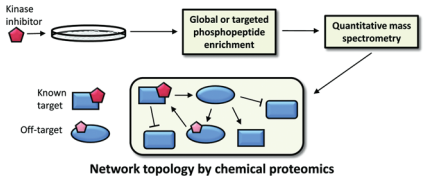
In this ISSUE

Mapping Kinase Inhibitor Targets

Cells respond to environmental signals by regulating protein phosphorylation signaling networks. Irregular perturbation of this network triggers several major human diseases such as cancer, autoimmunity, and diabetes. Thus, small molecule kinase inhibitors are a tempting and potentially lucrative area of pharmaceutical research. Development of therapeutics that specifically target the signaling network, however, has been met with limited success. In this issue, Carlson and White (DOI: 10.1021/cb1002834) review current chemical phosphoproteomic and chemical genetic methods which elucidate the direct targets of kinase inhibitors and yield insight into mapping the kinome.

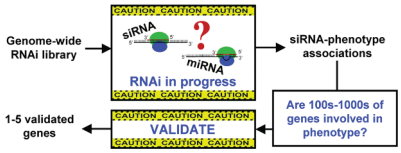
System-wide approaches to interrogating the kinome have been developed for chemical inhibitors of phosphoproteins. Computational methods link this phosphorylation data to the underlying mechanisms by which the signaling network elicits cellular responses. Genetic approaches also provide insight of network structure and system-wide effects of targeted therapeutics. Better understanding of signaling network topology is of great importance toward the development of therapeutics of human disease.



A Guide to Successful RNAi Screens

Over the past decade, RNA interference (RNAi) has been indicated for genome-wide studies of gene function. While informative, the utility of this tool has been hampered by false positives. In this issue, Sigoillot and King (DOI: 10.1021/cb100358f) address the underlying reasons for off-target effects and provide a guide of important issues to consider during studies of candidate genes based on RNAi screens.

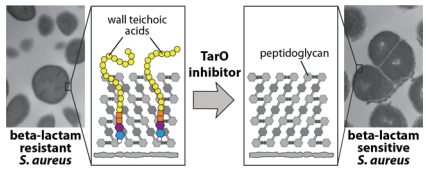
The mechanism of RNAi involves formation of the protein complex, RISC. This complex is comprised of one strand of a small double-stranded RNA, such as short-interfering RNA (siRNA) or microRNA (miRNA), with Argonaute and other regulatory proteins. The single-stranded RNA guides RISC to its target mRNAs, which are degraded by the Argonaute protein. RNAi-based screens have identified new components in numerous cellular pathways. However, a high level of false positives usually due to nonspecific targeting by siRNA or miRNA component hampers these screens. Researchers must therefore treat the results obtained from RNAi screens with caution and conduct additional independent experiments to confirm their observations. Follow-up experiments using multiple siRNAs or structurally modified siRNAs limit undesirable off-target effects and provide avenues for validating screen results. When paired with such experimental rigor, RNAi-based screening can reach its enormous potential as an important discovery tool.



Resisting MRSA

Responsible for approximately 20,000 deaths annually in the U.S. alone, Methicillin-resistant *Staphylococcus aureus* (MRSA) is among the most well-known and clinically important strain of antibiotic-resistant bacteria. The common mechanism of β-lactam resistance is inactivation by β-lactamases. In MRSA, however, β-lactam resistance is mediated through a peptidoglycan transpeptidase, penicillin-binding protein 2A. This unusual mechanism imparts MRSA with a decreased susceptibility to β-lactams. In this issue, Campell *et al.* (DOI: 10.1021/cb100269f) report a novel strategy to sensitize MRSA to β-lactams by targeting wall teichoic acid (WTA) biosynthesis.

Taking advantage of this alternate mechanism, the authors show that MRSA can be sensitized to β-lactams by the concurrent inactivation of two classes of nonessential enzymes, TarO, an enzyme which catalyzes the first step in wall teichoic acid biosynthesis, and penicillin-binding proteins. MRSA exhibits a dose-dependent kill curve with increasing concentrations of the β-lactam when simultaneously treated with tunicamycin, an inhibitor of WTA expression. The inhibitory effects of this compound combination strongly suggest a link between WTA expression and the assembly of the outer matrix of the bacterial cell wall, peptidoglycan. Transmission electron microscopy images also suggest that inhibiting WTA synthesis leads to defects in septum formation during cell division. Relying on the synergistic interactions of two nonessential enzymes, the authors took advantage of a synthetically lethal phenotype. The combined lethality of a TarO inhibitor and β-lactams may be the opening salvo for a new front in the endless struggle between bacterial resistance and therapeutic ingenuity.



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