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Spotlights on Recent *JACS* Publications

CLOSING THE GAP: LONG-RANGE CONTACTS IN SOLID-STATE PROTEIN NMR

Many important proteins in human biology resist structural analysis by X-ray crystallography and solution nuclear magnetic resonance (NMR) spectroscopy but are compatible with study by solid-state NMR. However, solid-state NMR comes with its own set of issues. While solution NMR provides information about the distances between hydrogen atoms in proteins, forming the basis for structure determination, in solid-state NMR signals from hydrogen atoms tend to overlap, making assignment and distance measurements difficult to attain. Markus Weingarth, Marc Baldus, and co-workers have developed a general approach for obtaining the side-chain proton contacts that define protein structure in solid-state NMR (DOI: 10.1021/ja412870m).

Scientists have found ways to detect solid-state NMR signals from hydrogen atoms in proteins that exchange with those in the surrounding water, but many interesting long-range interactions are between hydrogen atoms covalently attached to their amino acids. To detect those atoms, the researchers grow ubiquitin and membrane protein BamA under conditions that replace almost all the protein's protons with deuterons, which do not clutter up the NMR spectra.

The key was the addition of just a couple of protonated amino acids to the growth media, so they are incorporated into the proteins. This step makes the spectra, now containing only signals from certain types of amino acids, relatively easy to assign and provides numerous long-distance contacts between amino acid. This method may help scientists solve protein structures, detect protein−membrane interactions, and refine protein catalytic sites in future research.

Erika Gebel Berg, Ph.D.

MIXING IT UP: ATOMICALLY THIN NANOSHEETS MADE OF SEMICONDUCTOR ALLOYS

The development of functional optoelectronic devices is largely dependent upon advances in nanomaterials research. For the first time, researchers led by Anlian Pan and Xiangfeng Duan report atomically thin two-dimensional semiconductors with tunable optical properties (DOI: 10.1021/ja500069b).

The team has created the new class of ultrathin, spectrally responsive materials by mixing together semiconductors with different band gaps to create alloys of differing ratios. The triangular nanosheets, which are a single or a few atoms thick, exhibit spectral properties that are dependent on the ratio of the two semiconductors—MoS_2 and $MoSe_2$—present in the alloys.

The researchers verify the high quality of the resulting materials by measuring the shift in their spectral peak position, confirming that their photoluminescence is continuously tunable from 668 to 795 nm, the emission peaks for pure MoS_2 and $MoSe_2$, respectively. This new method for the creation of spectrally tunable nanosheets makes it possible to further investigate their potential for applications in nanoscale electronic and optoelectronic devices.

Christine Herman, Ph.D.

ANTICANCER COMPOUND HAS DOUBLE-EDGED CUTTING POWER

Basab Roy and Sidney M. Hecht have determined a novel mechanism that the anticancer compound bleomycin uses to cleave double-stranded DNA (DOI: 10.1021/ja500414a). Bleomycins are a class of compounds produced by bacteria that have been used for decades to treat several forms of cancer. Scientists think they work by inducing double-strand breaks at select locations in DNA, but the exact details of their therapeutic mechanism are still unclear.

To investigate this further, the researchers test the cutting action of one clinically applied bleomycin, in complex with iron(II), on 10 hairpin DNA sequences known to strongly bind the compound. Bleomycin produces many double-strand cuts in the DNA at closely spaced intervals. Notably, the researchers discover a new way that bleomycin cleaves DNA. In addition to a previously described mechanism called coupled cleavage, they also find instances of non-coupled cleavage. In this new mechanism, double-strand cuts may represent two independent cleavage events carried out by a reactivated bleomycin molecule rather than subsequent cuts by a single activated bleomycin.

The study offers insight into bleomycin's cancer-fighting power, which the authors say could be explained by its close association with DNA sequences—and its ability to nick DNA strands repeatedly—as a consequence of the close association.

Deirdre Lockwood, Ph.D.

SORTING OUT HOW STRUCTURE AFFECTS FUNCTION

Neal J. Zondlo and co-workers use circular dichroism and nuclear magnetic resonance to examine how differential phosphorylation and OGlcNAcylation affect the structure of proline-rich peptide sequences (DOI: 10.1021/ja407156m). As a model, the researchers study tau, an intrinsically disordered neuronal protein that has been implicated in Alzheimer's disease. In tau, phosphorylation is associated with a misfolded, aggregated, and toxic form of the protein, while OGlcNAcylation promotes formation of a stable, soluble, and functional protein.

Phosphorylation and OGlcNAcylation are two common types of post-translational modifications. These small chemical modifications are added to proteins after their synthesis in the cell and are key modulators of protein function. Phosphorylation and OGlcNAcylation are frequently done on the same serine and threonine residues under different circumstances, and often result in distinct functional consequences.

The authors find that phosphorylation promotes polyproline helix formation in certain peptides, while GlcNAcylation inhibits it. In addition, they discover that phosphorylation on threonine has a greater influence on structure than phosphor-

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ylation on serine. The disorder-to-order transition observed upon amino acid phosphorylation, particularly on threonine residues, suggests that phosphothreonine may be a special locus for phosphorylation-mediated structural change in intrinsically disordered proline-rich peptides. Here, these findings are applied to tau, deciphering how structural changes associated with post-translational modifications might influence this protein's harmful function in neurodegenerative disease.
Eva J. Gordon, Ph.D.

A SWEETER MICROARRAY

When cells make proteins, they often decorate them with certain chemical modifications. These modifications enhance the function of the protein, for example, by enabling it to partake in signaling processes or to interact with other cells. One common modification is the carbohydrate *N*-acetyl glucosamine, which is added to proteins by an enzyme called *O*-GlcNAc transferase (OGT). *O*-GlcNAcylation is essential for proper cell development, and defects in the process have been linked to cancer and other diseases.

One challenge in exploring OGT activity is identifying which proteins it modifies. Tackling this challenge, Suzanne Walker and co-workers use large protein microarrays, in which thousands of diverse proteins are spatially arrayed on a protein-binding surface, to discover new OGT substrates (DOI: 10.1021/ja500451w). Among their discoveries is a protein called OTX2, which is involved in neural development and has also been implicated in brain cancer.

The study marks the first time that large protein microarrays have been used to identify substrates for *O*-GlcNAcylation. This approach can help decipher the role of this important modification in protein biology, and can be expanded to characterize other enzymes involved in protein glycosylation.
Eva J. Gordon, Ph.D.