Fab-ulous Studies of Phospholipase Cε

Phospholipase Cε enzymes are required for normal cardiovascular function, and their dysregulation can lead to cardiac hypertrophy and heart failure. PLCε cleaves phosphatidylinositol phosphates into inositol phosphates and diacylglycerol, increasing intracellular Ca^{2+} and activating protein kinase C. PLCε activity is increased by direct binding of the Rap1A GTPase, following stimulation of β adrenergic receptors. This pathway is required for maximum cardiac contractility, but sustained activation causes cardiac hypertrophy. Rap1A binds to the C-terminal Ras Association (RA) domain of PLCε, and we previously showed that activation requires long-range conformational changes in the lipase. However, the residues in PLCε involved in the intramolecular rearrangements are not known. As a first step, I used cryo-electron microscopy single particle analysis (cryo-EM SPA) to determine the 4 Å reconstruction of PLCε PH-C in complex with an antigen binding fragment (Fab). This is the largest fragment of PLCε biochemically characterized to date and is robustly activated by Rap1A. The structure defines the basal state of the enzyme and reveals a potential membrane binding surface on the PH domain. These studies set the stage for investigating the structure Rap1A–PLCε PH-C complex and its mechanism of activation. Ultimately, this work supports long-term efforts to develop small molecule modulators of the lipase and its activated complex for treating cardiac hypertrophy.

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