Proteomics Can Complement Genomics to Identify New Regulatory Pathways, Biomarkers, and Drug Targets, According to Expert Panel

The study of genomics in combination with proteomics, known as proteogenomics, is helping researchers better understand genetic contributions to protein levels and activity and to identify new regulatory pathways and proteins that are causal in disease. These findings may provide prognostic biomarkers and robust targets for drug development, according to a panel of proteogenomics experts.

In February, the panel discussed why researchers should adopt proteogenomic methods, how these methods are currently being applied, challenges in the field, and potential future directions during a GenomeWeb Virtual Roundtable, sponsored by Olink.

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Speakers at the GenomeWeb Virtual Rountdable, "Advances in Proteogenomics: How Proteomics Can Complement Genomic Analyses," sponsored by Olink

Why Researchers Should Adopt Proteogenomics

The panelists' consensus was that, while proteomics and genomics offer numerous advantages as standalone disciplines, researchers get the best of both worlds when the two fields of study are combined. Claudia Langenberg, professor of computational medicine at the Berlin Institute of Health at Charite, argued that, while proteins are very good at reflecting health and disease states and are therefore very good at disease prediction and prognosis, fully understanding disease mechanisms requires the integration of genetics and proteomics. This integration allows researchers to identify the genetic determinants that underlie protein levels and activity, circumventing the influence that disease may have on protein levels as they are measured at any given point in the population.

Michael Snyder, professor of genetics at Stanford University, added that the genome is predictive, at best, and that measuring RNA levels — which frequently do not correlate with protein levels — cannot provide a complete picture of cell state and activity. He contended

that proteins provide a much closer readout to phenotypes and offer particularly powerful biomarkers for disease states.

Janne Lehtiö, professor of medical proteomics at Karolinska Institute and director of the Clinical Proteomics Mass Spectrometry Facility at SciLife Lab, further suggested that marrying proteomics with genomics could open new possibilities to examine the influence of sequence variants on protein levels and how this impacts phenotypic regulation.

How Proteogenomics is Currently Being Applied

Langenberg said that one of the most fruitful benefits of proteogenomic methods for her was that they enable not only the understanding of how epigenetic signals for the protein may be associated with a specific disease but how this may be shared with other, seemingly unrelated, diseases. These findings can lead to a totally new understanding of which mechanisms connect these different diseases, and she suggested that this may enable a more gene-centric definition of disease in the future. Langenberg went on to describe how she and colleagues can apply proteogenomics agnostically across all diseases that have been studied genetically without any prespecified hypotheses. She stated that this approach of using genetically anchored evidence to integrate different studies and different data types has delivered across the board of complex diseases, from cancer to infectious diseases such as COVID-19.

Mass Spectrometry Versus Affinity-Based Proteomics

Untargeted, mass spectrometry (MS)-based proteomics and targeted, affinity-based methods can complement each other, said Lethiö. High-throughput, affinity-based plasma proteomics can be powerful when combined with genotypic and other types of environmental data, he said. MS data can provide very good molecular phenotype readout, especially with tissue- or cell-based proteomics and the ability to look at protein variants, he explained. Langenberg added that it is remarkable that researchers are beginning to be able to screen so broadly and can therefore understand the value of proteins that they were previously unable to measure. However, she cautioned that downscaling and validating discovery-scale assays for translation into clinical utility remains a challenge.

Karin Rodland, affiliate professor of cell, developmental, and cancer biology at Oregon Health and Science University and laboratory fellow at Pacific Northwest National Laboratory, also agreed that affinity-based proteomics can be a valuable complement to MS, especially when looking at the low abundance proteome as part of the biological spectrum. As an example, she explained that she would not use MS to measure cytokines in plasma, but would rather use an affinity-based proteomics technology because they can be more reproducible in that low-abundance protein range.

Future Developments

A future direction for the field will be integrating additional omics data, said Snyder, citing an example of studies on the effects of dietary fiber on reducing cholesterol levels in which a combination of proteomics and metabolomics provided complementary signatures that enabled the key mechanistic role of bile acids in the fiber/cholesterol relationship to be uncovered. These details would not have been discovered using only one omics approach, said Snyder, predicting that such combinations of technologies will become standard practice in future studies.

Langenberg expressed her excitement at the trend for large-scale biobank initiatives facilitating higher-powered studies with data available to all, which will enable better mechanistic insights and enhance the ability to predict a range of different diseases that are currently poorly identified. She concluded, “Patient-based studies that can look at prognostic stratification and differences in prognosis [through both single-cell and blood-based] biomarker studies is a huge area that’s been largely untapped.”

Lehtiö agreed that the most promising future developments are likely to focus on clinical applications. “We are very interested in using proteogenomics in clinical trials and incorporating the molecular phenotype with genotype and clinical phenotype. That’s very important,” he said. He also highlighted the importance of proteogenomics in the field of cancer immunotherapy. “The whole immune system with all its mediators, soluble mediators, and receptors, is covered by proteomics and proteome. So, we really need to look at that in order to understand the immune evasion mechanisms and the early responses,” Lehtiö concluded. “Proteogenomics is going to be very valuable in all aspects: in diagnostics, in stratification, and prognostics, but, very importantly, in precision medicine and treatment response.”

The entire Virtual Roundtable can be viewed on-demand

Watch the webinar

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