From AI-driven synthetic biology to prediction of molecular phenotypes

1.3
Characterizing proteome regulation and cell signaling by nascent proteomics: an aha-experience

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Proteomics has proven a powerful approach to investigate alterations in proteome composition that are caused by cellular perturbations, and to understand regulation of the underlying biological processes. In a common approach this is approached by determining changes in overall protein expression levels, however this lacks sensitivity to detect events with a small effect size, or that occur at a rapid time scale. Here, we show that the proteome-wide analysis of newly synthesized proteins provides a powerful measure to investigate proteome response, providing more direct insight in the biological processes that are induced by a specific perturbation. In particular, we have established a methodology that combines concomitant pulse-labeling of cells with azido-homoalanine (AHA) and SILAC amino acids, to allow capture of nascent proteins by click-chemistry, and identification and quantification by subsequent mass spectrometry. We have applied this methodology to investigate prime and secondary effects of the oncogene Myc, occurring within hours upon targeted degradation of Myc. In addition, we have determined the proteome effects of oncogenic mutations in EGFR, KRAS, BRAF, and PI3K, and of drugs that inhibit MAPK and PI3K-AKT-mTOR signaling in various ways, obtaining a large and dynamic data set that we integrated to infer the function and crosstalk of oncogenic drivers and pathways. Furthermore, the method can be tuned to specifically investigate protein degradation, which we have applied to understand turnover of ribosome subunits upon translational stress. Finally, to increase the throughput of this approach, we have generated magnetic sepharose beads that allow multiplexed and standardized enrichment of newly synthesized proteins on a robotic platform. Collectively, this provides a powerful workflow to systematically investigate proteome adaptation across multiple conditions.

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1.4
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The quantitative understanding of central molecular dogma processes will open the opportunity to design socioeconomically important gene products, ultimately developing highly efficient therapies and engineering microorganisms that can shift us from a fossil to a bio-based society. Towards this, we couple computer and biological sciences by bringing state-of-the-art machine learning (ML) into systems and synthetic biology frameworks. Furthermore, to transform human biology into a predictive discipline of phenotypes, we are adapting proteomics for the large scale collection of data to get insights into human populations. I will show our recent work on proteomic responses to nutritional interventions and drug treatments and discuss recent developments in population-scale studies.

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