Conformational Regulation of Phospholipase C Enzymes

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Phospholipase Cβ and ε enzymes are essential for normal cardiovascular function, as they hydrolyze phosphatidylinositol lipids at cellular membranes to generate second messengers that increase intracellular calcium and activate downstream kinases. These proteins also have low basal activity, but are stimulated following the activation of G protein coupled receptors and receptor tyrosine kinases through direct interactions with G proteins. Using PLCβ as a model system, we have begun characterizing how the membrane itself regulates PLCβ adsorption and activity with atomic force microscopy and functional studies. We are also using structural biology and biochemical assays to begin characterizing the structure and regulation of PLCε, alone and upon binding the Rap1A GTPase. Rap1A is the best characterized activator PLCε in the heart, and chronic activation results in cardiovascular disease. We have shown that PLCε is conformationally heterogeneous in solution, with its PH and RA domains contributing to maximum basal activity and stability. The C-terminal RA domain has been previously identified as the Rap1A binding site. We propose the conformational flexibility of this RA domain is essential for Rap1A-dependent activation, and that the mechanism has an allosteric component. Taken together, these studies provide the insights into the molecular basis underlying basal and activated phosphatidylinositol hydrolysis by PLCε.