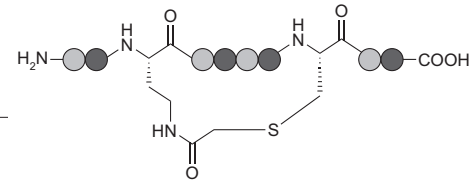
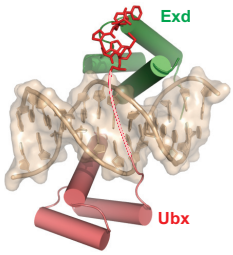
ACS chemical biology

In this ISSUE



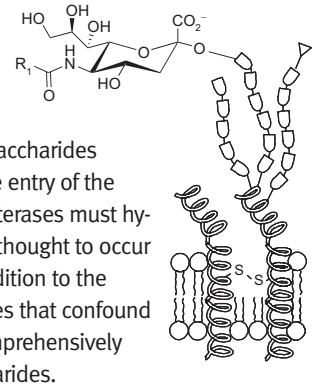
Driving a Chemical Wedge between Proteins and DNA

Direct interactions between many proteins have been shown to enhance formation of complexes of these proteins with DNA. Interactions between side chains of proteins and the edges of base pairs in the target DNA have also been demonstrated to be important in specificity. What is often ignored is that binding of one protein to the DNA recognition site can allosterically modulate the binding of a subsequent protein by altering DNA structure and conformational flexibility at a second binding site. Moretti *et al.* (p 220 and Point of View p 207) demonstrate, using chemical wedges, that these allosteric modulations play an important role in the assembly of protein–DNA complexes.



Transcription factor Extradenticle (Exd) forms a cooperative DNA-binding complex with the transcription factor Ultrabithorax (Ubx) of the homeobox transcription factor family. Exd thereby controls processes key to the development of many animals. The authors designed minor-groove binding polyamide molecules that induced DNA structural changes to the Exd binding site and were able to demonstrate a specific role for allosteric modulation in Exd binding to DNA, even in the absence of Ubx. Ultimately, perturbing DNA geometry to precisely regulate protein–DNA complex formation promises an unparalleled level of control of cellular processes.

Glycobiology: How Sweet the Bond!



The incorporation of synthetic sugars with novel chemical properties into cellular glycans is an innovative approach in the metabolic engineering of cells. To increase cellular uptake, monosaccharides are often modified with short chain fatty acids (SCFAs). Prior to the entry of the synthetic monosaccharide into cellular glycosylation pathways, esterases must hydrolyze the SCFA from the rest of the monosaccharide, and this is thought to occur through the activity of nonspecific proteases. Unfortunately, in addition to the monosaccharides, SCFAs display a wide array of biological activities that confound metabolite design. Aich *et al.* (p 230 and Point of View p 203) comprehensively describe the biological activities of SCFAs attached to monosaccharides.

The authors overturn the assumption that the biological activities of SCFA–monosaccharide hybrid molecules arise simply from the hydrolysis products—the free SCFAs and monosaccharides. Remarkably, SCFA–monosaccharide analogs that differed only in the position of the free hydroxyl group boasted vastly different biological activities. Analogs with the free hydroxyl at the C1 position are prospective anticancer leads, whereas those with the free hydroxyl at the C6 position are ideal for metabolic engineering.

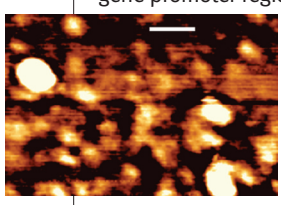
Peptides Not Constricted by Peptidases

Human urotensin II (hU-II), one of the most potent vasoconstrictors known, is a cyclic peptide with a single disulfide bridge between two cysteine residues. This peptide is found most notably in peripheral blood vessels, the heart, and the kidneys. It causes an increase in intracellular calcium concentrations by activating a specific G-protein coupled receptor. Previous studies have shown that the disulfide bridged region of hU-II is essential for activity. Unfortunately, the disulfide bond is reducible under physiological conditions, and the resulting linearized peptide is more susceptible to peptidases. Sako *et al.* (p 241) report a new system for generating cyclic peptides using a nonstandard amino acid with a chloroacetyl group in the side chain. When the peptide also contains a cysteine residue, spontaneous displacement of the chloride gives a covalent nonreducible thioether link.

Using this system, the authors created a peptidase-resistant hU-II analog with biological activity. This method should now allow the synthesis of stable cyclic peptides that might be useful starting points in designing agonists and antagonists of various target receptors.

DNA Quadruplexes: Form and Function

DNA sequences with long runs of neighboring guanines have been known to form four-stranded secondary structures known as DNA guanine-quadruplexes. Interestingly, a number of cancer-related genes have been shown to possess quadruplex-forming sequences in the gene promoter regions, and recent evidence has linked these structures to telomere preservation, DNA recombination, and gene regulation.



Soldatenkov *et al.* (p 214) demonstrate for the first time that the abundant human nuclear protein poly(ADP-ribose) polymerase (hPARP-1) binds to DNA quadruplexes and that this association is functionally relevant.

These results are intriguing because hPARP-1 is associated with the control of DNA repair pathways and the maintenance of genome stability. It is known that hPARP-1 senses duplex DNA ends and other lesions associated with DNA damage. The authors have shown now that quadruplex DNA stimulates the activity of hPARP-1, and they propose that this interaction is involved in gene expression.

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