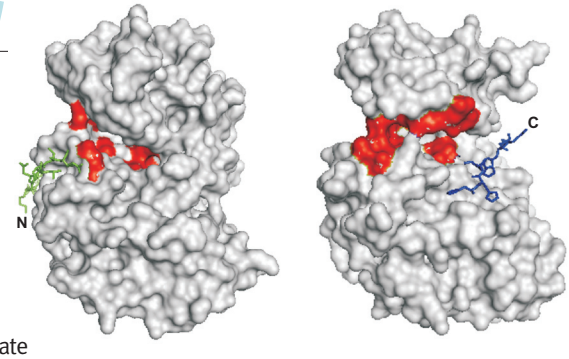
ACS chemical biology

In this ISSUE



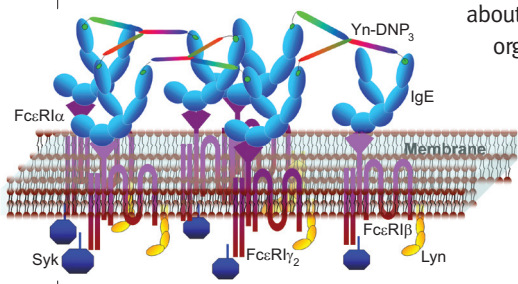
Kinase Substrates Go Modular

The importance of protein phosphorylation events in biological processes can hardly be overstated, and the role of certain kinases in cancer progression has propelled them to the top of the hit list of anticancer targets. However, effectively modulating the activity of a specific kinase amid the entire kinome is a formidable challenge. Fernandes *et al.* (p 665) now present a method for the creation of novel peptide-based kinase substrates that incorporate built-in specificity for a kinase of interest.

Using the mitogen-activated protein kinase extracellular-regulated kinase (ERK) as a model system, the authors designed modular peptide substrates for ERK that were composed of an ERK phosphorylation sequence, a flexible linker, a docking peptide derived from ERK binding elements in various protein substrates and activators of ERK, and a fluorophore for detection purposes. The authors hypothesized that the docking peptides would provide an effective mimic of the specificity and reaction efficiency that occurs with natural ERK substrates. Indeed, the binding affinities and phosphorylation efficiencies of the designed peptides were enhanced by 200- and 150-fold, respectively, compared with substrates containing only the phosphorylation sequence. The modularity of these novel kinase substrates suggests that this approach could be used in the design of more specific, efficient substrates for many other kinases as well.

Going the Distance

In white blood cells, inflammatory and allergic responses are mediated by the interaction between the immunoglobulin E (IgE) antibody and its receptor, FcεRI. Antigen-mediated cross-linking of the IgE–FcεRI complex triggers a cascade of signaling events, but little is known about the spatial organization of the receptors required to elicit an effective and appropriate response. Sil *et al.* (p 674 and Point of View p 652) create a series of trivalent IgE ligands to probe the effects of distance between ligands engaged in cross-linking interactions.

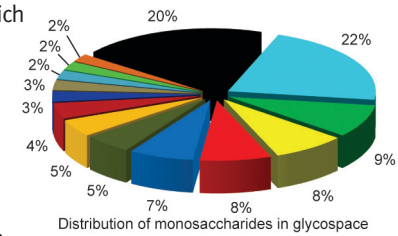


The ligands were designed to bind to anti-2,4-dinitrophenyl (DNP) IgE and were composed of three DNP groups separated by rigid, Y-shaped DNA scaffolds of defined lengths. The effects of the ligands on degranulation, early tyrosine phosphorylation events, and calcium mobilization in white blood cells demonstrated a length dependence such that ligands with shorter spacing between antigens stimulated stronger responses than those with longer spacing. In contrast, the magnitude of calcium release from intracellular stores was not dependent on spacer length. The results suggest that the distance between cross-linked IgE–FcεRI complexes can profoundly influence cellular responses.

Glycospace Exploration

Carbohydrates are an important class of biomolecules that play a critical role in information transfer. Unlike linearly constructed DNA and proteins, however, carbohydrates contain branched structures and are also composed of more individual building blocks than protein or DNA, increasing their complexity considerably. In an effort to get a handle on mammalian oligosaccharide diversity, or "glycospace", Werz *et al.* (p 685) conduct a systematic analysis of the structures that have been deposited in the databank GLYCOSCIENCES.de.

GLYCOSCIENCES.de contains >20,000 structures of carbohydrates from all species. Focusing on the 3299 mammalian carbohydrate structures present in the database, the authors first addressed some basic questions about the composition, average size, chain length, and amount of branching found in these structures. This information, combined with detailed analyses of the stereochemistry and linkages found in the structures, was used to derive a minimal set of monosaccharide building blocks from which the majority of mammalian oligosaccharides could theoretically be assembled. Astonishingly, only 36 building blocks were found to be needed to construct 75% of the mammalian oligosaccharides studied. This analysis provides important contributions toward an overall description of mammalian glycospace as well as the development of a systematic strategy for the synthesis of mammalian oligosaccharides.



Distribution of monosaccharides in glycospace

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