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Spotlights

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Spotlights on *JACS* Publications

EXPANDING THE REACH OF TOP-DOWN PROTEOMICS

Jenny Brodbelt and colleagues introduce a proteomics method to characterize intact proteins of up to 29 kDas by dissociating them with ultraviolet light in an Orbitrap mass spectrometer (DOI: 10.1021/ja4029654).

Proteomics has advanced in the past decade through "top-down" analyses to characterize intact proteins using mass spectrometry. With these methods, researchers can determine fine-scale modifications and mutations of proteins that are relevant to disease, such as post-translational modifications and single-nucleotide polymorphisms. The characterization of these protein features was much more limited in traditional "bottom-up" approaches, which require enzymatic digestion of proteins and sequencing of the resulting fragments.

But the top-down approach has been restricted to characterizing relatively small (<10 kDa) proteins because larger proteins are difficult to dissociate by the other ion activation methods which give gaps in sequence coverage. Now Brodbelt and colleagues have introduced a new method, ultraviolet photodissociation in an Orbitrap mass spectrometer, to expand the protein sequence coverage. They apply the method to analyze proteins up to 29 kDa and characterize a protein associated with Alzheimer's disease and cancer, identifying a point mutation and several protein modifications. The method allows researchers to explore a larger range of proteins—and their role in disease—with top-down proteomics. **Deirdre Lockwood, Ph.D.**

COME UNDONE: HOW UREA INDUCES RNA UNFOLDING

Urea has played an important role in helping researchers understand the intricacies of folding and unfolding of protein structures. Researchers are now extending the same type of urea-based experiments to another essential class of biological molecules—complex, folded RNA structures. But the details of how urea, a neutral molecule with a large dipole, causes RNA to unfold are not known.

Now Changbong Hyeon and colleagues have carried out molecular simulations to understand the details (DOI: 10.1021/ja406019s). The investigators used a 36-nucleotide structure called the preQ1-riboswitch from the bacterium *Bacillus subtilis* as a model because it has both secondary and tertiary structural motifs.

Hyeon and colleagues demonstrate that the urea-induced RNA unfolding process is opposite to the protein unfolding process. With proteins, urea molecules first penetrate the protein structure to destabilize it before water enters in a second step to complete the denaturation. With RNA, the investigators show that water penetrates first by slipping into the tiny gaps between base pairs to destabilize the RNA structure. Urea subsequently completes the denaturation process by solvating the exposed bases via hydrogen bonding and stacking. The investigators say urea's ability to both hydrogen bond and base stack makes it an effective denaturant of nucleic acids. **Rajendrani Mukhopadhyay, Ph.D.**

IN PURSUIT OF THREADED LASSOS

James Link and Mikhail Maksimov mine the genome of the freshwater bacterium *Asticcacaulis excentricus* in pursuit of lasso peptides, unusually stable, cyclic peptides named for their unique fold that resembles a threaded lasso (DOI: 10.1021/ja4054256). Made exclusively by bacteria, these compounds likely function in nature as defense molecules against other organisms, yet they also have activity against some pharmacologically relevant targets.

The authors characterize a gene cluster that encodes two lasso peptides, called astexin-2 and astexin-3, as well as an enzyme called AtxE2. They find that, in contrast to other lasso peptide-associated enzymes that transport the peptides out of the cell, AtxE2 is an isopeptidase that deconstructs the threaded lasso into its inherently less stable linear counterpart. They also analyze the evolutionary history of lasso peptides and discover that lasso peptide gene clusters come in two flavors: one that contains a transporter enzyme and another that houses an isopeptidase.

Many questions remain regarding the biosynthesis and mechanism of action of lasso peptides, including the functional significance of their unique fold and the purpose of the enzyme that unravels them. The biochemical and evolutionary insights gained in this study will facilitate engineering and further characterization of the members of this intriguing peptide family. **Eva J. Gordon, Ph.D.**

SWAPPING METAL EXPANDS RANGE IN NEGATIVE THERMAL EXPANSION MATERIALS

Negative thermal expansion (NTE) materials contract instead of expanding when heated. When mixed with more common metals that expand under heat, they can form a composite that neither expands nor contracts upon heating. This is valuable in technologies such as reflective grating devices, optical mirrors, and machinery parts. However, finding materials that do this in practice is relatively rare, due to the narrow temperature window under which they show NTE effects. In addition, most of the known NTE materials have small thermal expansion effects, so have limited value.

Now Laifeng Li and co-workers have found a way to expand this NTE behavior window (DOI: 10.1021/ja405161z). The compound $La(Fe,Si)_{13}$ undergoes a phase change where there is a coinciding change in both magnetism and volume. It also exhibits NTE behavior, but only over a narrow temperature range. The researchers replaced the Fe with Co, and the transition temperature widely broadened and even includes room temperature. The effect was also large enough to counter thermal expansion in metallic composites. This discovery may be valuable for volume sensitive devices in the future, leading to machines that run better and optical devices that stay in tune. **Leigh Krietsch Boerner, Ph.D.**

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