surface in association with the extensive membrane network around the parasite, where it might interfere with choline uptake and thereby inhibit phosphatidylcholine biosynthesis.

Much further testing is needed before the drug could be used for human studies. Also, G25 needs to be injected, although preliminary experiments have identified analogues with the oral bioavailability necessary for the ultimate goal of a pill form that could be used prophylactically, like chloroquine.

Peter Kirkpatrick

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KINASE INHIBITORS

Pocket remedy

The link between p38 mitogen-activated protein (MAP) kinase (p38) and many diseases has led to an avalanche of research dedicated to finding inhibitors of this signal-transduction molecule. In *Nature Structural Biology*, Regan and colleagues report their contribution to this quest, which is particularly intriguing because they have found a highly potent and selective inhibitor that, instead of targeting the ATP-binding site, forms a new allosteric binding pocket.

p38 is a Ser/Thr kinase that has a crucial role in regulating the production of proinflammatory cytokines, and elevated levels of these cytokines are associated with several autoimmune diseases, such as rheumatoid arthritis, diabetes and inflammatory bowel disease. The researchers carried out a high-throughput screen for kinase inhibitors, and identified a diaryl urea that they called compound 1.

To define the binding mode of this new compound, Regan and colleagues determined the crystal structure of the human-p38–compound-1 complex. When an inhibitor binds to all known protein Ser/Thr kinases, the highly conserved Asp-Phe-Gly (DFG) motif within the active site, which is required for binding, forms a so-called 'DFG-in' conformation, in which the Phe residue is buried in a hydrophobic pocket in the groove between the two lobes of the kinase.

But the complex between the kinase and compound 1 requires a large conformational change of the DFG motif, and forms a 'DFG-out' conformation, in which the all-important Phe residue moves (by 10 Å) to a new position. Here, one face of the Phe side chain helps to shield the inhibitor, whereas the other face is exposed to solvent. This movement exposes a large hydrophobic pocket in the kinase that is spatially distinct from the normal ATP-binding pocket, and the hydrophobic chain in compound 1 is inserted deep within this pocket.

Structure–activity relationship (SAR) studies confirmed the importance of the hydrophobic interactions in this new pocket, and solution studies found that the compound showed slow binding kinetics, which are characteristic of the observed requirement for conformational change.

So, it seems that compound 1 uses a new mechanism to inhibit p38. Unlike most protein-kinase inhibitors, which use the ATP-binding pocket to compete directly with ATP binding, the compound indirectly competes with ATP binding by stabilizing a conformation of the kinase that is incompatible with ATP binding.

The authors made three main structural changes to compound 1 to develop BIRB 796, a picomolar inhibitor of human p38 that has a 12,000-fold increase in binding affinity compared with compound 1. The selectivity of BIRB 796 for p38 inhibition seems to be high, as it did not inhibit 12 other kinases, including members from both the MAP and other kinase families. This is important, because designing selective inhibitors against the ATP-binding site is a huge challenge due to the high homology between kinase active sites. Phase I trials indicate that BIRB 796 is well tolerated and shows good pharmacokinetic and pharmacodynamic properties. It has also shown anti-inflammatory effects in a trial with human endotoxemia patients, and is now being evaluated in Phase II clinical trials for various diseases, including rheumatoid arthritis.

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