This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.

ACS SyntheticBiology

Editorial

pubs.acs.org/synthbio

Special Issue on Synthetic Photobiology

Synthetic photobiology is a discipline at the intersection of photobiology, bioengineering, and synthetic biology. It relies on the mechanistic understanding of light-induced changes in photoreceptor proteins to design (i) light-activated proteins with new functions and (ii) gene circuits that can be controlled by light in a predictable, and ideally, programmable manner. Synthetic photobiology in many ways is synonymous with optogenetics. However, historically, optogenetics has been associated with the use of native or modified rhodopsin light-activated ion channels and pumps to control neuronal activity. Synthetic photobiology is perhaps a more encompassing term that emphasizes engineering aspect intrinsic to all synthetic biology.

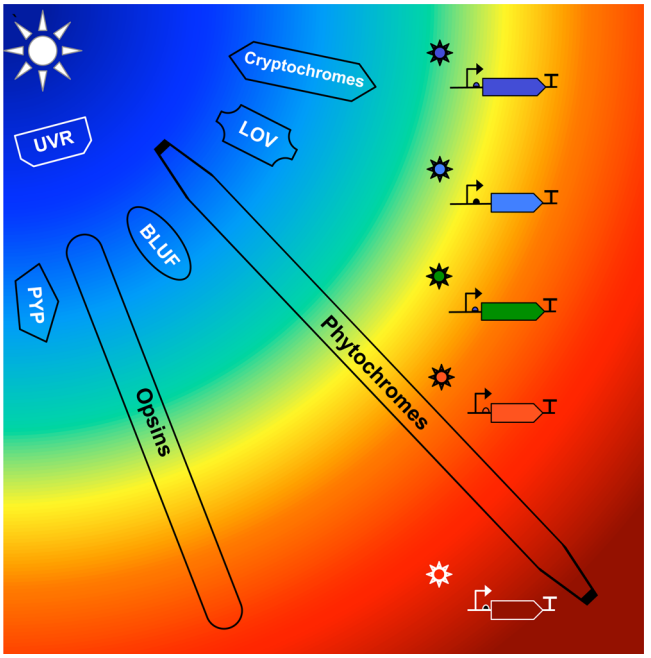
Semantics aside, what is so unique about light that it can claim a slice of synthetic biology all to itself? After all, chemical inducers are currently more commonly used than light, yet it would be absurd to envision synthetic IPTG-biology or synthetic arabinose-biology. The answer is in the unique properties of light that distinguish it from all chemical stimuli—spatial and temporal precision. Spatially, light can operate at subcellular resolution because it can be focused onto a small region within a cell. Temporally, light can be turned on and (importantly!) off instantaneously. Chemicals (drugs) do not come close to such high spatiotemporal resolution, which is often necessary to control cellular processes with physiologically relevant parameters.

To use light for bioengineering purposes, we rely on the suite of light-activated protein modules designed by Mother Nature. Various organisms sense light to optimize their photosynthetic activity, to avoid photooxidative damage, for vision, motility, and even to enhance virulence. A treasure trove of photoreceptor proteins exists in plants, animals, and especially in the enormous number of microorganisms. Note that whereas sensing changes in the light environment is a common biological phenomenon, sensing other wave stimuli (radio and electromagnetic waves or ionizing radiation) simply is not that common, and that natural receptors for these wave stimuli that would be amenable for engineering are hard to come by.

All protein photoreceptors contain light-absorbing chromophores, usually small molecules with conjugated double bonds. More rarely, chromophores are formed by the amino acid residues of the photoreceptor proteins. Seven photoreceptor types appear to have been most evolutionarily successful. These include receptors of UV light (UVR); blue light (sensors of blue light using FAD [BLUF]); light, oxygen, and voltage sensors [LOV]; photoactive yellow proteins [PYP]; cryptochromes [CRY]; and receptors that can sense light in different spectral regions (rhodopsins and phytochromes [PHY]). All natural photoreceptors have a modular architecture, wherein photosensory modules can be linked to and control diverse output activities. In the past decade and a half, the mechanisms underlying photoreceptor operation have been deciphered for most photoreceptor types. It is the growing understanding of these mechanisms that has opened up the opportunities for engineering new light-activated proteins and building light-controlled gene circuits.

A collection of articles in this Synthetic Photobiology Special Issue of *ACS Synthetic Biology* is representative of the current state of the field. These articles describe different engineering approaches that were applied to photoreceptors of several classes to gain photocontrol of diverse outputs. One line of inquiry is exemplified by the study from the Möglich lab. The researchers investigated how point mutations in the LOV photoreceptor module affect signaling properties of a synthetic blue-light activated protein histidine kinase. Modifying properties of the photoreceptor is important because such manipulations allow researchers to adjust the photoreceptor performance to the demands of specific applications.

The study by the Hahn lab also used a LOV domain photoreceptor, however, for a different purpose. These researchers wanted to adapt the LOV module to regulate mammalian Ser-Thr kinases. By relying on the conserved light-inducible conformational change in the C-terminal helix of the LOV domain, they engineered LOV domain fusions with peptide inhibitors of two different mammalian kinases. Their study is a fine example of how knowledge of light-induced conformational changes combined with clever protein engineering can be used to control signaling pathways in living cells, and through these pathways to control cell behavior.



The articles from the Tabor, Tucker, and Webber groups describe optimization of existing and engineering of novel light-

Special Issue: Synthetic Photobiology

Received: November 4, 2014
Published: November 21, 2014

 © 2014 American Chemical Society dx.doi.org/10.1021/sb500350t | *ACS Synth. Biol.* 2014, 3, 780−781

activated gene expression circuits for bacterial (Tabor), yeast (Tucker), and mammalian cells (Webber). These researchers focused on testing and modifying pairs of proteins whose interactions are controlled by light (light-dependent dimerizers). The goal of such optimization is to increase the dynamic range of photoactivated circuits and to lower unwanted background activity in the dark. These groups worked with light-dependent dimerizers containing photoreceptors from the UVR, LOV, CRY, and PHY families. Some of the unexpected findings that emerged from these studies are that dynamic ranges for the same light-dependent dimerizers may differ significantly depending on the cell type, and that moderate light-dependent interactions can be drastically improved by systematic optimization of a system's genetic makeup. The Tabor and Webber groups show how gene expression in the same cells can be controlled by light of two and three different colors, respectively. To identify parameters that would allow photoreceptors of three different kinds (UVR, LOV, and PHY) to function orthogonally, Webber and colleagues sought help in mathematical modeling. The multicolor gene regulatory control systems described in these papers will allow fine-tuned regulation of multiple cellular targets, which may be necessary for studying complex cellular behavior.

Finally, the study from my laboratory proposes the use of second messengers, in this case c-di-GMP, as new synthetic photobiology tools. Second messengers are attractive (i) because they can convey the light signal to different kinds of downstream receptors and (ii) because they amplify the primary signal, which may be important when light availability is limited. As proof of principle, we designed a bacterial system for light-induced synthesis and degradation of c-di-GMP. Coupled with the c-di-GMP-dependent transcription factors, this system creates light-inducible, c-di-GMP-mediated gene regulatory circuits. When transferred to organisms that lack c-di-GMP (e.g., mammalian and some bacterial cells), these circuits are expected to operate orthogonally to the native systems. Because mammals are the primary target for such systems, c-di-GMP synthesis is controlled by the bacteriophytochrome photoreceptor that senses far-red/near-infrared light. Such light penetrates much deeper into mammalian tissues than visible light.

Only time will tell whether or not bacteriophytochrome-based systems can be successfully adapted to control cellular processes in live mammals. The cyanobaterial or plant PHYs that absorb in the red/far-red spectrum (explored in this issue by the Tucker, Tabor, and Webber groups) may prove more robust, in spite of the complexity associated with the chromophore synthesis for these photoreceptors. What is clear is that moving into mammals remains a formidable challenge for the field. By overcoming this challenge, we could greatly improve our understanding of mammalian development and disease and likely contribute to disease treatments. The spectacular success of optogenetics in neurobiology is an example to emulate. Other frontiers in synthetic photobiology include optimization and standardization of photosensory modules to facilitate on-demand engineering of photoactive proteins with desired functions. Standardization of the parts for light-responsive gene circuits is another area of improvement. These and other challenges are expected to continue attracting bright minds to synthetic photobiology and ensure the bright future of this field.

Mark Gomelsky*

Department of Molecular Biology, University of Wyoming, Laramie, Wyoming 82071, United States

AUTHOR INFORMATION

Corresponding Author

*Phone: 1-307-766-3522. E-mail: gomelsky@uwyo.edu.

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.