# Resolving Phospholipase C Regulation

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Phospholipase C β (PLCβ) increases intracellular calcium in response to diverse hormones, regulating numerous processes including cell proliferation and survival. Dysregulation of its expression or activity contributes to heart disease, cancer, and other pathophysiological conditions. PLCβ interacts with the cytoplasmic leaflet of the plasma membrane, where it hydrolyzes phosphatidylinositol-4,5-bisphosphate ($PIP_2$) to produce second messengers that increase intracellular $Ca^{2+}$ and activate protein kinase C. PLCß exists in an autoinhibited state that is relieved via direct interactions with the heterotrimeric G protein subunits, $G\alpha_q$ and Gβγ, and the membrane, coupling lipase activity to stimulation of G protein-coupled receptors. Prior structural and functional studies have revealed how $G\alpha_q$ binds to and activates PLCβ, but where Gβγ binds to PLCβ to regulate its activity is controversial. Using cryo-electron microscopy, we have determined a series of reconstructions of the Gβγ–PLCβ complex, allowing identification of the Gβγ binding surface, as well as an unexpected role for Gβγ as a potential scaffold for PLCβ, wherein a pre-activated complex is maintained at the membrane.