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Editorial overview: Omics: The maturation of chemical biology

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Alan Saghatelian performed his graduate and postdoctoral research at the Scripps Research Institute. And in 2006 he began his independent career as an assistant professor in the Department of Chemistry and Chemical Biology at Harvard University. His research program at Harvard focused on the discovery and characterization of novel lipids and peptides using biological mass spectrometry. In 2014, Prof. Saghatelian moved to the Salk Institute, where he is currently holds the Dr. Frederik Paulsen Chair.

Daniel K Nomura obtained his PhD from the University of California, Berkeley and was a postdoctoral fellow at The Scripps Research Institute. In 2011, he began his independent career as an assistant professor in the Department of Nutritional Sciences and Toxicology at the University of California, Berkeley. His research program is focused on using chemoproteomic and metabolomic platforms to map metabolic drivers of human diseases. He is now an associate professor in the Departments of Nutritional Sciences and Toxicology and Chemistry at UC Berkeley.

Eranthie Weerapena obtained her PhD from the Massachusetts Institute of Technology and pursued postdoctoral studies at The Scripps Research Institute. She began her independent career in 2010 as an assistant professor in the Department of Chemistry at Boston College. Her research program is focused on using chemical-proteomic methods to investigate cysteine-mediated protein activities and the regulation of these proteins under conditions of oxidative stress.

The term chemical biology was coined to describe a scientific approach that utilized small molecule organic chemicals to study biology. At first, these molecules were bioactive natural products and some drugs with no clear mechanism of action. By identifying the protein targets of small molecules, chemical biology characterized proteins with important functions in varied biological processes.

The success of these original studies led to efforts to democratize chemical biology through combinatorial chemistry and high-throughput screening so that small molecule probes of any biological process could be found. The ability to discover small-molecule probes for any biological process allowed researchers to tap into the power of chemical biology to elucidate biological mechanisms without needing a known natural product. These efforts were successful, and numerous small-molecule probes for a variety of biological processes were found in this way. Furthermore, the promise of being able to translate small-molecule probes into a clinical candidate expanded efforts in this area.

To most biologists, the term chemical biology is limited to small molecule screening or medicinal chemistry, but the reality is that chemical biology has grown from an approach to an emerging field that utilizes many aspects of chemistry to investigate biology. This maturation is reflected in this issue of Current Opinion in Chemical Biology, which highlights the diversity of science taking place at the interface of chemistry, biology, and medicine.

The contribution by Koehler describes the application of the newest approaches in chemical screening to identify specific probes of proteins in the complex milieu of a cell or organism. In some cases, the focus shifts from all proteins to a specific class of proteins, usually proteins that are fundamentally important in biology and disease. An example of this is the kinase family of proteins, which modulate all signal transduction and are therefore excellent targets to probe biological mechanisms, and develop new drugs. The review by Arkin highlights how the realization that some kinases obtain mutations that introduce a cysteine can be used to chemoselectively target these enzymes. In doing so, basic principles in chemical reactivity are being exploited to develop new medicines.

A major challenge in chemical biology has been the identification of protein target(s) of chemicals in complex mixtures, like those found in cells or tissues. The contribution by Nomura explains the latest methods in chemoproteomics that combine the latest methods in small-molecule probe design (organic chemistry) with proteomics (analytical) chemistry to rapidly

and thoroughly identify protein targets of specific small molecules across the entire proteome.

Chemical biologists have also developed important methods to determine interactions between natural molecules in cells and tissues. Wang details the use of chemoproteomics to determine cellular proteins that have undergone electrophilic lipidation, which occurs due to oxidative stress and breakdown of lipids. This approach will help define the key steps involved in the biology of oxidative stress, and may eventually lead to new insights on how to inhibit damaging pathways.

Of course, nature uses small molecule modifications of proteins in the form of post-translational modifications (PTMs) to carry information within the cell. The chemoproteomics methods developed for finding targets of synthetic and natural small molecules can also be extended to include key PTMs. Hang's contribution highlights the modification of proteins with fatty acids. Thompson's review discusses the detection of a PTM of growing importance in biology and disease, protein citrullination, through the development of a novel chemoproteomics strategy. This method leads to greater insight into this important PTM than was available before. More generally, these two examples highlight the use of chemical probes for discovering and studying key PTMs, increasing knowledge about the role of this modification in biology.

One advantage of using small-molecule probes is that variants can be readily synthesized as chemical probes. However, the situation is more challenging when dealing with biopolymers. As a result, different technologies have been developed for elucidating chemical interactions between biopolymers. In this issue, Zhu describes the use of protein microarray technology to probe biopolymer interactions, which can explain key interactions and networks found within cells. Protein microarrays are high-throughput and flexible and enable screening of different biopolymers (e.g. protein–protein and protein–DNA) in a rapid manner. This approach is particularly valuable given the importance of such interactions in building cellular signaling networks.

Just as important as protein modification, is the modification of DNA and RNA, referred to as epigenetics. He provides a terrific review of the impact of the biology and chemical biology of RNA epigenetics, which include the development of new chemical methods for the identification of RNA modifications. Once identified, the role of these modifications in the regulation of RNA structure and function can be better understood, underscoring the importance of these approaches to furthering knowledge of RNA biology.

To connect all of these pathways to underlying changes in the cell, Rabinowitz describes the role of metabolism in controlling DNA and protein methylation and acetylation, respectively. Intriguingly, this contribution defines a mechanism where changes in the cellular concentrations of metabolites can contribute to gene regulation through changes in DNA and histone biochemical modification. This paradigm is different from the classical models of gene regulation that require activation of a transcription factor, or receptor, to trigger changes in transcription. Moreover, 'biochemical' signaling between metabolites and biopolymers might prove to be more general, and similar strategies might be uncovered in other cellular pathways as well.

Together these examples highlight the use of chemistry in the form of chemical synthesis and analytical chemistry (proteomics and metabolomics) to make fundamental contributions to our understanding of biology. It is no surprise that chemical biologists have also played a central role in the development of analytical methods to interrogate biological systems. For example, Heck details the combination of next-generation sequencing and proteomics to identify new proteins and provide higher confidence in protein assignments. Patti describes the state of the art in metabolomics analysis to define changes in the cellular metabolome. Lastly, Northen describes the newest methods to collect metabolomics data, which will make these metabolomics methods and their data more available in the future.

Chemical biology started as an approach that relied on organic chemistry to make biologically active small molecules that could be used to probe biology and has grown to a field that is interested in the molecular underpinnings of biology. The reviews presented here highlight the breadth of chemical biology while also emphasizing that these methods all share the use of chemistry and chemical methods to investigate biology. In this way, chemical biology is inclusive of all chemistry as it is applied to biology. Chemical biology will continue to grow as more chemists are drawn towards the most complex chemistry problem of all: understanding how a combination of inanimate chemicals can give rise to life.