

Minireview:

**Thematic Minireview Series: Cell Biology
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Henrik G Dohlman
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Thematic Minireview Series: Cell Biology of G protein Signaling

Henrik G. Dohlman

From the Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill,
Chapel Hill, North Carolina 27599-7260

ABSTRACT

This thematic series is on the topic of cell signaling from a cell biology perspective, with a particular focus on G proteins. G protein-coupled receptors (GPCRs, also known as 7-transmembrane receptors) are typically found at the cell surface. Upon agonist binding, these receptors will activate a GTP-binding G protein at the cytoplasmic face of the plasma membrane. Additionally, there is growing evidence that G proteins can also be activated by non-receptor binding-partners, and they can signal from non-plasma membrane compartments. The production of second messengers at multiple, spatially distinct locations represents a type of signal encoding that has been largely understudied. The first mini-review in the series describes biosensors that are being used to monitor G protein signaling events in live cells. The second describes the implementation of antibody-based biosensors to dissect endosome signaling by G proteins and their receptors. The third describes the function of a non-receptor, cytoplasmic activator of G protein signaling, called GIV (Girdin). Collectively the advances described in these articles provide a deeper understanding and emerging opportunities for new pharmacology.

The classical view of G protein signaling begins with an extracellular stimulus. A broad array of molecules, including photons, single atoms (e.g. protons and calcium), odors, biogenic amines (e.g. epinephrine and dopamine), phospholipids, glycoprotein hormones and even enzymes (e.g. thrombin) are detected by G protein-coupled receptors. Once activated, these receptors engage a G protein heterotrimer, or in some cases beta-arrestins. G proteins exchange GDP for GTP, and the dissociated alpha and beta/gamma subunits initiate biochemical

processes inside the cell, most classically the production of second messengers such as cAMP.

The Journal of Biological Chemistry has a rich tradition of publishing papers on GPCRs, G proteins, and their regulators. For example, RGS proteins (regulators of G protein signaling) accelerate GTP hydrolysis, and so they act in opposition to receptors to limit signal transduction. Much of this literature has focused on mechanistic aspects of G protein function or modification, with less attention paid to the movement and distribution of component proteins within the cell. Given that most hormones and neurotransmitters cannot cross the plasma membrane, it seemed natural to assume that receptors and G proteins must also reside at the plasma membrane in order to function. Proteins located elsewhere were thought to be in transit, either to or from their primary site of action. However it has long been known that at least one family of GPCRs, the light receptors epitomized by rhodopsin, are not at the cell surface but are densely packed within oval-shaped “discs” inside the rod and cone cells of the retina. Thus at least some G protein-coupled receptors act primarily from inside the cell. This view has been expanded by recent findings that are the focus of this minireview series. The contributed articles are from three leading laboratories that are each pioneers in their respective fields.

The first minireview in the series is by Terri Clister, Sohun Mehta and Jin Zhang (1). This article begins with a nice summary of G protein signaling, including new insights to how G protein function is regulated in space and time. Much of the work they describe has benefitted from the development of sensitive and versatile biosensors. In general, these consist of proteins or protein fragments that emit an optical (usually fluorescent) signal based on changes in biochemical activity. When such biosensors are paired with high-resolution microscopy they can reveal highly detailed spatial and temporal

information about molecular changes inside the cell, such as occur when a cell moves towards a gradient stimulus. These tools provide information that is often lost in the aggregate data from biochemical analysis, and they have begun to reveal dramatic cell-to-cell variation in the response to stimuli. The authors describe current biosensor design, and go on to provide specific examples of biosensors being used to monitor receptor and G protein (or arrestin) activation, translocation to and from the plasma membrane, and the localized production of chemical second messengers. Finally they discuss new efforts to manipulate cellular processes, for example using light-activated GPCRs to target G protein activation within a narrow segment of a cell. The ability to locally measure and activate G protein signaling will surely advance our understanding of cell signaling gradients, both outside and inside the cell.

The second paper in the series is written by Nikoleta G. Tsvetanova, Roshanak Irannejad, and Mark von Zastrow (2). These authors focus on GPCR and G protein trafficking to the endosomal compartment. They outline a mechanism whereby the internalization of activated receptors leads to a 'second wave' of G protein signaling from endosomes. Older genetic studies in yeast as well as pharmacological studies in mammalian cell culture had indicated a role for endomembrane pools of activated G proteins. Direct evidence for GPCR and G protein activation at endosomes comes from recent work by the von Zastrow group. They adapted single domain antibody fragments, originally developed to stabilize activated GPCRs and G proteins for the purpose of x-ray crystallography, as genetically-encoded biosensors. When used in conjunction with live cell fluorescence imaging, these investigators noticed two waves of activation, one at the plasma

membrane and a second, more sustained, wave at endosomes. These waves of protein activation correlate with waves of second messenger production, and these two readouts exhibit similar sensitivities to endocytic inhibitors and agonist withdrawal. These findings challenge long held views that equate receptor endocytosis with desensitization. Given that many physiological processes depend on the timing and location of intracellular signals, understanding these processes is of paramount importance in physiology and pharmacology.

The third article is by Mikel Garcia-Marcos, Pradipta Ghosh, and Marilyn G. Farquhar (3). These authors focus on new functions of GIV (also known as Girdin), one of an expanding group of proteins that activate G proteins but which are not necessarily localized to the plasma membrane and do not resemble typical GPCRs. GIV is found both at the plasma membrane and internal membranes and is activated by multiple surface receptors, including receptor tyrosine kinases. While the mechanistic details are still being elucidated, there are compelling genetic data to indicate a major role for GIV in cell migration and in the progression of cancer metastasis, as well as nephrosis and liver fibrosis.

What do these findings mean for biological chemists? Given the long history of GPCRs, as well as of receptor tyrosine kinases, as drug targets, there is a strong rationale for investigating non-receptor activators as potential drug targets as well. Indeed, past drug discovery efforts were based on long-held views that may no longer be entirely valid. With emerging evidence for activators of G proteins that are not receptors, and that are not even at the plasma membrane, we can perhaps look forward to a 'second wave' of G protein-related discoveries within the pages of the *Journal of Biological Chemistry*.

REFERENCES

1. Clister, T., Mehta, S., and Zhang, J., Single-cell Analysis of G-protein Signal Transduction. 10.1074/jbc.R114.616391
2. Tsvetanova, N.G., Irannejad, R., and von Zastrow, M., GPCR signaling via heterotrimeric G proteins from endosomes. 10.1074/jbc.R114.617951
3. Garcia-Marcos, M., Ghosh, P., and Farquhar, M.G., GIV/Girdin transmits signals from multiple receptors by triggering trimeric G protein activation. 10.1074/jbc.R114.613414