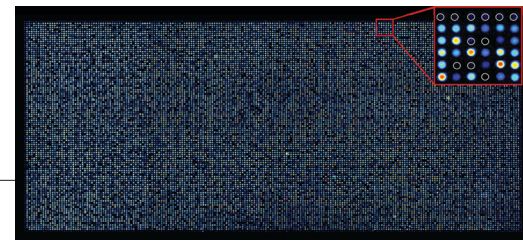
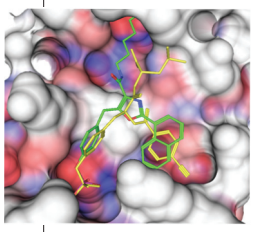
ACS chemical biology

In this ISSUE

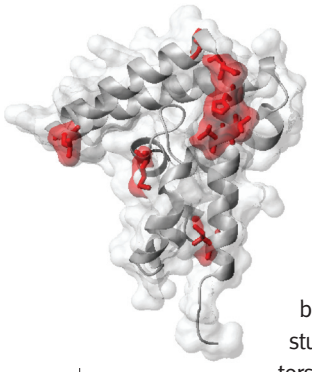


New Drugs Target Cancer STATs

Signal transducer and activator of transcription (STAT) proteins are transcription factors that regulate many cellular processes in mammalian cells. Abnormal activation of STAT3, a member of the STAT family, enhances cell cycle progression while hindering apoptosis, or programmed cell death. Because of the significant role of STAT3 in the development of tumors and blood malignancies linked to many types of cancers, it is an attractive target for cancer drugs. However, most current inhibitors target tyrosine phosphorylation of STAT3, and the efficacy of these inhibitors is limited because non-phosphorylated STAT3 can also be involved in cancer development. In this issue, two studies reveal the effectiveness of targeting other interactions of STAT3 for developing novel cancer drugs.



As a result of activating stimuli, STAT3 is phosphorylated on a crucial tyrosine residue by upstream kinases. Subsequently, phosphorylated STAT3 monomers dimerize through interactions between SH2 (phosphotyrosine binding) domains. In one study, Siddiquee *et al.* (p 787) present a small molecule that inhibits STAT3 dimerization. SH2 domain interactions in the dimer interface were interrogated with a small molecule. An oxazole-based peptidomimetic was designed and shown to be an inhibitor of STAT3. The authors describe the mechanism of this inhibition and show that this small molecule can also restrict the growth of cancer cell lines expressing high levels of activated STAT3.



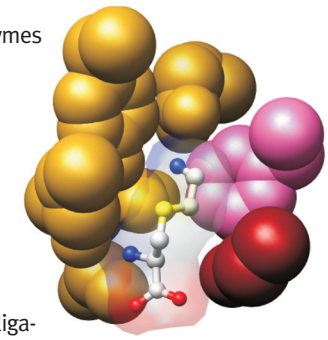
Timofeeva and colleagues (p 799) turn their attention to the N-domain of STAT3. This region is involved in a number of protein–protein interactions, and the second α-helix of this domain is hypothesized to be involved in STAT3 dimerization. In this study, the authors design peptide inhibitors directed toward the second α-helix and demonstrate the targeting of this region as a promising means of combating cancer. The authors identified a potent inhibitor from a library of synthetic peptide analogues. This peptide was rationally modified to enhance potency, cell permeability, and stability. The modified peptide specifically targets STAT3 and inhibits the survival of breast cancer cells by inducing apoptosis. Both of these studies provide exciting new leads in the search for cancer therapeutics.

To Phosphorylate, or Not To Phosphorylate?

Kinases are enzymes that catalyze the phosphorylation of specific target residues. These enzymes play key roles in cell signaling, and altered activities are often associated with cancer cells. As such, knowing the primary substrate specificity of a kinase is essential to dissecting its cellular function. In humans, it is estimated that ~90 of the 500 kinases are tyrosine kinases. On page 810, Pouchain *et al.* describe a new procedure for the rapid determination of tyrosine kinase substrate specificity.

The authors report the design of a peptide nucleic acid encoded library that can be screened against a specific kinase and then resolved using a DNA microarray. A 10,000-member peptide library was tested with several kinases, including the Abelson tyrosine kinase. Substrates that were phosphorylated were analyzed, and a number of known and new targets were identified. The method described by the authors is fast, efficient, and generally applicable for determining the function of other kinases.

Resistance is Hardly Futile



Aminoacyl-tRNA synthetases are enzymes that catalyze the ligation of amino acids to cognate transfer RNAs (tRNA) in all cellular organisms. Because the accuracy of attaching the correct amino acid to the proper tRNA is essential to maintaining the fidelity of protein translation, these enzymes have developed strategies to reject noncognate substrates. Remarkably, ligation of the amino acid lysine to its tRNA can be catalyzed by one of two structurally unrelated lysyl-tRNA synthetases. Because these enzymes differ in the capacity to discriminate against specific small-molecule inhibitors and are not found together in most organisms, they are attractive targets for selective inhibition. On page 819, Ataide *et al.* show that the class II lysyl-tRNA synthetase is the primary cellular target of the antibiotic *S*-(2-aminoethyl)-L-cysteine (AEC).

Previously, it had been suggested that AEC targets the lysine riboswitch, a lysine-sensing RNA structure. Here, using a genetic screen, the authors identified strains of *Escherichia coli* resistant to AEC that possess mutated synthetases but have wild-type lysine riboswitches. This demonstrates that the lysine riboswitch is not the primary target. The authors note that resistance to AEC correlates with a decrease in binding of the antibiotic in the active site of the enzyme. This study sheds light on the mechanism of resistance to an antibiotic and could be useful in the design of other selective inhibitors.

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