



Roles of G-protein-coupled receptor signaling in cancer biology and gene transcription

Bryan D Spiegelberg and Heidi E Hamm

G-protein-coupled receptors (GPCRs) are ubiquitous mediators of signal transduction across mammalian cell membranes. Among other roles, GPCRs are known to regulate cellular motility, growth and differentiation, and gene transcription, three factors central to the biology of cancer. Because GPCRs are tractable drug targets, mechanisms by which receptors and their associated proteins impact cellular transformation and metastasis might lead to novel cancer therapies. Recent work has elucidated mechanisms explaining correlations between cancer progression and the expression of GPCRs, such as a protease-activated receptor (PAR1), and G-proteins, such as $G_{\alpha_{12/13}}$. Of special interest, the discovery of novel nuclear roles for heterotrimeric G-proteins expands the direct impact of G-protein signaling on processes fundamental to the pathology of cancer.

Addresses

Department of Pharmacology, Vanderbilt University, Nashville, TN 37232, USA

Corresponding author: Hamm, Heidi E (heidi.hamm@vanderbilt.edu)

Current Opinion in Genetics & Development 2007, 17:40–44

This review comes from a themed issue on Genetic and cellular mechanisms of oncogenesis Edited by Sara A Courtneidge and Benjamin G Neel

Available online 22nd December 2006

0959-437X/\$ – see front matter © 2006 Elsevier Ltd. All rights reserved.

DOI 10.1016/j.gde.2006.12.002

Introduction

G-protein-coupled receptors: signal transduction and involvement in human disease

G-protein-coupled receptors (GPCRs) are crucial intermediates in the transmission of extracellular information into intracellular responses. Activated GPCRs typically control cellular physiology by releasing the signaling potential of inactive heterotrimeric G-proteins [1]. These inactive heterotrimers consist of a guanine diphosphate-bound G_{α} subunit, which maintains a high affinity for a $G\beta\gamma$ functional monomer. Upon activation by a cognate ligand or signal, a GPCR catalyzes the exchange of GTP for GDP on the G_{α} subunit, resulting in a decreased affinity of G_{α} for $G\beta\gamma$. This alteration causes dissociation of the subunits [1] or rearrangement of the heterotrimer [2], allowing G_{α} and $G\beta\gamma$ to interact with and to modulate the activities of a diverse and growing repertoire of effector molecules [1,3].

Aberrant functioning of GPCR pathways leads to several important human diseases, including endocrine and vision disorders [4]. Accordingly, GPCR-mediated signaling holds a position of prominence in clinical pharmacology [5,6]. In cancer therapy, however, GPCR-targeted drugs are used only peripherally. For instance, GPCR-targeting analgesics, such as the opioid receptor agonist oxycodone (Oxycontin), are used in pain management. Here, we review recent advances that have revealed fundamental links between GPCR-mediated pathways and cancer biology and gene transcription. Thus, future chemotherapy development might be poised to take advantage of the vast knowledge of GPCRs and their ligands.

This review highlights recent data linking G-protein-coupled receptors and their intracellular messaging partners, heterotrimeric G-proteins, to the biology of cancer. We emphasize the burgeoning field of nuclear heterotrimeric G-proteins and discuss potential implications for a direct regulation of gene transcription by heterotrimeric G-proteins.

GPCRs in cancer biology

Although GPCRs and heterotrimeric G-proteins have not garnered the notoriety of p53, Ras, PTEN (Phosphatase and tensin homologue deleted on chromosome ten) or other noteworthy oncogenes and tumor suppressors, a large body of evidence links aberrant G-protein signaling to cancer development and progression. For example, a recent examination of publicly available gene expression data identified a variety of types of GPCRs that are overexpressed in diverse types of cancer tissues [7]. Causal relationships have been established by the discovery of the transforming abilities of certain GPCRs [8] and heterotrimeric G-proteins [9–11].

Some GPCRs have clear functional links to cancer biology. For example, the role of chemokine receptors in regulating cellular movement dovetails well with their prominent position in cancer cell metastasis [12]. Similarly, the normal function of growth factor receptors, such as the *Endothelial differentiation* gene (*EDG*) phospholipid receptors, parallels the involvement of the Lysophosphatidic acid (LPA) EDG receptor in aberrant growth and differentiation in prostate cancer [13].

The links between cancer and some GPCRs, by contrast, are somewhat more cryptic. For example, Protease-activated receptor 1 (PAR1), the receptor for the coagulation factor thrombin, most notably functions within the

cardiovascular system [14]. Interestingly, PAR1 was identified as a strong transforming factor in an expression screen in NIH3T3 fibroblasts [15]. It also has been shown to be involved in mediating the invasiveness of several types of cancer, including melanoma [16], breast cancer [17] and prostate cancer [18,19]. As such, the molecular mechanisms underlying the relationship between PAR1 and cancer biology have been studied intensively [20]. Signaling through PAR1-activated $G\alpha_{i/o}$ has been found to exert a dominant-negative effect on tumor progression and invasiveness [21]. The positive effects of other heterotrimeric G-proteins activated by PAR1, including $G\beta\gamma$, $G\alpha_q$, and $G\alpha_{12/13}$, can be unmasked *in vitro* through the inhibition of $G\alpha_{i/o}$ [21,22]

The role of endogenous thrombin in the mediation of metastasis through PAR1 is unclear. Thus, the discovery of a novel PAR1-activating factor has promoted additional interest in the cancer biology of this receptor. Matrix metalloproteinase 1 (MMP1), an enzyme that has been linked to cancer progression through its role in degrading the extracellular matrix [23], was found to unveil the tethered ligand of PAR1 by a mechanism similar to that of thrombin [24*,25]. Moreover, MMP1 activity, probably supplied by surrounding fibroblasts and not the tumor cells themselves, is sufficient to activate the pro-invasive activity of the receptor [24*]. This finding suggests a model by which normal cells provide tumor-promoting signals and has led to the proposal of novel therapeutic regimes [24*].

$G\alpha_{12/13}$ proteins in metastasis

The oncogenic potential of GPCRs is the result of a complex interplay among downstream heterotrimeric G-proteins. The transforming potential of various classes of $G\alpha$ subunits have been discovered through overexpression of constitutively active mutants. Interestingly, $G\alpha_{12/13}$ proteins seem to be the most potent oncogenes, because they comprise the only family for which overexpression of wild type proteins has been found to be transforming [9,10]. Recent work has linked the enigmatic $G\alpha_{12/13}$ family to proteins involved in cell migration and thus to important processes mediating cancer cell invasion. Although immediate downstream effectors of $G\alpha_{12}$ and $G\alpha_{13}$ are continually emerging [26], intriguing biological interactions with cell-survival signals such as mitogen-activated protein kinase (MAPK) cascades and, especially, monomeric G-proteins (e.g. Ras, Rac and Rho [9]) have placed these proteins in a position of prominence with regard to aberrant cell growth. For example, overexpression of either wild type or constitutively active mutants of $G\alpha_{12}$ and $G\alpha_{13}$ has revealed potent transforming ability in several *in vitro* model systems [10].

In addition to its apparent involvement in the anomalous growth patterns leading to tumor development, recent research has demonstrated a striking impact of $G\alpha_{12/13}$

signaling on the cellular invasiveness underlying tumors' metastatic potential. In a pair of reports, for example, Kelly *et al.* [27,28*] showed that $G\alpha_{12/13}$ signaling had no effect on cell growth in both breast cancer and prostate cancer models. However, overexpression of a constitutively active mutant of $G\alpha_{12}$ augmented cellular movement in *in vitro* models [27,28*]. This enhancement was mirrored in *in vivo* models in which inhibition of $G\alpha_{12}$ or downstream signaling significantly inhibited the invasiveness of engineered tumors [27,28*].

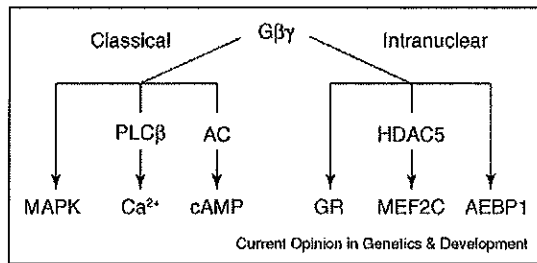
Although signaling through Rho clearly plays a major role in this aspect of $G_{12/13}$, at least some of the effect has been found to be Rho-independent [28*]. Thus, a contributor to the impact of $G_{12/13}$ on cancer biology might be a novel direct interaction with cadherins, a family of integral membrane proteins involved in mediating cell-cell adhesion. $G\alpha_{12/13}$ has been reported to interact with the cytoplasmic domain of cadherins, altering their interaction with cytoplasmic proteins such as β -catenins [29,30]. Interestingly, binding by $G\alpha_{12}$ also regulates extracellular functions of E-cadherin [31]. In particular, Meigs *et al.* discovered that this inside-out regulation negatively impacts the ability of E-cadherin to mediate cell-cell adhesion [32], suggesting that the role of $G_{12/13}$ in cancer progression is more direct than previously appreciated.

G-proteins in the nucleus

Given that aberrant gene expression is a major factor in cancer, interactions between G-proteins and transcription are of fundamental importance. Indirect effects of G-protein signaling on gene transcription have been well established. For instance, both $G\alpha$ - and $G\beta\gamma$ -dependent mechanisms are major modulators of MAPK signaling cascades [33], leading to phosphorylation and activation of transcription factors and other partner proteins [34]. Recent discoveries of several novel roles for G-proteins suggest that direct effects augment the classical effects of G-proteins on gene expression (Figure 1). In this regard, GPCR signaling is similar to other cell surface receptor paradigms that also participate in direct communication with the nucleus. For example, a proteolytic fragment of the receptor tyrosine kinase ErbB4 translocates to the nucleus and interacts with transcriptional machinery [35,36]. Similarly, stimulation of the Notch receptor leads to the translocation of the intracellular domain to the nucleus, where it serves as a transcriptional activator and plays emerging roles in oncogenesis and cancer biology.

Direct intranuclear effects of the canonically plasma membrane-localized heterotrimeric G-proteins should not be surprising, for several reasons. First, the subcellular distribution of G-proteins and their associated factors appears to be quite dynamic within the living cell. In several systems, for example, internalization of heterotrimeric G-proteins has been found to mirror that of the receptor upon phosphorylation and desensitization

Figure 1



A central role for $G\beta\gamma$ in regulation of gene expression. Signaling through $G\beta\gamma$ influences gene expression through several classical pathways involving the enzymes phospholipase C β (PLC β) and adenylyl cyclase (AC), and thus the secondary messengers Ca^{2+} and cAMP, as well as mitogen-activated kinase (MAPK) cascades. Recently, several direct, intranuclear connections between $G\beta\gamma$ and gene transcription have been described, involving the transcription factors MEF2C and GR as well as the co-regulators HDAC5 and AEBP1.

[37,38]. Second, there is a precedent for the localization of populations of heterotrimeric G-proteins within the nucleus as well as other intracellular organelles [39]. Recent data have suggested a dynamic trafficking of one G-protein isoform, $G\beta_5$, between the plasma membrane and the nucleus [40]. $G\beta_5$ had been observed within the nucleus of several cell types [41], but the discovery that the protein R7BP associates with the $G\beta_5$ binding partner RGS7 [42*,43] enabled the identification of a mechanism for nuclear import. R7BP is reversibly palmitoylated, a modification that defines its subcellular distribution and enables a shuttling between the nucleus and the plasma membrane [40].

The idea that G-protein signaling may directly affect gene transcription came with a series of discoveries that G-proteins can interact with and affect the activity of proteins directly involved with transcription. First, Park *et al.* [44] discovered through a yeast two-hybrid screen that the transcriptional co-repressor Adipocyte enhancer-binding protein (AEBP) binds directly to $G\gamma_5$. This interaction results *in vivo* in an inhibition of the transcriptional co-repression activity of AEBP [44]. Moreover, levels of $G\gamma_5$ protein correlate inversely with AEBP activity following the application of adipogenic stimulation, suggesting a functional link between particular isoforms of $G\beta\gamma$ and AEBP *in situ* [44].

Second, Kino *et al.* [45**] showed convincingly that canonically plasma membrane-bound $G\beta\gamma$ exists at least in part in the nucleus, and that nuclear import is enhanced through a novel interaction with a nuclear hormone receptor, the glucocorticoid receptor (GR). Through a yeast two-hybrid screen, the authors discovered that GR interacts directly with both a $G\beta$ isoform and a structural homolog, receptor for activated C-kinase 1 (RACK1). $G\beta\gamma$ activation, through overexpression or stimulation

of a GPCR, results in a significant inhibition of the transcriptional activity of GR, mirrored by an accumulation of $G\beta\gamma$ at GR elements [45**]. These results further the findings of Park *et al.* [44] by suggesting that the modulation of transcription by heterotrimeric G-proteins, $G\beta\gamma$ in particular, is not confined to a particular transcription factor or biological system.

Although not involving heterotrimeric G-proteins directly, a third report has further solidified the role of GPCR signaling in the regulation of transcription. β -arrestin1 (β arr1), which is typically considered as a cytosolic protein mediating both the desensitization of receptor signals and the coupling of activated receptors to certain downstream pathways [46], has been shown to cycle between the nucleus and the cytoplasm [47,48**]. Kang *et al.* [48**] demonstrated that nuclear entry can be influenced strongly by the activation of specific GPCRs, in particular the $G_{i/o}$ -coupled δ -opioid receptor. Moreover, this research demonstrated a potential mechanism by which intranuclear β arr1 influences transcription: the regulation of histone acetylation at particular promoter sites. Intranuclear β arr1 interacts with the histone acetylase p300 and recruits it to specific regions within the chromosome, resulting in enhanced transcription of target genes, including p27 and c-fos [48**]. Nuclear import of β arr1 and transcriptional regulation occur rapidly in response to δ -opioid receptor agonist challenge, further suggesting that GPCRs can communicate directly with the nucleus and transcription factors [48**].

Finally, through a yeast two-hybrid screen, we identified another novel G-protein-interacting molecule that suggests a role for G-proteins in the nucleus [49]. We found that $G\beta\gamma$ interacts directly and in a signal-responsive manner with two class II histone deacetylases, HDAC4 and HDAC5 [49]. Through this direct interaction, $G\beta\gamma$ activation causes an augmentation of transcription mediated by the HDAC5-responsive transcription factor MEF2C [49]. Thus, we concluded that $G\beta\gamma$ is an inhibitor of the transcriptional co-repression activity of certain HDACs.

In addressing the mechanism by which $G\beta\gamma$ impacts the biological activity of HDAC5, we discovered that $G\beta\gamma$ directly interacts with both the N and the C termini of the enzyme (BD Spiegelberg and HE Hamm, unpublished). The known transcription factor binding site resides in the large N-terminal domain of the enzyme [50]; therefore, we predicted that $G\beta\gamma$ binding to this region would interfere competitively with its ability to bind to MEF2C. In investigating this point, however, we found that instead of inhibiting HDAC5-MEF2C complex formation, $G\beta\gamma$ actually binds directly to MEF2C as well, thereby suggesting that the $G\beta\gamma$ -HDAC5 interaction exists as part of a much larger complex and that the inhibition of the biological activity of HDAC5 takes

the form of an allosteric diminution of catalysis (BD Spiegelberg and HE Hamm, unpublished).

Conclusions

GPCRs represent a rich source of validated drug targets in several therapeutic regimens [5,6]. As more data linking these systems to the development and progression of cancer emerge, GPCRs and their associated factors will become increasingly attractive as targets for novel strategies targeting tumors and metastasis. Particularly exciting in this regard is the rapidly growing field linking G-proteins directly to normal and aberrant gene transcription.

Acknowledgements

We thank Dr Songhai Chen for critical reading of the manuscript. Unpublished work discussed in this review was supported by the National Institutes of Health (EY10291).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Hamm HE: **The many faces of G protein signaling.** *J Biol Chem* 1998, **273**:669-672.
 2. Bunemann M, Frank M, Lohse MJ: **G_i protein activation in intact cells involves subunit rearrangement rather than dissociation.** *Proc Natl Acad Sci USA* 2003, **100**:16077-16082.
 3. Cabrera-Vera TM, Vanhauwe J, Thomas TO, Medkova M, Preininger A, Mazzoni MR, Hamm HE: **Insights into G protein structure, function, and regulation.** *Endocr Rev* 2003, **24**:765-781.
 4. Spiegel AM, Weinstein LS: **Inherited diseases involving G proteins and G protein-coupled receptors.** *Annu Rev Med* 2004, **55**:27-39.
 5. Pierce KL, Premont RT, Lefkowitz RJ: **Seven-transmembrane receptors.** *Nat Rev Mol Cell Biol* 2002, **3**:639-650.
 6. Hopkins AL, Groom CR: **The druggable genome.** *Nat Rev Drug Discov* 2002, **1**:727-730.
 7. Li S, Huang S, Peng S-B: **Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression.** *Int J Oncol* 2005, **27**:1329-1339.
 8. Whitehead IP, Zohn IE, Der CJ: **Rho GTPase-dependent transformation by G protein-coupled receptors.** *Oncogene* 2001, **20**:1547-1555.
 9. Dhanasekaran N, Dermott JM: **Signaling by the G12 class of G proteins.** *Cell Signal* 1996, **8**:235-245.
 10. Radhika V, Dhanasekaran N: **Transforming G proteins.** *Oncogene* 2001, **20**:1607-1614.
 11. Landis C, Masters S, Spada A, Pace A, Bourne HR, Vallar L: **GTPase inhibiting mutations activate the α chain of Gs and stimulate adenylyl cyclase in human pituitary tumours.** *Nature* 1989, **340**:692-696.
 12. Kakinuma T, Hwang S: **Chemokines, chemokine receptors, and cancer metastasis.** *J Leukoc Biol* 2006, **79**:639-651.
 13. Daaka Y: **Mitogenic action of LPA in prostate.** *Biochim Biophys Acta* 2002, **1582**:265-269.
 14. Coughlin SR: **Protease-activated receptors in hemostasis, thrombosis and vascular biology.** *J Thromb Haemost* 2005, **3**:1800-1814.
 15. Whitehead I, Kirk H, Kay R: **Expression cloning of oncogenes by retroviral transfer of cDNA libraries.** *Mol Cell Biol* 1995, **15**:704-710.
 16. Tellez C, Bar-Eli M: **Role and regulation of the thrombin receptor (PAR-1) in human melanoma.** *Oncogene* 2003, **22**:3130-3137.
 17. Even-Ram S, Uziely B, Cohen P, Grisaru-Granovsky S, Maoz M, Ginzburn Y, Reich R, Vlodavsky I, Bar-Shavit R: **Thrombin receptor overexpression in malignant and physiological invasion processes.** *Nat Med* 1998, **4**:909-914.
 18. Yuan T, Lin M: **Protease-activated receptor 1: a role in prostate cancer metastasis.** *Clin Prostate Cancer* 2004, **3**:189-191.
 19. Cooper CR, Chay CH, Gendernalik JD, Lee HL, Bhatia J, Taichman RS, McCauley LK, Keller ET, Pienta KK: **Stromal factors involved in prostate carcinoma metastasis to bone.** *Cancer* 2003, **97**(3 Suppl):739-747.
 20. Ruf W, Mueller B: **Thrombin generation and the pathogenesis of cancer.** *Semin Thromb Hemost* 2006:061-068.
 21. Faivre S, Regnaud K, Bruyneel E, Nguyen Q-D, Mareel M, Emami S, Gespach C: **Suppression of cellular invasion by activated G-protein subunits G α o, G α i1, G α i2 and G α i3 and sequestration of G β γ .** *Mol Pharmacol* 2001, **60**:363-372.
 22. Nguyen Q-D, Faivre S, Bruyneel E, Rivat C, Seto M, Endo T, Mareel M, Emami S, Gespach C: **RhoA- and RhoD-dependent regulatory switch of G α subunit signaling by PAR-1 receptors in cellular invasion.** *FASEB J* 2002, **16**:565-576.
 23. Sato H, Takino T, Miyamori H: **Roles of membrane-type matrix metalloproteinase-1 in tumor invasion and metastasis.** *Cancer Sci* 2005, **96**:212-217.
 24. Boire A, Covic L, Agarwal A, Jacques S, Sherif S, Kuliopulos A: **PAR1 is a matrix metalloproteinase-1 receptor that promotes invasion and tumorigenesis of breast cancer cells.** *Cell* 2005, **120**:303-313.
- The authors linked two important aspects of cancer biology with their discovery that MMP1 is a potent activator of the GPCR PAR1. Targeting of PAR1 was suggested as a more specific way to inhibit the effects of MMP1 in cancer therapy.
25. Goerge T, Barg A, Schnaeker E-M, Poppelmann B, Shpacovitch V, Rattenholl A, Maaser C, Luger TA, Steinhoff M, Schneider SW: **Tumor-derived matrix metalloproteinase-1 targets endothelial proteinase-activated receptor 1 promoting endothelial cell activation.** *Cancer Res* 2006, **66**:7766-7774.
 26. Neves SR, Ram PT, Iyengar R: **G protein pathways.** *Science* 2002, **296**:1636-1639.
 27. Kelly P, Stemmler LN, Madden JF, Fields TA, Daaka Y, Casey PJ: **A role for the G12 family of heterotrimeric G-proteins in prostate cancer invasion.** *J Biol Chem* 2006, **281**:26483-26490.
 28. Kelly P, Moeller BJ, Juneja J, Booden MA, Der CJ, Daaka Y, Dewhirst MW, Fields TA, Casey PJ: **The G12 family of heterotrimeric G proteins promotes breast cancer invasion and metastasis.** *Proc Natl Acad Sci USA* 2006, **103**:8173-8178.
- G α ₁₂ protein was found to be increased in models of early stages of breast cancer. G α ₁₂ signaling did not influence growth or transformation, however. Rather, it enhanced cell motility and therefore metastasis of cancer cells.
29. Kaplan DD, Meigs TE, Casey PJ: **Distinct regions of the cadherin cytoplasmic domain are essential for functional interaction with G α ₁₂ and β -catenin.** *J Biol Chem* 2001, **276**:44037-44043.
 30. Meigs TE, Fields TA, McKee DD, Casey PJ: **Interaction of G α ₁₂ and G α ₁₃ with the cytoplasmic domain of cadherin provides a mechanism for β -catenin release.** *Proc Natl Acad Sci USA* 2001, **98**:519-524.
 31. Gumbiner BM: **Regulation of cadherin-mediated adhesion in morphogenesis.** *Nat Rev Mol Cell Biol* 2005, **6**:622-634.
 32. Meigs TE, Fedor-Chalken M, Kaplan DD, Brackenbury R, Casey PJ: **G α ₁₂ and G α ₁₃ negatively regulate the adhesive functions of cadherin.** *J Biol Chem* 2002, **277**:24594-24600.
 33. Pierce KL, Luttrell LM, Lefkowitz RJ: **New mechanisms in heptahelical receptor signaling to mitogen activated protein kinase cascades.** *Oncogene* 2001, **20**:1532-1539.

34. Yang S-H, Sharrocks AD, Whitmarsh AJ: **Transcriptional regulation by the MAP kinase signaling cascades.** *Gene* 2003, **320**:3-21.
35. Ni CY, Murphy MP, Golde TE: **g-Secretase cleavage and nuclear localization of ErbB-4 receptor tyrosine kinase.** *Science* 2001, **294**:2179-2181.
36. Linggi B, Carpenter G: **ErbB receptors: new insights on mechanisms and biology.** *Trends Cell Biol* 2006, **16**:649-656.
37. Akgoz M, Kalyanaraman V, Gautam N: **Receptor-mediated reversible translocation of the G Protein $\beta\gamma$ complex from the plasma membrane to the golgi complex.** *J Biol Chem* 2004, **279**:51541-51544.
38. Azpiazu I, Akgoz M, Kalyanaraman V, Gautam N: **G protein $\beta\gamma$ 11 complex translocation is induced by Gi, Gq and Gs coupling receptors and is regulated by the α subunit type.** *Cell Signal* 2006, **18**:1190-1200.
39. Willard FS, Crouch MF: **Nuclear and cytoskeletal translocation and localization of heterotrimeric G-proteins.** *Immunol Cell Biol* 2000, **78**:387-394.
40. Hepler JR: **R7BP: a surprising new link between G proteins, RGS proteins, and nuclear signaling in the brain.** *Sci STKE* 2005, **2005**:pe38.
41. Zhang J-H, Barr VA, Mo Y, Rojkova AM, Liu S, Simonds WF: **Nuclear localization of G protein $\beta 5$ and regulator of G protein signaling 7 in neurons and brain.** *J Biol Chem* 2001, **276**:10284-10289.
42. Drenan RM, Doupnik CA, Boyle MP, Muglia LJ, Huettner JE, Linder ME, Blumer KJ: **Palmitoylation regulates plasma membrane-nuclear shuttling of R7BP, a novel membrane anchor for the RGS7 family.** *J Cell Biol* 2005, **169**:623-633.
- Regulation of the palmitoylation state of the RGS7 binding protein was found to dictate the nuclear-cytoplasmic distribution of the $G\beta_5$ -RGS7 complex, indicating a potential mechanism for nuclear delivery of heterotrimeric G-proteins.
43. Martemyanov KA, Yoo PJ, Skiba NP, Arshavsky VY: **R7BP, a novel neuronal protein interacting with RGS proteins of the R7 family.** *J Biol Chem* 2005, **280**:5133-5136.
44. Park J-G, Mulse A, He G-P, Kim S-W, Ro H-S: **Transcriptional regulation by the $\gamma 5$ subunit of a heterotrimeric G protein during adipogenesis.** *EMBO J* 1999, **18**:4004-4012.
45. Kino T, Tulpakov A, Ichijo T, Chheng L, Kozasa T, Chrousos GP: **G protein β interacts with the glucocorticoid receptor and suppresses its transcriptional activity in the nucleus.** *J Cell Biol* 2005, **169**:885-896.
- A physical and functional interaction between $G\beta\gamma$ and a transcription factor revealed a new role for nuclear heterotrimeric G-proteins. Importantly, GPCR stimulation activated the GR- $G\beta\gamma$ interaction, suggesting that $G\beta\gamma$ mediates a direct communication between receptors at the plasma membrane and the nucleus.
46. Reiter E, Lefkowitz RJ: **GRKs and β -arrestins: roles in receptor silencing, trafficking and signaling.** *Trends Endocrinol Metab* 2006, **17**:159-165.
47. Beaulieu J-M, Caron MG: **β -Arrestin goes nuclear.** *Cell* 2005, **123**:755-757.
48. Kang J, Shi Y, Xiang B, Qu B, Su W, Zhu M, Zhang M, Bao G, Wang F, Zhang X: **A nuclear function of β -Arrestin1 in GPCR signaling: regulation of histone acetylation and gene transcription.** *Cell* 2005, **123**:833-847.
- β -Arrestin1, classically involved in desensitization of GPCR signaling, was found to translocate to the nucleus upon receptor activation. Novel interactions with a histone acetylase revealed a central role in regulation of gene transcription.
49. Spiegelberg BD, Hamm HE: **$G\beta\gamma$ binds histone deacetylase 5 (HDAC5) and inhibits its transcriptional co-repression activity.** *J Biol Chem* 2005, **280**:41769-41776.
50. Bertos NR, Wang AH, Yang X-J: **Class II histone deacetylases: structure, function, and regulation.** *Biochem Cell Biol* 2001, **79**:243-252.