Proteome integral solubility alteration assay sensitivity.

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Abstract

In cell lysates, living cells, and organisms, a variety of substances, including medicines and monomolecular stimuli, change the physicochemical properties of proteins. These changes can be detected by adjusting the application of a component that affects stability and solubility, such as increased temperature. Drug concentration or agent intensity/concentration can be employed as a second dimension of variation. The Proteome Integral Solubility Alteration (PISA) assay significantly increases the analysis throughput for an unlimited number of factor variation points as compared to conventional methods, which fit curves to protein solubility data collected at various temperatures and drug doses. The PISA technique will likely be widely used in chemical biology and drug development. The idea behind thermal proteome profiling (TPP) is that proteins denature and become insoluble when heated. When proteins interact with tiny molecules (such medicines or metabolites), nucleic acids, or other proteins, as well as when they undergo post-translational modifications, their thermal stability may change. TPP tracks the melting profile of hundreds of expressed proteins using multiplexed quantitative mass spectrometry-based proteomics. It's significant that this method can be applied in vitro, in situ, or in vivo. It has been successfully used to investigate protein-protein and protein-metabolite interactions as well as drug targets and off targets. In order to research fundamental biological processes and their underlying mechanisms, TPP offers a unique perspective on protein state and interactions in their natural context and at a proteome-wide level.

Keywords: Chemical biology, Drug development, Mass spectrometry, Protein stability, Proteomics, Tandem mass tag, Target deconvolution.

Introduction

By enabling a comprehensive view of the proteome in its natural setting, mass spectrometry-based proteomics have revolutionised the study of protein biology. For instance, the study of protein abundances, turnover, localisation, or post-translational modifications falls under this category. Proteomics techniques have recently been used to investigate and study the physicochemical characteristics of proteins on a systemic level [1]. Additionally, it has been demonstrated that proteins change their heat stability after being phosphorylated, shedding light on TPP's capacity to record intracellular signalling. For instance, dasatinib's suppression of the BCR-ABL tyrosine kinase alters the thermal stability of this signalling pathway's proteins, including CRKL. Recent research has showed that phosphorylated proteins can exhibit a different melting profile from their non-phosphorylated counterparts. Analogous to how a protein's redox state can affect its melting behaviour, we predict that similar stabilising activities for more post-translational modification types are still to be discovered [2]. Thermal proteome profiling is a part of a larger class of recently developed tools based on changes in proteome stability, which also includes other approaches to study heat-induced protein aggregation as well as approaches based on different ideas like differential proteolytic access upon ligand binding, changes in protein interactions or conformation, known as limited proteolysis, or the inference of protein stability from rates of oxidation. To now, TPP is the only technique that enables this kind of research in living cells. This tutorial focuses on the TPP experimental setup and its most recent advancements, various data processing techniques, the methodology's present limits, and potential future advancements [3].

For the purpose of describing how the samples are multiplexed for mass spectrometry analysis, some TPP combinations have been given unique names. The original TPP technique is now commonly referred to as temperature range TPP (TPP-TR) to denote that a range of temperatures is multiplexed inside the same mass spectrometry experiment. This information is displayed as melting profiles for each protein during data processing. These kinds of studies can be utilised to contrast various situations (e.g., drug vs. vehicle, or gene knock-out vs. wild type). Since the various circumstances are examined in many mass spectrometry runs, it is often less sensitive than the two-dimensional technique (2D-TPP). Thermal proximity

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coaggregation (TPCA), which states that proteins that interact often have similar melting curves, is based on TPP-TR [4].

The in vivo environment of cells can also be preserved using intact tissues. These can either be gathered or subjected to a disturbance, or they can be gathered after the perturbation has been applied to the entire organism and subjected to a thorough analysis. This enables the gathering of several tissues from a single animal, giving rise to a comprehensive understanding of the disturbance in the body. Blood and other biological fluids may also be obtained. These might provide novel treatment monitoring techniques or illness biomarkers in the future [5].

Conclusion

In conclusion, TPP is a recently created technique that offers proteome-wide details on protein states and interactions in vitro, in situ, and in vivo. This opens up fresh perspectives on fundamental biological processes and enables the investigation of the mechanisms underlying a wide range of disturbances.

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