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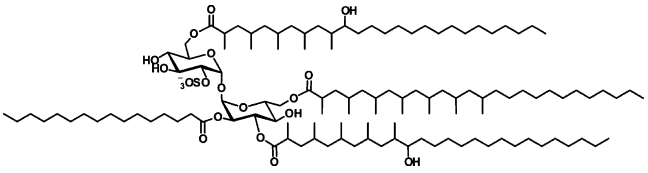
SORTING OUT SULFATIDES

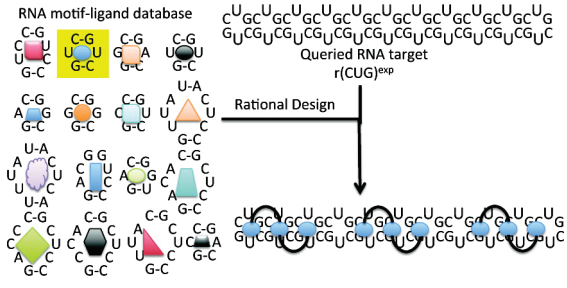
Mycobacterium tuberculosis, the bacteria behind tuberculosis, has a particularly intricate cell wall that serves to protect the pathogen from the outside environment. The cell wall also harbors compounds essential to the survival and virulence of the bacteria. Though the functions of many of the cell wall components are known, glycolipids called sulfatides remain poorly characterized. Gilmore *et al.* (DOI: 10.1021/cb200311s) now examine the role of the most abundant cell wall sulfatide, sulfolipid-1 (SL-1), in *M. tuberculosis* virulence.



First, using purified and synthetic SL-1, the authors found that SL-1 triggers a transcriptional profile in white blood cells distinct from that induced by other proinflammatory compounds. In addition, to probe the function of SL-1 within the bacteria, they created an engineered strain of *M. tuberculosis* that lacks the sulfatide. Intriguingly, their results suggest that SL-1 may actually promote the survival of human white blood cells and increase the susceptibility of the bacteria to an antimicrobial peptide. These insights into how sulfatides modulate *M. tuberculosis* activity will inform the design of new strategies to combat this deadly pathogen.

DRUGGING RNA

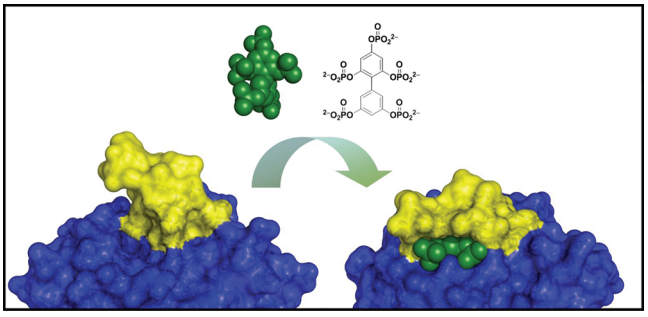
As drug targets go, RNA is underexplored and uniquely challenging, yet brimming with potential. For example, the multisystem disorder myotonic dystrophy is caused by the presence of an expansion of r(CUG) repeats in the 3′ untranslated region of the mRNA of dystrophia myotonica protein kinase, resulting in repeating internal loops. These loops are attractive drug targets because they fold into a hairpin that sequesters muscleblind-like 1 protein, leading to alternative splicing defects, reduction of nucleocytoplasmic transport of mRNA, and formation of nuclear foci. Childs-Disney *et al.* (DOI: 10.1021/cb200408a) now present the design of multivalent ligands that target the repeating r(CUG) motif.



Building from a bis-benzamide known to bind 5′CUG/3′GUC, an oligomeric compound displaying multiple copies of the bis-benzamide at defined intervals, was created to target the repeating r(CUG) motif. When tested in cell culture models of myotonic dystrophy, the compounds improved alternative splicing and translational defects and disrupted formation of nuclear foci. In addition to identifying inhibitors of the r(CUG) motif, this approach points to the exciting prospect of targeting other expanded repeat-containing RNA transcripts with designed, multivalent compounds.

CLOSING THE LOOP ON SHIP2

Phosphoinositides are phospholipids that reside in the cell membrane and play important roles in signaling and membrane trafficking. Certain kinases and phosphatases, such as Src homology 2-domain-containing inositol-phosphatase-2 (SHIP2), are involved in controlling levels of the various phosphorylated variants of phosphoinositide in the cell. These enzymes are enticing drug targets, as they have been linked to numerous diseases including cancer and diabetes. Efforts to target SHIP2 *via* rational drug design have been hampered, however, by the lack of structural information surrounding the enzyme in complex with a ligand. Mills *et al.* (DOI: 10.1021/cb200494d) now present the X-ray crystal structure and molecular dynamics simulations of SHIP2 bound to a synthetic ligand.



The structure illuminated numerous key interactions between the ligand and the active site of the enzyme, and the molecular dynamics simulations revealed the presence of a loop that encloses the ligand. Together, these results offer exciting clues about how to design effective inhibitors of this thus far elusive drug target.

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