Structure of the p110/p85 heterodimeric phosphoinositide 3-kinase (PI3K)

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Phosphoinositide 3-kinases and their lipid product, phosphatidylinositol-(3,4,5)-trisphosphate (PtdIns(3,4,5)P₃), are key to a variety of cellular processes. Mutations in the catalytic subunit of PI3Kα are among the most common in human cancers. Broad-spectrum PI3K inhibitors result in increased apoptosis, decreased proliferation and reduced metastasis in tumor models. Understanding the structural mechanisms of PI3K regulation may facilitate development of isozyme-specific therapeutics.

The class I PI3Ks are heterodimers, consisting of a p110 catalytic subunit and a p85 regulatory subunit. Regulatory subunits have multiple roles in the function of PI3K: they downregulate basal PI3K activity, stabilize the catalytic subunit, and enable activation of the PI3K downstream of receptor tyrosine kinases. Common to all regulatory subunits are two SH2 domains (nSH2 and cSH2) that flank an intervening coiled-coil domain (iSH2), and common to all catalytic subunits are the N-terminal adaptor-binding (ABD), the Ras-binding (RBD), C2, helical and catalytic domains. Interaction between the iSH2 domain and the ABD maintains the catalytic and regulatory subunits as a tight, constitutive heterodimer. The nSH2 and cSH2 domains bind phosphorylated tyrosines in YXXM motifs found in activated receptors and adaptor proteins, and this interaction activates the heterodimeric PI3K. The nSH2-iSH2 unit constitutes the minimal fragment of the regulatory subunit that can regulate PI3K activity: it both inhibits the basal activity and facilitates activation by binding phosphotyrosine peptides.

We have determined the structure of the core of the catalytic subunit of PI3Kγ [1], which has a domain arrangement identical to p110α. This structure has provided a working model for extensive efforts directed toward developing isotype-specific, PI3K inhibitors [2]. Our objective is to understand the three-dimensional architecture of the intact p110α/p85 heterodimer, because it is loss of the inhibitory interaction of the p85 regulatory subunit that appears to be the basis for one common type of oncogenic mutation in the p110α catalytic subunit.

Based on our X-ray crystal structure of the complex of the ABD with the iSH2 domain and our model of the catalytic core of PI3Kα, we proposed a model of how the regulatory subunit would interact with the full-length p110α catalytic subunit [3]. We collected SAXS data for a several PI3K complexes, including the intact p110/p85 heterodimer. Our initial analysis of the results for a p110/iSH2 complex indicate that our proposed model closely fits the SAXS data (Figure 1). Our ongoing work is aimed at using all of the SAXS data sets and the X-ray crystallography data for subcomplexes to establish a model for the full-length p110/p85 complex.

![Figure 1: The left panel illustrates the calculated scattering curve for our p110/iSH2 model (black line) superimposed on the observed scattering curve for the complex (red line). The model is illustrated in the right panel.](image-url)
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References