2023 Hitchhiker Abstract:

Title: Structural Insights into Phospholipase Cε

Authors:
Elisabeth E. Garland-Kuntz[a], Kadidia Samassekou[a], Vaani Ohri[b], Isaac J. Fisher[a], Kaushik Muralidharan[b], Abigail Gick[c], Morgan Laskowski[a], Emmanuel Oluwarotimi[a], Taiwo Ademoye[a], Jiaqi Xiao[b], Satchal K. Erramilli[d], Anthony A. Kossiakoff[d], & Angeline M. Lyon[a,b]

Affiliations:
[a]Department of Chemistry, [b]Department of Biological Sciences, and [c]College of Pharmacy, Purdue University, West Lafayette, IN, 47907, USA
[d]Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, IL, USA

Abstract
Cardiovascular disease remains the leading cause of death worldwide, and phospholipase Cε (PLCε) is one of the players implicated in these disease pathways. Once activated downstream of G protein-coupled receptors and receptor tyrosine kinases, PLCε hydrolyzes membrane phosphoinositide lipids to produce inositol phosphates and diacylglycerol. These secondary messengers allow release of intracellular calcium stores and activation of pro-inflammatory pathways via protein kinase C. In PLCε, the highly conserved lipase core domains are flanked by N- and C-terminal regulatory domains, including an uncharacterized N-terminal region and CDC25 domain, and two C-terminal Ras association (RA) domains. We and others have shown that many of these regulatory domains are flexibly connected to the core, but it is unclear how these regions modulate basal activity and/or regulation by small GTPases. Using new tools, including AlphaFold2 and cryo-electron microscopy with domain-specific antigen binding fragments (Fabs), we are interrogating the structure and membrane binding surface of larger PLCε variants and the full-length enzyme. In parallel, we are using cell-based activity assays to probe inter-domain interactions and to begin characterizing the membrane binding surface of the lipase. These data will further our understanding of PLCε and aid in developing small molecule allosteric modulators as potential therapies in cardiovascular disease.