LEAD DISCOVERY

Designing selective PI3K inhibitors

Phosphoinositide 3-kinases (PI3Ks) are involved in many vital cell functions and their dysregulation has been implicated in the pathology of various disorders. Pharmacological and genetic studies have highlighted the importance of developing isotype-specific inhibitors of these enzymes. Inhibitors of PI3Ks have entered clinical trials, including several isotype-specific agents; however, the structural determinants mediating selectivity and potency of these agents are poorly understood — partly because there is a lack of crystal structures for all of the isotypes. Now, Williams and colleagues report the first crystal structure of the δ isoform of the class IA PI3K (PI3Kδ), alone and in complex with a broad range of inhibitors, revealing strategies to aid the design of improved therapies.

The family of PI3Ks comprises three classes of structurally related lipid kinases that catalyse the ATP-dependent phosphorylation of phosphoinositide substrates. Class 1A members are heterodimers consisting of a p110 catalytic subunit and a p85 regulatory subunit. Impaired signalling of PI3Kδ results in severe defects in innate and adaptive immune responses, and its dysregulated activity has been associated with cancer, rheumatoid arthritis and asthma. Therefore, specific targeting of this isoform has significant therapeutic potential, and so the authors set out to understand the mechanisms underlying isoform selectivity.

To do this, they developed a novel expression and purification strategy, and co-crystallized the p110δ catalytic core in complexes with a broad range of chemically diverse isoform- or pan-selective class IA PI3K inhibitors, some of which are currently in clinical trials. The structures and molecular dynamics simulations helped identify key molecular features contributing to PI3Kδ inhibitor selectivity.

Analysis of the inhibitor-bound structures revealed four regions within the ATP-binding pocket that are important for selective inhibitor binding: an adenine pocket, a specificity pocket, an affinity pocket and the hydrophobic region II located at the mouth of the active site. They also identified key residues and interactions within these regions that mediate inhibitor specificity and potency.

Furthermore, the most selective inhibitors, such as IC87114 and PIK-39, were found to adopt a propeller shape when bound to the enzyme. This stabilized a conformational change that opened the hydrophobic specificity pocket in the active site. The development of propeller-shaped inhibitors that also interacted with the affinity pocket increased potency. By contrast, this conformational change was not observed following binding of flat compounds, such as DL06, DL07, ZSTK474, AS5 and GDC-0941, which are multiple- or pan-selective inhibitors.

Structural analysis of a third type of inhibitor, AS15, revealed additional features that promote PI3Kδ inhibitor selectivity. Although AS15 does not adopt a propeller-shaped conformation and therefore does not open the specificity pocket, it still exhibits selectivity. To do this, it establishes unique p110δ-specific interactions by making extensive use of a hydrophobic patch between specific residues adjacent to the adenine-binding pocket.

These structural insights may assist in the design of future therapeutic PI3Kδ inhibitors. The novel expression and purification strategy developed by these authors is also being extended to all class IA PI3K isoforms.

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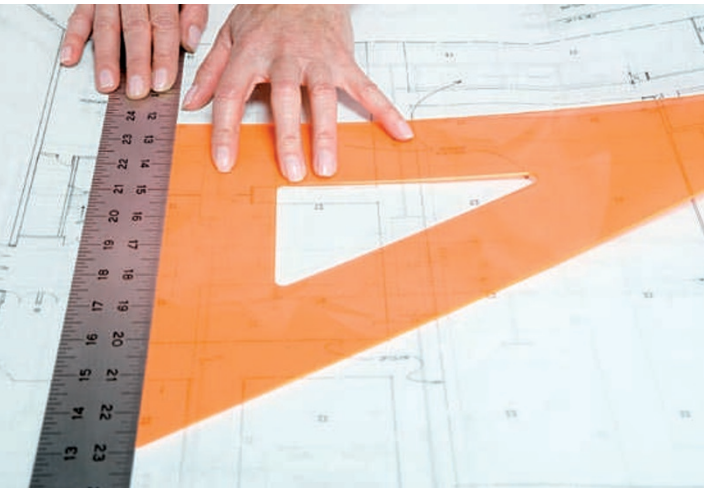

IMAGE SOURCE

ORIGINAL RESEARCH PAPER Berndt, A. *et al.* The p110δ structure: mechanisms for selectivity and potency of new PI(3)K inhibitors. *Nature Chem. Biol.* 10 Jan 2010 (doi:10.1038/nchembio.293)

FURTHER READING Liu, P. *et al.* Targeting the phosphoinositide 3-kinase pathway in cancer. *Nature Rev. Drug Discov.* **8**, 627–644 (2009) | Rommel, C. *et al.* PI3Kδ and PI3Kγ: partners in crime in inflammation in rheumatoid arthritis and beyond? *Nature Rev. Immunol.* **7**, 191–201 (2007) | Rückle, T. *et al.* PI3Kγ inhibition: towards an 'aspirin of the 21st century'? *Nature Rev. Drug Discov.* **5**, 903–918 (2006)