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Spotlights on Recent *JACS* Publications

FINE TUNING OF GLYCOPEPTIDES YIELDS UNIQUE SELF-ASSEMBLED NANOSTRUCTURES

There is much interest in creating synthetic glyco-conjugate structures composed of peptides and sugar groups that mimic the self-assembling nanostructures found in nature. Researchers led by Guosong Chen report a new class of artificial glycopolypeptides that undergo a more complex hierarchical self-assembly process than previously observed (DOI: 10.1021/jacs.6b05044).

The team uses alternative amphiphilic gylcopolypeptide brushes and shows these brushes can be tailored to yield a variety of self-assembled morphologies, including nanowires, nanoribbons, and compound micelles. Which nanostructure is formed depends on the ratio of sugar units to amino acid species in the structure. They study the nanowire morphology in more detail, observing the step-by-step process of self-assembly that takes place during its formation: micellization, assembly of the micelles into nanofilaments that subsequently sprout branches, and finally, the arrangement of the branched nanofilaments into nanowires. The authors say the constructs will lead to a deeper understanding of the mechanisms by which natural glycoconjugates self-assemble, while also expanding the library of synthetic materials that mimic complex biological molecules.

Christine Herman, Ph.D.

DIOXYGEN ACTIVATION WITH BIOMIMETIC METAL COMPLEXES: UNDERSTANDING AND OPTIMIZATION

The activation of atmospherically abundant dioxygen (O_2) into water is ubiquitous in biology, driving nutrient metabolism and the synthesis of key biomolecules, among other reactions. In nature, metalloenzymes overcome the reaction's sluggish kinetics, but, in the laboratory, an incomplete understanding of the reaction's mechanism has slowed the development of biomimetic metal complexes that activate dioxygen.

Most research in this area has utilized proxies for dioxygen, simplifying mechanistic studies, but missing out on subtleties of the dioxygen reaction. Sumit Sahu and David Goldberg review the few, recent significant studies that have explored the activation of dioxygen itself by iron and manganese complexes (DOI: 10.1021/jacs.6b05251).

The authors detail a series of experiments studying the activation of dioxygen by heme and nonheme iron and manganese complexes. Spectroscopic methods reveal key metastable intermediates in the reaction pathway. By comparing the complexes, the authors unravel the importance of solvent, spin state, redox potential, external coreductants, and ligand architecture in dioxygen activation. For example, studies in nonheme metal complexes demonstrate that a high-spin ground state facilitates dioxygen activation. This and other insights may help scientists design biomimetic complexes that activate dioxygen.

Erika Gebel Berg, Ph.D.

PROBING PEROXIDASES' MECHANISM WITH A NONCANONICAL NUDGE

Heme peroxidases promote a variety of oxidative transformations and are exploited as biocatalysts for biotechnological applications (e.g., biosensors, wastewater treatment). An aspartate-histidine-iron (Asp-His-Fe) catalytic triad, and specifically the hydrogen bonding interaction between the Asp and His residues, is considered essential to the activity of these enzymes. However, it is challenging to define the role played by this conserved interaction in the peroxidase catalytic mechanism. Traditional methods to probe such interactions, involving canonical mutations of the catalytic residues, lead to a dramatic reduction in catalytic efficiency, which limits the degree of mechanistic information that can be uncovered.

Anthony Green, Donald Hilvert, and colleagues introduce a new approach: replacing the critical histidine residue in ascorbate peroxidase with a noncanonical amino acid, *N*-methylhistidine, which disrupts the Asp-His hydrogen bond without causing major structural changes in the active site (DOI: 10.1021/jacs.6b07029). The results are surprising: instead of diminishing enzyme activity, the noncanonical modification enhances its catalytic properties. This work sheds light on the mechanism of this important class of enzymes and shows noncanonical mutations may help to uncover the subtleties of other enzymatic mechanisms. Such fundamental understanding may provide guidance for re-engineering enzymes to augment or alter their catalytic properties.

Deirdre Lockwood, Ph.D.

FRET-BASED SMALL MOLECULE DETECTION OF PEROXYNITRITE

As with many other endogenously produced molecules, peroxynitrite ($ONOO^-$) plays a role in cellular functions but can cause injury to cell components, including proteins, DNA, lipids, iron–sulfur clusters, and thiols, if its levels get out of control. Studies show a correlation between $ONOO^-$ and numerous pathological conditions, including cardiovascular and neurodegenerative diseases, inflammation, and diabetes. Thus, researchers are interested in developing reliable assays for better understanding the role of $ONOO^-$ in disease, and for the diagnosis of peroxynitrite-related disease.

Xuhong Qian and colleagues report a FRET-based small molecule probe for semiquantitative determination of endogenous $ONOO^-$ inside mitochondria of living cells (DOI: 10.1021/jacs.6b06398). The probe takes advantage of differential reactivity of two fluorophores, Cy3 and Cy5, toward $OONO^-$, which results in a ratiometric fluorescent signal that can be used to detect the molecule at levels as low as 0.65 nM. This two channel probe surpasses existing one channel probes by overcoming complications due to photobleaching, uneven loading, or fluctuation in excitation intensity, making it a promising tool for peroxynitrite biology that could lead to a better understanding of the role of $OONO^-$ in biological processes.

Christine Herman, Ph.D.

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