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Spotlights on Recent *JACS* Publications

CRYSTALLIZING CONFORMATIONALLY DYNAMIC PROTEINS? TRY TETHERING

In X-ray crystallography, uniformity is key: proteins must adopt a uniform structure and orient themselves in a regular array to form the crystals that drive structure determination. The structures of conformationally dynamic proteins are particularly difficult to solve by X-ray crystallography for this reason. Here, Anna Mapp and colleagues identify small-molecule stabilizing ligands that allow them to crystallize and solve the structure of the GACKIX domain of the CBP/p300 coactivator protein for the first time (DOI: 10.1021/ja3122334).

The researchers perform a so-called Tethering screen for small molecules that could form disulfide bonds with GACKIX, identifying two hits. After characterizing the impact of these compounds on GACKIX dynamics, they crystallize and obtain the 2.0 Å structure of the protein−small molecule complex, "enabling for the first time the crystallographic characterization of this important motif."

This specific work could lead to the development of, for instance, chemical antagonists of CBP/p300 function, the authors note. But more broadly, their results "suggest that Tethering may be an exceptionally enabling approach for obtaining long-sought X-ray crystallographic data for conformationally dynamic proteins." **Jeffrey M. Perkel**

THE MAKING OF METHYLATED ARGININE

To facilitate investigation of the role of arginine methylation in biological processes, Danica Fujimori and co-workers have developed a chemical method for incorporating methylarginine into proteins (DOI: 10.1021/ja3108214).

Modification of certain amino acids with chemical entities such as phosphate, acetate, or methyl groups in many proteins relays a distinct message to the cell, such as that a particular signaling pathway should be initiated or a certain gene should be transcribed. Methylation of the amino acid arginine is becoming increasingly recognized as a key messenger of processes involved in gene transcription, DNA repair, and RNA trafficking, but the molecular details associated with this process are not well understood.

The method developed by the researchers relies on the chemical synthesis of special methylated arginine analogues and the generation of mutant proteins strategically designed to react with these analogues. Proteins called histones, which act as spools that DNA winds around, were chosen to develop this approach because arginines in these proteins are often methylated as part of their normal function. The chemically methylated histones behave similarly to naturally methylated histones and will enable various structural and biochemical investigations of these important proteins. In addition, this approach can be extended to other protein families to which a single reactive cysteine can be introduced, potentially providing a general method for exploration of the biology of arginine methylation. **Eva J. Gordon, Ph.D.**

SPATIAL CONTROL OF PROTEIN LABELING? IT'S LOGICAL

In proteomics, as in real estate, it's location, location, location. Purifying bulk proteins often is not enough; researchers want to concentrate on proteins expressed only in certain cells or under specified conditions. Here David Tirrell and colleagues describe a genetic circuit that enables tight spatial control of protein labeling and purification (DOI: 10.1021/ja400448f).

The researchers build a logical AND circuit from a methionyl-tRNA synthetase (MetRS) that they modified to accept the methionine analogue azidonorleucine (Anl). Anl provides the azide half of a "click chemistry" reaction, in which an alkyne-containing fluorophore, for example, can be tethered to an azide-modified protein.

The team split its mutant MetRS into two inactive pieces. Expression of one piece is governed by IPTG, the other by arabinose; only cells that encounter both molecular "inputs" label newly formed proteins with Anl. When the team placed bacteria containing both constructs in a microfluidic channel with IPTG and arabinose flowing in parallel, laminar streams, and added an alkyne-containing fluorophore, only cells in the center of the channel—exposed to both IPTG and arabinose—took up the label.

The resulting system enables "spatially controlled proteomic labeling of cells", the authors note. With the right inputs, researchers could restrict protein isolation to cells receiving multiple defined cellular messages. Thus, it "provides a powerful new tool for targeted analysis of cellular protein synthesis." **Jeffrey M. Perkel**

A SILICON VERSION OF A METATHESIS INTERMEDIATE

An olefin metathesis reaction starts with two carbon−carbon double bonds, snips each alkene in half, and then reconnects the double bond. The new molecule contains pieces from each of the starting molecules and is constructed via a metallacyclobutane intermediate. Vladimir Ya. Lee, Akira Sekiguchi, and their colleagues have built a titanium silylene complex that performs this same cycloaddition chemistry (DOI: 10.1021/ja401072j).

In olefin metathesis, the metallacyclobutane intermediate is formed from the [2+2] cycloaddition of an alkene to a transition metal carbene complex. Silicon forms a similar cyclic complex, but these cycloadducts are unable to undergo subsequent cycloreversion and further react with an alkene to perform a complete olefin metathesis reaction. The newly synthesized silatitanacyclobutenes are stable up to 100 °C, and now the researchers are looking for starting materials—including alkenes—that might be able to complete the metathesis cycle.

Olefin metathesis is an important industrial transition metal-catalyzed reaction. For example, in petroleum refining, metallacyclobutane-mediated reactions are used to make

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substituted double bonds from molecules that have alkenes dangling at the end of a chain. The researchers suggest that the new titanium silylene-derived catalyst might lead to the development of novel organosilicon materials, which can be used in coatings, lubricants, and surfactants. **Melissae Fellet, Ph.D.**

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