–12256
46. Gaudet, R., Bohm, A., and Sigler, P. (1996) *Cell* **87,** 577–588
47. Schneider, T., Igelmund, P., and Hescheler, J. (1997) *Trends Pharmacol. Sci.* **18,** 8–11
48. Jan, L., and Jan, Y. (1997) *Curr. Opin. Cell Biol.* **9,** 155–160
49. Krapivinsky, G., Gordon, E., Wickman, K., Velimirovic, B., Krapivinsky, L., and Clapham, D. (1995) *Nature* **374,** 135–141
50. Huang, C., Slesinger, P., Casey, P., Jan, Y., and Jan, L. (1995) *Neuron* **15,** 1133–1143
51. Kunkel, M., and Peralta, E. (1995) *Cell* **83,** 443–449
52. Ikeda, S. (1996) *Nature* **380,** 255–258
53. Herlitze, S., Hockerman, G., Scheuer, T., and Catterall, W. (1997) *Proc. Natl. Acad. Sci. U. S. A.* **94,** 1512–1516
54. Zhang, S., Coso, O., Lee, C., Gutkind, J., and Simonds, W. (1996) *J. Biol. Chem.* **271,** 33575–33579
55. Page, K., Stephens, G., Berrow, N., and Dolphin, A. (1997) *J. Neurosci.* **17,** 1330–1338
56. De Waard, M., Liu, H., Walker, D., Scott, V., Gurnett, C., and Campbell, K. (1997) *Nature* **385,** 446–450
57. Zhang, J., Ellinor, P., Aldrich, R., and Tsien, R. (1996) *Neuron* **17,** 991–1003
58. Qin, N., Platano, D., Olcese, R., Stefani, E., and Birnbaumer, L. (1997) *Proc. Natl. Acad. Sci. U. S. A.* **94,** 8866–8871
59. Tang, X., and Downes, C. (1997) *J. Biol. Chem.* **272,** 14193–14199
60. Stephens, L. R., Eguinoa, A., Erdjument-Bromage, H., Lui, M., Cooke, F., Coadwell, J., Amrcka, A. S., Thelen, M., Cadwallader, K., Tempst, P., and Hawkins, P. T. (1997) *Cell* **89,** 105–114
61. Stoyanov, B., Volinia, S., Hanck, T., Rubio, I., Loubtchenkov, M., Malek, D., Stoyanova, S., Vanhaesebroeck, B., Dhand, R., Nurnberg, B., *et al.* (1995) *Science* **269,** 690–693
62. Pumiglia, K., LeVine, H., Haske, T., Habib, T., Jove, R., and Decker, S. (1995) *J. Biol. Chem.* **270,** 14251–14254
63. Langhans-Rajasekaran, S. A., Wan, Y., and Huang, X. Y. (1995) *Proc. Natl. Acad. Sci. U. S. A.* **92,** 8601–8605
64. Whiteway, M., Wu, C., Leeuw, T., Clark, K., Fourest-Lieuvin, A., Thomas, D., and Leberer, E. (1995) *Science* **269,** 1572–1575
65. Inouye, C., Dhillon, N., and Thorner, J. (1997) *Science* **278,** 103–106
66. Simon, M., De Virgilio, C., Souza, B., Pringle, J., Abo, A., and Reed, S. (1995) *Nature* **376,** 702–705
67. Harhammer, R., Gohla, A., and Schultz, G. (1996) *FEBS Lett.* **399,** 211–214
68. Franco, M., Paris, S., and Chabre, M. (1995) *FEBS Lett.* **362,** 286–290
69. Watson, A., Aragay, A., Slepak, V., and Simon, M. (1996) *J. Biol. Chem.* **271,** 28154–28160
70. Raymond, J. (1995) *Am. J. Physiol.* **269,** F141–F158
71. Gudermann, T., Schoneberg, T., and Schultz, G. (1997) *Annu. Rev. Neurosci.* **20,** 399–427
72. Hildebrandt, J. (1997) *Biochem. Pharmacol.* **54,** 325–339
73. Kleuss, C., Scherubl, H., Hescheler, J., Schultz, G., and Wittig, B. (1993) *Science* **259,** 832–834
74. Liu, Y., Jakobs, K., Rasenick, M., and Albert, P. (1994) *J. Biol. Chem.* **269,** 13880–13886
75. Dippel, E., Kalkbrenner, F., Wittig, B., and Schultz, G. (1996) *Proc. Natl. Acad. Sci. U. S. A.* **93,** 1391–1396
76. Macrez-Lepretre, N., Kalkbrenner, F., Morel, J., Schultz, G., and Mironneau, J. (1997) *J. Biol. Chem.* **272,** 10095–10102
77. Errede, B., Cade, R., Yashar, B., Kamada, Y., Levin, D., Irie, K., and Matsumoto, K. (1995) *Mol. Reprod. Dev.* **42,** 477–485
78. Shieh, B., and Zhu, M. (1996) *Neuron* **16,** 991–998
79. Huber, A., Sander, P., Gobert, A., Bahner, M., Hermann, R., and Paulsen, R. (1996) *EMBO J.* **15,** 7036–7045
80. Venkatakrishnan, G., and Exton, J. H. (1996) *J. Biol. Chem.* **271,** 5066–5072

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