Proteoform Analysis to Fulfill Unmet Clinical Needs and Reach Global Standardization of Protein Measurands in Clinical Chemistry Proteomics

Yuri E.M. van der Burgt, PhD[a,b,*], Christa M. Cobbaert, PhD[a]

KEYWORDS

• Proteomics • Mass spectrometry • Clinical chemistry proteomics • Measurand • Protein quantification • Proteoforms • Protein glycosylation

KEY POINTS

- Biomarkers play a crucial role in the pursuit of individualized patient treatment.
- Although genomic and transcriptomic analyses are of great value in the clinic, the complexity of the human body largely arises from variations in protein identities and quantities.
- Large-scale exploratory efforts have been applied on retrospective studies of (large) clinical cohorts of body fluids, such as plasma or serum samples, searching for novel biomarkers.

INTRODUCTION

Protein Biomarkers in Precision Medicine

In the pursuit of individualized patient treatment, biomarkers play a crucial role. Although genomic and transcriptomic analyses are of great value in the clinic, the complexity of the human body largely arises from variations in protein identities and quantities. In basic research, mass spectrometry (MS)–based proteomics has greatly contributed to an understanding of cellular functions at a molecular level.[1–3] Also,

[a] Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center (LUMC), PO Box 9600, Leiden 2300 RC, The Netherlands; [b] Center for Proteomics and Metabolomics, Leiden University Medical Center (LUMC), PO Box 9600, Leiden 2300 RC, The Netherlands

* Corresponding author. Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center (LUMC), PO Box 9600, Leiden 2300 RC, The Netherlands.
E-mail address: y.e.m.van_der_burgt@lumc.nl

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large-scale exploratory efforts have been applied on retrospective studies of (large) clinical cohorts of body fluids, such as plasma or serum samples, searching for novel biomarkers. Hitherto the number of new protein markers that made it from MS-based proteomics into the clinic is very limited.[4] Rather than having a technological origin, key reasons for this translation lag are the use of invalid samples, lack of thoughtful study designs, silo thinking of the stakeholders involved, and lack of appropriate test evaluation and adequate test standardization.[5] In clinical laboratories, proteins in body fluids are routinely tested for diagnostic and prognostic purposes as well as for therapy monitoring. It is, however, widely acknowledged that there is room for improvement with regard to sensitivity and specificity levels of current medical tests.[6] Moreover, clinically effective disease-specific tests that support diagnoses at an early and curable stage are still lacking for a wide variety of diseases. Aiming and searching for novel (protein) biomarkers should start by defining specific unmet clinical needs with the clinicians according to the test evaluation checklist.[5,7] Interestingly, post-translational modifications (PTMs) on proteins have often not been taken into account because of technical challenges and the increased complexity of the resulting data. PTMs on *existing* protein biomarkers provide an additional structural layer to quantitative levels of individual proteins with potential for patient stratification. Here, the often ignored presence of PTMs in protein tests and their implication for clinical chemistry proteomics (CCPs) are discussed.

What Is the Proteoform Hypothesis?

Comprehensive proteome information contributes to a systems-level understanding of human biology and, thus, disease.[3,8] Recently, interest in protein PTMs with regard to biological and clinical relevance has emerged as an additional layer in proteomics and has been coined as proteoform analysis.[9,10] The term *proteoform* was proposed in 2012 "to designate all of the different molecular forms in which the protein product of a single gene can be found"[11] and was swiftly adapted by the proteomics community. Although protein isoforms and PTMs are long known from gel electrophoresis and chromatography, in the early days of proteomics identifications (IDs) were based on so-called peptide (mass) fingerprints with the aim to determine *any* protein product from a single gene (and not *each*). An inherent effect was that the focus switched to the number of protein IDs and that isoforms were not considered anymore.[12] Since the beginning of this century, with the availability of the human genome, MS-based peptide sequencing has been optimized and turned into the method of choice for bottom-up proteomics (ie, identification of proteotypic peptides after digestion with a protease). Instrument development benefitted from the large growth in MS proteomics applications and was further developed with regard to speed and user friendliness. Moreover, these innovations led to ultrahigh-resolution platforms, such as orbitraps and Fourier ion cyclotron resonance mass spectrometers, that provide improved mass precision and accuracy and consequently yield more confident IDs.[13] Furthermore, these high-end platforms allow for a mass measurement of proteins in their intact form and offer a wide range of fragmentation techniques. So-called top-down proteomics studies have converged into a renewed interest in protein isoforms (ie, proteoforms) and have opened an exciting field within clinical MS.[10] Proteoforms arise from a single gene from changes due to genetic variations, alternatively spliced RNA transcripts, and PTMs (**Fig. 1**). An example of the last involves histone modifications that in a biological context are referred to as epiproteomic signatures.[14,15] Note that structurally related protein forms from different genes are not grouped together to ensure that the proteoform terminology remains compatible with a gene-centric approach.[16]

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