Direct regulation of G protein signal strength as a new drug target?

Heterotrimeric GTP-binding proteins (G proteins) remain an important but elusive target in drug discovery. G proteins adapt cell behavior in response to signals generated by cell surface receptors, G protein coupled receptors (GPCRs). Clinical interest in G proteins stems from their vital role in the healthy regulation of various physiological processes. Additionally, aberrant signaling by G proteins is linked to human disease.

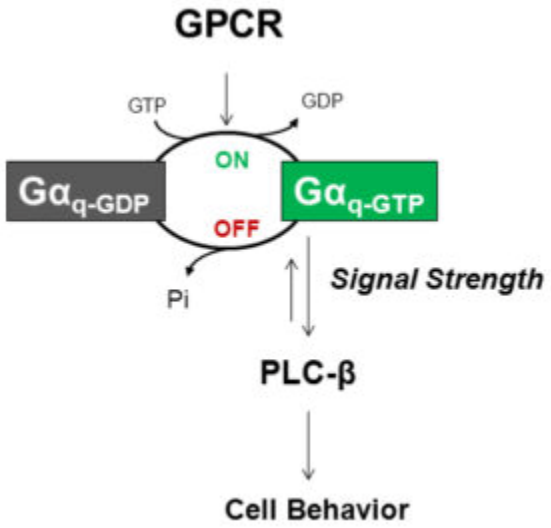

Fig. 1. GPCRs turn “ON” Gαq signaling by catalyzing the exchange of bound -GDP for GTP. Signaling is turned “OFF” by an intrinsic GTPase activity which hydrolyzes the GTP back to GDP. Gαq-GTP signals with its effector, PLC-β. PLC-β also regulates signal output by accelerating the GTPase activity, specific to Gαq. The molecular basis for regulation of signal strength has been unclear, a feasible drug target has not been identified.

Therapeutic manipulation of G protein signaling has largely been focused on the GPCR, i.e. identification of a selective agonist (activator) or antagonist (inhibitor) of the receptor. Although direct targeting of a G protein holds the promise of greater effectiveness (efficacy) and less toxicity, interest in this approach has been limited. A feasible drug target has remained elusive. The molecular basis for signal strength by G proteins has been unclear.

However, as surveyed in the review by Litosch (2016), research is now beginning to unravel the details of this important step in signaling, at least for one member of the G protein family. The G_q subfamily of G proteins has been under intense scrutiny due to its association with the cognitive decline of Alzheimer’s disease, hypertension, cardiac hypertrophy, cancer and other diseases.

G_q signaling is initiated upon the binding of an agonist (hormone, neurotransmitter) to a GPCR (Fig. 1). The agonist-bound GPCR turns "ON" G_q signaling by catalyzing the replacement of bound guanosine diphosphate (GDP) with guanosine triphosphate (GTP) on the $G\alpha_q$ subunit. $G\alpha_{q\text{-}GTP}$ engages binding partners, aka effectors, to orchestrate cell behavior. Signaling is turned "OFF" by an intrinsic $G\alpha_q$ GTPase activity which hydrolyzes bound GTP to GDP.

While $G\alpha_q$ has many effectors, PLC-β is the major effector, regulating cellular response through the elevation of cytosolic Ca^{2+} levels. Importantly, PLC-β also regulates $G\alpha_q$, functioning as a GTPase activating protein (GAP), i.e. PLC-β accelerates $G\alpha_q$ GTPase activity. Co-ordination of these dual PLC-β functions, effector and GAP, has been proposed to play an important role in the regulation of signal strength.

A feasible drug target to take advantage of this regulatory process has not been forthcoming. However, research has sought to overcome this impasse. Structural analysis has identified binding sites that mediate a functional interaction between activated $G\alpha_q$ and its effectors, both shared and unique to different effectors. Blocking these binding sites could be an approach to suppress signal output.

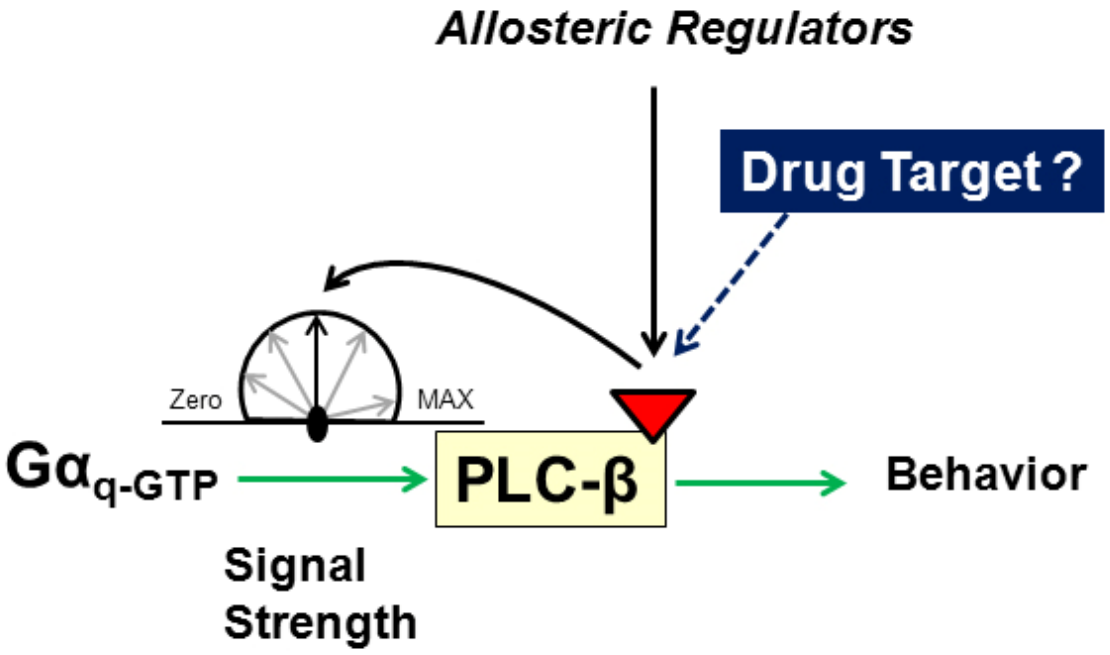

Fig. 2. Allosteric regulators can manipulate signal strength at the level of PLC-β (see text). These regulators represent potential drug targets to control Gαq signal strength in the maintenance of health and treatment of disease.

Perhaps, more exciting, is the evidence which increasingly supports the idea that signal strength may be regulated by endogenous molecules or allosteric regulators. These allosteric regulators appear to work at the level of PLC-β lipase/GAP.

The PLC-β molecule has a coiled-coil domain, long known to be essential and specific to maximum $G\alpha_q$ regulation, both lipase and GAP. Regulators have been identified, including some novel molecules, which regulate maximum signal output, dependent on the PLC-β coiled-coil domain. These data suggest new drug targets to directly manipulate $G\alpha_q$ signal strength are on the horizon.

Irene Litosch
Department of Molecular and Cellular Pharmacology,
University of Miami Miller School Of Medicine (University Of Miami)
Miami, Florida 33136, USA

Publication

Decoding Gαq signaling.
Litosch I
Life Sci. 2016 May