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Spotlights on Recent *JACS* Publications

FOLLOWING PHOTORECEPTOR EXCITATION

The protein UVR8 is a dimeric photoreceptor that is found throughout the plant kingdom and is involved in the regulation of more than 100 genes. Researchers are intrigued by its unique chromophore—it is a "proteinogenic" chromophore, so called because it is composed of amino acids instead of a more typical exogenous co-factor chromophore. Yet scientists have been in the dark about what exactly happens in between photoexcitation of the UV-B-absorbing tryptophan side chains in UVR8 and the protein's monomerization, which triggers gene expression.

A new report by Tilo Mathes, Gareth Jenkins, John Kennis, and colleagues sheds light on the processes that occur in the femtoseconds following UVR8 photoexcitation (DOI: 10.1021/jacs.5b01177). The team uses time-resolved fluorescence and transient absorption spectroscopy and observes a proton-coupled electron transfer (PCET) reaction at the dimer interface. The result is the formation of a neutral tryptophan radical species that is stable for hundreds of microseconds. This study provides experimental evidence of UVR8's molecular signaling mechanism as well as the formation and nature of its photoproduct. More broadly, the work sheds light on how proteins' environments help modulate PCET reactions.

Christine Herman, Ph.D.

UNDERSTANDING THE WEAKEST LINKS FOR LIGHT–ELECTRIC CONVERSION

Van der Waals interactions are the weakest of the intermolecular interactions, driven by polar fluctuations between otherwise neutral molecular neighbors. Van der Waals interfaces, where a critical and still somewhat mysterious action of light–electric interconversion often takes place, are important for optoelectronics.

In a solar cell, light can bump an electron from its normal position to a higher energy state in a molecule. Sometimes, the electron remains associated with its former location instead of moving away to create electric current. This residual association can be problematic, as free carriers are desired in many optoelectronic applications.

In a recent Perspective, Xiaoyang Zhu and colleagues discuss the mechanisms behind this charge separation in two types of van der Waals interfaces (DOI: 10.1021/jacs.5b03141). A careful literature review reveals that electron delocalization—an electron's ability to spread out—may in some instances promote the formation of free electrons, and in others may hinder it. The researchers stress the importance of competition between electron localization and delocalization within a specific energy landscape. Currently, a lack of suitable experimental tools hinders attempts to solve the puzzles behind these bound states, but the authors point with some optimism to new experimental capabilities on the horizon.

Jenny Morber, Ph.D.

TRANSIENT PROTON PATHWAYS STABILIZE THE CALCIUM PUMP IN MUSCLE CELLS

L. Michel Espinoza-Fonseca and G. Lizbeth Ramírez-Salinas have performed microsecond molecular dynamics simulations, revealing the existence of very short-lived hydrophobic pores that allow the passage of protons required to stabilize a transmembrane pump during calcium ion transport (DOI: 10.1021/jacs.5b03814).

The contraction of muscles depends on the rapid distribution of calcium ions into the muscle cell's cytoplasm—the intercellular fluid that also contains the nucleus, mitochondria, and vacuoles—through a network of tubules and sacs, called the sarcoplasmic reticulum (SR). Calcium ions are then removed from the cell via exchange with protons by a calcium pump system in the SR membrane. This exchange helps establish the low cytoplasmic calcium levels required for relaxation of the muscle cell. The process is powered by the hydrolysis of the energy carrier adenosine triphosphate.

Slow, millisecond structural transitions in the transmembrane pump system are known to form pathways for the exchange of calcium ions and protons. However, an additional fast, microsecond pathway for protons is required to maintain the stability of the calcium pump system. The authors' simulations have helped to clarify the nature of these transient microsecond structural transitions that can explain the mechanism of calcium–proton exchange in muscle cells.

Alexander Hellemans

POWERFUL NEW TOOL DETECTS ELECTROCHEMICAL REACTION INTERMEDIATES

Desorption electrospray ionization coupled with mass spectrometry (DESI-MS) has found broad applicability in the sensitive, selective detection and characterization of reaction products. Now, Timothy Brown, Hao Chen, and Richard Zare report a new application for this method—to detect fleeting electrochemical reaction intermediates in solution (DOI: 10.1021/jacs.5b03862).

By employing a rotating "waterwheel"-style electrode with fast transfer of electrogenerated species from the electrode surface to the gas phase for MS detection, this setup can capture reaction intermediates on the millisecond time scale. As proof-of-principle, the authors readily detect signals associated with products and intermediates in the well-understood electrochemical oxidation of triphenylamine.

The researchers then turn to the biologically relevant molecules uric acid and xanthine, to see whether they are able to observe transient intermediates. For uric acid oxidation, a diimine intermediate with a half-lifetime of 23 ms is detected by DESI-MS, confirming a mechanism postulated on the basis of earlier trapping experiments. The power of this new technique is further illustrated when the authors detect a previously unobserved diimine reaction intermediate in the electrooxidation of xanthine. This study presents a new

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application with more versatility and power to tackle challenges in modern analytical and bioanalytical chemistry.
Hui Jin, Ph.D.

SMALL MOLECULE TAKES FRESH AIM AT AN IMPORTANT CELL SIGNALING PATHWAY

Several inflammatory diseases, such as type 1 diabetes, occur when a particular class of proteins goes awry. The same proteins, which belong to a critical cellular signaling pathway called JAK/STAT, are also implicated in some cancers. Given their clinical importance, researchers have focused on these proteins as drug targets.

The proteins, known as kinases, are enzymes dedicated to transferring phosphate groups from one molecule to another within the signaling pathway. To date, most drug candidates attack the active sites of JAK/STAT kinases. But now Bridget Wagner and colleagues describe how a small molecule called BRD0476 inhibits JAK/STAT kinases in a unique way (DOI: 10.1021/jacs.5b04284). The investigators demonstrate that BRD0476 does not attack the kinases themselves. Instead, BRD0476 takes aim at an associated and functionally important deubiquitinase protein called ubiquitin-specific peptidase 9X (USP9X). The small molecule inhibits the activity of a JAK2 kinase by modulating the interaction between it and USP9X.

By influencing the interaction, BRD0476 has opposing, but desirable, effects. In a model of type 1 diabetes, BRD0476 stops an important class of insulin-producing pancreatic cells from dying; in a colon cancer cell line, it promotes the death of cells. The investigators suggest that USP9X can be an important drug target for inflammatory diseases.
Rajendrani Mukhopadhyay, Ph.D.

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