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Quantitative proteomics of model organisms

Yuehan Feng[1,2], Valentina Cappelletti[2] and Paola Picotti

Abstract

Surveying of entire proteomes is primarily enabled by mass spectrometry-based proteomics technologies. Advances in the last decade have significantly reduced the effort involved in global or targeted quantitative proteome analyses and have facilitated the collection of increasingly more comprehensive proteomics data for different species. Here we review how mass spectrometry-based tools enable mapping and quantitative profiling of proteomes and post-translational modifications from various model organisms. Further, we discuss recent proteomic approaches that enable exploration of the topological organization, dynamic turnover, structural features, and other properties of model organism proteomes beyond protein expression profiles.

Addresses

Institute of Molecular Systems Biology, Department of Biology, ETH Zurich (ETHZ), Zurich, Switzerland

Corresponding author: Picotti, Paola (picotti@imsb.biol.ethz.ch)

[1] Present address: Stanford Genome Technology Center, Stanford University, 3165 Porter Drive, Palo Alto, CA 94304, USA.[2] Equal contribution.

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Model organism, Shotgun proteomics, Targeted proteomics, Mass spectrometry, Posttranslational modification.

Introduction

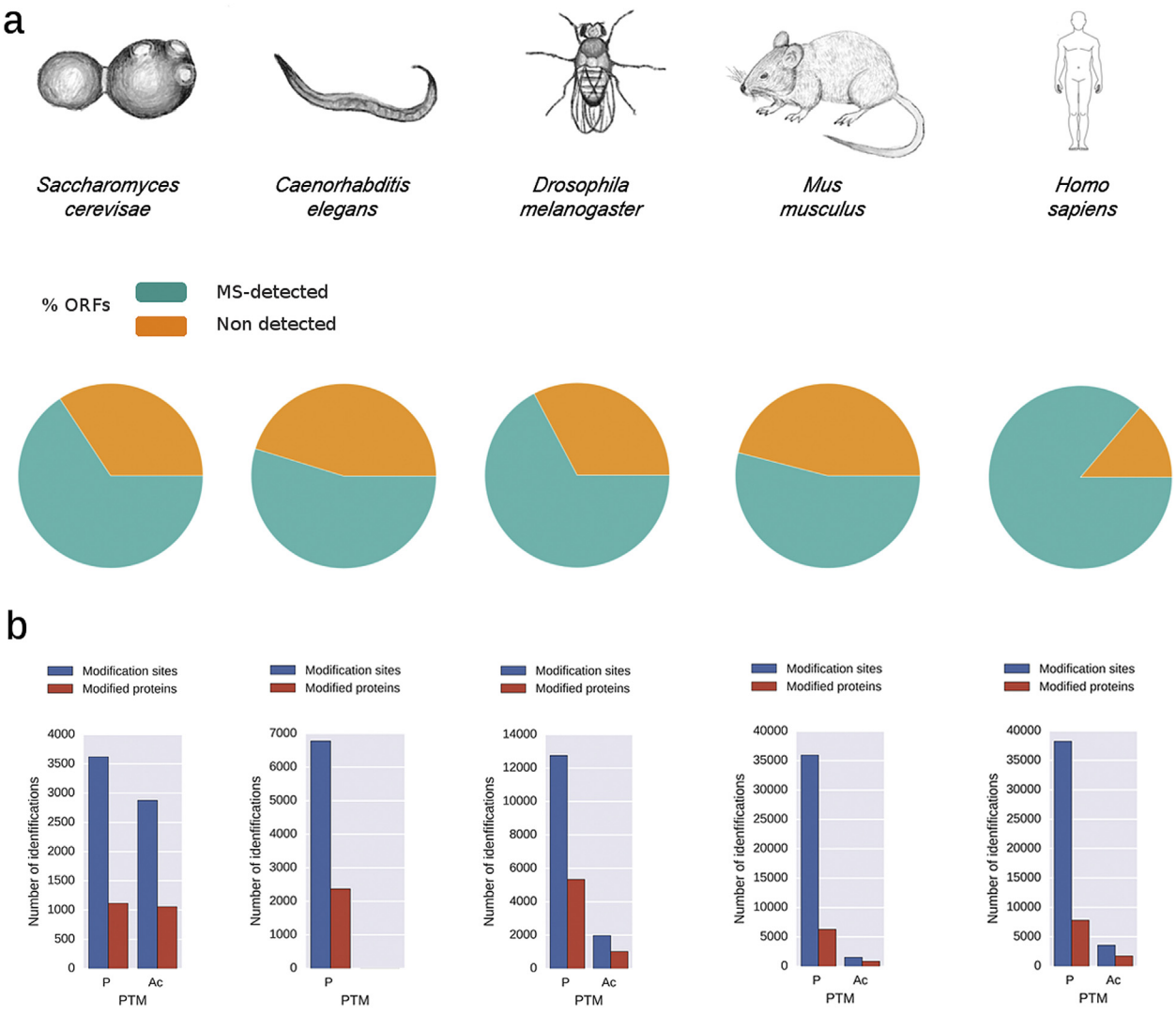
Advances in genomics and genetic engineering technologies in the last two decades have transformed model organisms from tools for study of conserved processes in biological sciences to general platforms that can be deployed to address the diversity and complexity of living species [1,2]. Whereas the genome mostly remains static over the lifespan of an organism, the proteome changes during development, in response to external stimuli, and due to countless molecular events that contribute to the organism's proper functioning. Further, compared to transcriptome-level data, proteomic readouts account for post-transcriptional, translational and post-translational effects on protein levels, structure, and function.

Thanks to recent developments in mass spectrometry (MS), MS-based proteomics technologies can be used to profile the vast majority of a proteome in a high-throughput manner [3]. It should be noted that the depth of these analyses still trails that of genome or transcriptome studies due to the striking dynamic range in a complex proteome and to the lack of a PCR-like procedure to amplify low-abundance protein species. Nevertheless, proteome-wide analyses of protein expression and post-translational modifications (PTMs) have supported classical and systems biology studies and have enabled a variety of biological questions to be addressed [4].

Two major bottom-up proteomics strategies have been described: unbiased and targeted proteomic analyses. In common between the two approaches is the conversion of proteins into peptides and peptide separation by liquid chromatography. Unbiased analyses attempt the simultaneous interrogation of an entire proteome and are traditionally based on automated peptide sequencing by LC-MS/MS followed by peptide identification from MS spectra by database searching (shotgun proteomics). Conversely, targeted proteomic analyses rely on the targeted measurement (as in the case of selected reaction monitoring (SRM) MS) or targeted data extraction (as in the case of data-independent (DIA) analyses) of MS signals from peptides mapping to predefined sets of proteins of interest. The two approaches have become less distinct with the recent development of repositories of targeted proteomic assays for the interrogation of complete proteomes or the targeted extraction of data for every putative protein in a sample [5–7].

In quantitative proteomic analyses using any of the aforementioned MS approaches, detection of proteins is complemented with information on protein abundance differences across differently perturbed samples. The choice of approach to be used is typically dictated by the biological question to be addressed and by specific performance features of the techniques. Shotgun proteomics approaches are ideally suited for discovery-driven experiments as they provide a comprehensive survey of the proteome but have limited quantification capabilities across large sample sets due to issues such as semi-stochastic proteome sampling. Targeted proteomics based on SRM is the gold-standard for the quantification of specific sets of proteins across multiple samples at high precision and sensitivity but suffers from a low degree of multiplexing [8]. The recently developed DIA approaches aim to overcome the shortcomings of the other techniques by enabling precise

Figure 1



Overview of proteome and PTMs mapping efforts in five organisms. (a) Proteome coverage across the different species. Numbers of ORFs were retrieved from the Uniprot database. The highest human proteome coverage to date has been achieved by the pooling of protein identifications from various tissues and cell types [44]. (b) Analyses of the most commonly surveyed post-translational modifications: protein phosphorylation and acetylation. Numbers of identified proteins and phosphorylation and acetylation sites are from the following studies: *S. cerevisiae* [14,19,20]; *C. elegans* [28,30]; *D. melanogaster* [34,36,79]; *M. musculus* [38,80]; and *H. sapiens* [44,46,50]. ORF, open reading frame; P, phosphorylation; Ac, acetylation.

quantitation on a proteome-wide scale and are now starting to gain momentum [9].

In this short review, we discuss how quantitative proteomics has advanced and shaped studies on model organisms by the in-depth characterization of their proteomes. Furthermore, we highlight recent methodological progress enabling dissection of model organism proteomes from a variety of biologically relevant perspectives.

Toward complete proteome maps of model organisms

Quantitative analyses of expressed proteomes have been enabled by technological progress in MS instrumentation that have resulted in decreases in analysis time, reduced sample fractionation, and increasing depth of the proteome profiling [4]. Compared to protein expression, PTMs have a more transient nature, allowing a cell to rapidly and reversibly respond to intracellular and extracellular stimuli. Therefore, the PTM map is more conditional and volatile than the proteome map. In addition, PTM profiling necessitates targeted enrichment procedures that depend on the modification of interest [10]. In the following sections, we provide an overview of recent advances in proteome-wide quantitative investigations of proteins and PTMs from four eukaryotic model organisms routinely surveyed in systems biology research: yeast (*Saccharomyces cerevisiae*), worm (*Caenorhabditis elegans*), fly (*Drosophila*