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New technologies and their impact on 'omics' research

Editorial overview

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The use of the suffix 'ome' is defined in the Oxford English dictionary as 'being used in cellular and molecular biology to form nouns with the sense "'all constituents considered collectively"'. Interestingly, the use of the 'ome' suffix in biology dates back to the early 1900s when it was first used to describe a 'biome' and genome (although originally in German as genom). Over the past few decades, the use of the omics suffix has rapidly increased, due in a large part, to the rapid growth in technologies that allow global analysis of samples on a systems level. The familiarity of the 'omics' term also was rapidly advanced by the completion of the human genome in the early 2000s. Since that time, we have seen the term 'omics' move beyond use for genomics and proteomics and gain acceptance for a diverse array of systems biology applications. In this issue, we have assembled an 'omics' volume where we have selected reviews that cover the current and emerging fields that are being impacted by 'omics'-based approaches. We have specifically focused on relatively new 'omics' fields and ones in which chemical tools have been important or essential for the success of the method. In all cases, rapid technological advances have had a dramatic impact on how these 'omic' methods are performed.

It seems only appropriate to start the volume with a review on one of the most mature 'omics' fields, namely transcriptomics. The review by McGettigan, focuses on recent advances and applications for transcriptomics, specifically as the result of the rapidly declining cost of DNA sequencing. Some of the more exciting advances such as single cell transcriptomics, that have become possible as the result of technological advances, are discussed. The review also highlights some of the challenges that the field faces, with a specific focus on tools for data analysis of ever increasingly complex data sets.

The remainder of the volume focuses on 'omics' methods that are being applied to the study of protein modification and function. We begin our shift toward proteins with a series of reviews on post-translational modifications. It is becoming increasingly clear that neither the gene nor the primary amino acid sequence is sufficient to define the structure and function of a protein. In many cases, both co-translational and post-translational modifications are required to ensure the proper three-dimensional structure of the molecules through engagement with essential quality control systems. Biologically, post-translational modifications (PTMs) are a means of producing subsets of proteins that can diversify the structure, function or location of a molecule, thus multiplying the potential roles of a single gene product. Moreover, this diversity can be attained without recourse to genetic modification of the gene for the target protein.

The first set of PTM reviews focus on modifications in which a specific chemical entity is post-translationally added to proteins. One of the simplest

modifications is the addition of a single carbon methyl group. As outlined in the review by Afjehi-Sadat and Garcia, this modification can be added to a number of different amino acids in proteins, resulting in changes in overall protein function. In fact, methylation can serve as a switch to control important biological processes such as transcription, protein interaction, RNA editing and protein localization. Afjehi-Sadat and Garcia specifically focus on recent advances in mass spectrometry methods for 'omic' analysis of this PTM.

A similar type of protein PTM that is often used in cells to regulate protein function is the addition of lipid molecules such as palmitate. The addition of highly hydrophobic lipid tags is often used to induce localization of signaling molecules with cellular membranes or other proteins. In this volume, Hernandez *et al.*, outline recently developed methods for globally mapping palmitoylation events. This includes methods in which an analog of the natural palmitic acid is added to cells and used to metabolically label all palmitoylated proteins. Because the modified palmitate contains a latent tag, the resulting modified proteins can be isolated and identified by mass spectrometry. The review by Yount *et al.* builds on the discussion of these methods but also describes specific examples of how they can be used to study the role of palmitoylation in cellular immunity.

One of the most common post-translation modifications is glycosylation which takes place at various defined sites on proteins. This process is often essential for proper protein folding and trafficking. In addition, the presence of a glycan can be key for mediating interactions between proteins or between cells expressing glycoproteins on their cell surface. In the review by Zoldos *et al.*, the authors outline recent advances in glycomics methods that now allow comprehensive study of the repertoire of glycosylated proteins found in humans. The authors make the case that these recent advances in glycomics methods will be most beneficial when integrated with other 'omic' data sets such as genomic, lipidomics and epigenetic analysis. The review by Longwell and Dube also focuses on glycomics methods but discusses how these methods can be applied to decipher the bacterial 'glycocode'. Interestingly, many types of bacterial glycoproteins remain uncharacterized. Therefore, advances in our understanding of how bacteria use glycosylation will likely lead to the identification of much needed new targets for antibiotic development.

In addition to using PTMs as a way to positively mediate protein function (i.e. induce localization or facilitate folding), cells also have developed PTMs that induce destruction of a protein. All cells have machinery that controls the addition and removal of a small protein tag called ubiquitin. In most cases, attachment of a poly-ubiquitin chain to a protein induces association with the proteasome and subsequent degradation into peptide fragments. Thus, finding ways to globally map the dynamic process by which ubiqutin molecules are attached and removed from protein substrates is key to our understanding of many essential biological processes. The review by Sylvestersen *et al.* outlines recent advances in mass spectrometry methods that allow the composition of ubiquitin chains as well as exact sites of ubiquitin modifications on proteins to be assessed. The review also highlights the many biochemically distinct ways in which ubiquitin chains can be added to proteins, resulting in diverse biological outcomes. The related review by Kessler further builds on the discussion of methods for mapping ubiquitin composition and ubiquitinylation sites on proteins but goes on to discuss some of the more recent 'chemoproteomic' methods that have been applied to study the ubiquitin system. This includes the use of small molecules and chemical methods to isolate or inhibit regulators of the ubiquitinylation/de-ubiquitinylation process.

While the process of ubiquitinylation often results in the complete degradation and turnover of a protein, many types of proteolytic events are 'limited', resulting in the production of functionally important byproducts. Thus, 'omic' methods that allow specific limited proteolysis events to be globally mapped will help to shed light on pathways that are regulated by proteolysis. This will also help to identify important protease-regulated processes that could be therapeutically disrupted using protease inhibitors. Unfortunately, the process of selectively isolating newly formed N-termini from the sea of other N-terminal amines found in a cell is like looking for a needle in a haystack. The pair of reviews by Plasman *et al.* and Lange and Overall outline the very clever recent advances in methods that allow these specific N-termini to be identified.

Continuing with the theme of protein modification by proteolysis, we include a review by Lone *et al.* in which the focus is shifted from proteases to peptidases. Peptidases are enzymes that process small peptide substrates rather than proteins. There is a diverse array of bioactive peptides and many of these are produced by peptidases that act on larger peptide fragments. In this review, Lone *et al.* outline some of most recent advances in efforts to link up peptidases with specific, biologically important peptide substrates.

Many of the post-translational modifications to proteins outlined in the preceding chapters can also affect the way in which proteins interact with one another. Thus, new methods that allow specific protein-protein interactions to be analyzed on a global scale have great value to the 'omics' field and our understanding of protein networks. The review by Pham *et al.* outlines recent advances in the use of chemical tools that can be applied to 'interactome'

mapping. Specifically, the authors focus on methods that involve metabolic incorporation of chemical entities that induce crosslinks between proteins when they interact so that these interactions can be analyzed using proteomic methods.

In the final set of reviews we shift our attention to a subdiscipline of proteomics termed 'chemical proteomics'. This topic is of particular relevance for the chemical biology audience as it is centered on the use of small molecules to survey a specific subpopulation of a given proteome. Perhaps the most common type of chemical proteomic method involves using small molecule activity based probes (ABPs) that bind to target enzymes in an activity-dependent fashion. These probes therefore allow not only protein abundance to be monitored, but also more importantly, enzyme activity to be directly assessed. Since most enzymes are regulated by various post-translational control mechanisms, having tools that allow the activity of enzyme to be globally and dynamically monitored is extremely important. The review by Haedke *et al.* describes the makeup of a chemical probe and focuses on how selection of the reactive functional group controls the spectrum of proteins that are modified. The related review by Rudolf *et al.* also discusses the composition of chemical probes but focuses on how to control the ligation and then subsequent cleavage of the probe to release the protein targets of interest.

Following from the reviews about small molecule probes is a review by Lee and Bogyo which outlines some of the recent advances in methods that can be used to identify targets of small molecules. There has been a steady increase in the use of diverse small molecules to perturb biological processes. However, the process of identifying the relevant protein targets has remained difficult. This review highlights how recent advances in 'omics' technologies have helped to improve our ability to define the mechanism of action of small molecules that have specific effects in biological systems.

Although we have presented a diverse collection of 'omics' methods, we hope that you will find that there are important connections to be made between each contribution. Specifically, you should notice the common theme of the importance of new technologies as well as the increasing relevance of small molecules and chemical methods in 'omic' strategies. We believe that this set of reviews will help to give you a sense of the exciting advances in this continually growing area of research.