

Networking chemical biology

Closer interactions between chemical biology and systems biology have the potential to provide a more integrated understanding of how biology functions.

Chemical biology and systems biology have generated tremendous interest since their emergence as distinct fields over the last two decades. Beyond this similar history, systems biologists and chemical biologists share many methods and goals. For instance, both fields place an emphasis on high-throughput methodologies and on gaining a quantitative and dynamic understanding of biological processes. Additionally, bringing together scientists from diverse disciplines has been a catalyst of innovation in both areas. Despite these commonalities, until recently systems biology and chemical biology have largely evolved separately. As the fields increasingly intersect, there is an exciting opportunity to open up new research directions in both fields and to provide a more complete picture of how biological systems operate. In this issue we explore the emerging frontier of 'chemical systems biology'.

Chemical biology approaches have already provided a foundation for many current methods in 'omic' analysis, from phosphoprotein capture for mass spectrometry-based proteomics to functional glycomics. Scientists are now looking to investigate more labile and chemically complicated post-translational modifications and to gain finer levels of information about the activities and localizations of biomolecules. With these more challenging profiling targets, increasingly sophisticated chemical biology methods are likely to contribute to the next generation of omic approaches (p. 639). As a recent example, two new methods for profiling caspase substrates have more than doubled the known components of the apoptotic degradome (p. 651).

Chemical probes also have much to add to the systems biology toolbox. Perturbing a biological system and measuring the response is an important approach in systems analysis, and small molecules, as an acute and dose-controllable perturbation, should be ideal for many systems biology applications. However, the lack of well-characterized, specific chemical modulators that span the breadth of biology has limited their use so far. As chemical biologists develop robust chemical probes for a wider array of biological components and processes, small molecules are poised to play an important role in understanding network structure (p. 674) and dynamics (p. 643).

Beyond tools such as those described above, chemical biologists bring a molecular understanding of biological processes that is a critical foundation for efforts to decipher the mechanistic workings of biology. At the same time, incorporating the more integrated perspective and approaches of systems biology will open up new opportunities in chemical biology research.

Small molecules are notorious for interacting with multiple targets inside of cells and organisms. If uncharacterized, this promiscuity can limit the utility of chemical probes, not to mention the safety of drugs. Systems biology approaches may provide a framework for characterizing and visualizing the full complexity of interactions between small

molecules and biological systems. Such tools would enable an increasingly biologically relevant understanding of small-molecule action beyond a "one compound-one target" simplification (p. 635).

High-throughput methodologies are important components of both chemical biology and systems biology. In systems biology, large datasets that result from omic experiments are typically analyzed in their entirety and captured in publicly available databases. In contrast, in many cases high-throughput screening of chemical libraries results in scientists sifting through large collections of data to identify a few 'hits' to focus on in follow-up work. More routine database deposition of full screening datasets and increased integration of cheminformatic and computational systems biology tools would enable a more comprehensive use of chemical screening results.

In addition to offering new insights into biological systems, advances in chemical systems biology will have important applications in biotechnology and medicine. For example, knowledge of protein-protein interaction networks is already providing a foundation for synthetic biology advances, which should only continue with progress in more fully characterizing interactomes across a wider array of biological systems (p. 666). The robustness of biological networks, combined with the realization that many clinical drugs work by modulating multiple targets, suggests that developing more efficacious therapies may require combinations of drugs or single compounds with targeted polypharmacology. Achieving polypharmacology by design will require a new set of tools and skills that integrate pharmacology and network biology (p. 682). A report in this issue of a dual tyrosine kinase/lipid kinase-targeting small molecule provides a proof of concept for one approach to rational polypharmacology (p. 691 and p. 648).

Progress in chemical systems biology will benefit from increased opportunities for interactions between scientists from the different disciplines. A few recent conferences have focused on this interface, and some university departments have begun to juxtapose the two fields. For instance in 2006, the Department of Molecular Pharmacology at Stanford University changed its name to the Department of Chemical and Systems Biology "to reflect its increasing focus on the interrelated fields of chemical biology and systems biology" (<http://molepharm.stanford.edu/>). The enhanced opportunities for communication and collaborations that come from these interactions should further encourage advances in the field. Additionally, academic departments with this combined focus will provide the broad training necessary to produce the next generation of chemical systems biologists.

We hope this collection of articles provides a snapshot of the exciting interface between chemical biology and systems biology and stimulates the building of stronger networks between these fledgling fields. ■