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Spotlights on Recent *JACS* Publications

NEW INSIGHTS INTO CHAPERONES UNCOVERED

In the tightly woven ever-shifting environment of the chromosome, getting proteins to fold correctly and find their binding partners is critical. That is where chaperones come in. Garegin Papoian, Yamini Dalal, and colleagues perform molecular dynamics simulations and *in vivo* experiments investigating the interactions between the centromere-specific chaperone, Holliday Junction Recognition Protein (HJURP), and histone proteins, which manage genetic material in human chromosomes (DOI: 10.1021/jacs.6b05355). Their findings suggest that chaperones not only facilitate folding but also can promote correct interactions between histones themselves.

Centromere protein A (CENP-A), a centromere-specific variant of canonical histone 3, is essential for mitosis and centromere packing. The researchers are curious about the roles the chaperone HJURP plays in the interaction between key histone proteins, which might contribute to its unique biological function. Their molecular simulations and experiments indicate that HJUR, while potentially serving as a protein-folding chaperone, can also help CENP-A associate with its binding partners, which guarantees the stability of the binding without disruption from other factors. This study allows for general predictions about histone−histone interactions, and provides new insights into the underlying mechanisms governing the HJURP-mediated assembly of CENP-A nucleosomes *in vivo*.

Erika Gebel Berg, Ph.D.

STRUCTURES SHOW HOW A HEPATITIS C VARIANT EVADES ANTIVIRALS

In recent years, a diagnosis of hepatitis C has become more manageable thanks to a host of new antiviral treatments. Although oral combination therapies such as Harvoni, Viekira Pak, and Zepatier work well against the most common species of the virus, genotype 1, they are much less effective against the genotype 3 (GT-3) species, which causes nearly a third of infections worldwide. To design better drugs against GT-3, scientists want to understand how it evades therapeutic activity, but they have been limited by a lack of structure data on the target protease.

To fill in this gap, Celia Schiffer and colleagues determine high-resolution crystal structures of a chimeric form of the target GT-3 protease bound to three protease inhibitors in clinical development, asunaprevir, danoprevir, and vaniprevir (DOI: 10.1021/jacs.6b06454). Through structural studies and molecular dynamics simulations, the researchers show that GT-3 disrupts hydrogen bonding interactions and dynamic cross-correlations between the inhibitors and the active site of the protease. The work clarifies the mechanism behind GT-3's reduced response to treatment, and could help chemists develop new treatments to target this form of the virus.

Deirdre Lockwood, Ph.D.

THE MYSTERIOUS WATER DIMER CATION: A MOLECULAR YO-YO

Water splitting is a process to separate chemically water into hydrogen and oxygen. It holds great promise for renewable-energy technologies. For example, hydrogen obtained by water electrolysis can be used as a clean fuel to power electric cars. Catalysts play an important role in the first redox step in water splitting, the formation of water dimer cations $(H_2O)_2^+$. However, theoretical studies of this process have been complicated by the highly unusual and little understood vibrational spectra of these dimer cations, including dominant spectral features that are absent in common quantum chemistry simulations. Ryan Steele and co-workers have now been able to explain the unusual spectral features by taking into account the coupling of electronic and highly anharmonic nuclear motions in their computations (DOI: 10.1021/jacs.6b07182).

Comparisons of experimentally obtained spectra to computed ones indicate that the vibrational spectra of the cations reflect strongly coupled vibrational modes, resembling the motion of a yo-yo. The analysis demonstrates that a proper combination of modern experimental and computational infrared spectra may provide key data about water oxidation complexes involved in water-splitting, which could in turn facilitate future catalysts design.

Alexander Hellemans

EXPLORING PROTEIN PREFERENCES FOR PARTICULAR METALS

To stay healthy in a perilous environment, prokaryotes make cysteine-rich proteins that discriminate between essential and toxic metals, capturing selectively only the harmful species. How the proteins differentiate metals has often remained unclear, as structures of these toxic metal-binding proteins with and without metals are rarely available. To identify the mechanism for protein metal selectivity, Vincent Pecoraro, Jeanne Stuckey, and their team design metal-binding peptide proxies—three-stranded coiled coils—for the native proteins that can be readily examined with and without a bound metal (DOI: 10.1021/jacs.6b07165).

The researchers solve the crystal structures of a series of peptide−metal complexes. The structures reveal that the three cysteine ligands need to reorganize themselves in order to bind metals favoring trigonal planar or pseudo tetrahedral geometries like zinc and mercury. On the other hand, these proteins are preorganized to bind lead and arsenic that are in a trigonal pyramidal geometry, as the side chains are in an orientation that welcomes these metals without significant side chain movement. These insights may help scientists develop novel biomolecules that sequester toxic metals, such as lead, for example, in a water supply or understand how heavy metals may influence protein structure and dynamics, e.g., in human L1-retrotransposons, that contribute to heavy metal toxicity.

Erika Gebel Berg, Ph.D.

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"HELPING HAND" DISSOLVES TOUGH PEPTIDES FOR PROTEIN SYNTHESIS

To study large and complex proteins that cannot be made recombinantly, researchers often turn to chemical synthesis. However, this approach can be hamstrung by insoluble peptides that tend to aggregate and are impossible to purify. To alleviate this challenge, Michael Kay, Vincent Aucagne, and colleagues introduce a new tool, which they refer to as a "helping hand" to coax troublesome sequences into solution (DOI: 10.1021/jacs.6b05719).

Their answer is an easy-to-use link that can be introduced to the side chain of any lysine residue to enable temporary addition of a highly solubilizing poly-lysine tag. The linker remains present during peptide cleavage, purification, and chemical ligation, and is then removed with a gentle hydrazine treatment. The researchers show that this method enables the chemical synthesis of the 97-residue chaperone protein GroES, which has a highly insoluble C-terminal segment. They successfully make both L- and D-GroES, and characterization shows that they are pure, correctly folded, and functional. The new approach is generally applicable to the synthesis of many large and challenging proteins.

Deirdre Lockwood, Ph.D.

SETTLING A FOLDING DEBATE ONCE AND FOR ALL

Folded proteins get most of the credit in biology, but the unfolded state is key to understanding the process of protein folding. Moreover, some proteins do not fold at all, but instead do their work in an intrinsically unfolded state. Studying unfolded proteins, though, can be tricky. In two publications, researchers resolve a long-standing controversy in the folding field and confirm that proteins expand upon chemical denaturation (DOI: 10.1021/jacs.6b05443; DOI: 10.1021/jacs.6b05917).

In recent years, scientists had noticed a strange inconsistency in protein unfolding experiments. With most methods, proteins appear to expand upon addition of chemical denaturants, such as guanidinium chloride or urea: their radius of gyration increases with increasing denaturant concentration. However, small-angle X-ray scattering (SAXS) experiments often show no such expansion, leaving scientists to question the accuracy of the results.

To resolve this issue, the researchers carefully analyze two proteins, one of which is intrinsically unfolded. Keeping conditions as consistent as possible between samples, they evaluate the proteins' radius of gyration using SAXS, Förster resonance energy transfer (FRET), and other experimental techniques at varying guanidinium chloride or urea concentrations. Combined with computer simulations, the data shows that no discrepancy exists. Each method indicates protein expansion upon chemical denaturation. The findings settle concerns regarding the effect of chemical denaturants on the dimensions of unfolded and disordered proteins, and support the idea that these chemicals denature proteins by weakly associating with the protein backbone.

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