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Commentary

Protein biomarker discovery is still relevant and has entered a new phase

Yuri E.M. van der Burgt

Center for Proteomics and Metabolomics & Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, The Netherlands

Many of us have seen protein biomarker discovery studies that could not be replicated, and as a consequence have at least become sceptical about this topic or have even completely lost interest. Nevertheless, from the point-of-view of a patient, the urgent need for new and additional biomarkers remains. Clinical assays that are routinely performed to determine biomolecule concentrations in body fluids for prognosis, diagnosis and monitoring of certain diseases leave room for improvement with regard to both assay performance and statistical sensitivity and specificity. Furthermore, test standardisation is often lacking as a result of an undefined (uncharacterised) analyte. In a joint effort clinicians and researchers have been searching for protein markers since the early days of mass spectrometry(MS)-based proteomics. Exploratory case-control studies have been applied to retrospective clinical sample cohorts (plasma, serum, urine) resulting in a plethora of candidates. However, the number of protein markers that have made it into the clinic remains very limited [1]. Technical imprecision and the high complexity of the applied MS-based strategies were initially held responsible for this translation lag, but it has become apparent that primarily a (too) low number of samples, the inclusion of invalid specimens, and the lack of a thoughtful study design and standard protocols have hampered successful biomarker development. In the meantime, MS-technology has matured and enabled establishment of robust platforms that are suitable for quantitative biomolecule measurements in discovery studies [2]. By providing a bridge between basic discovery and clinical verification, these platforms allow the field of proteomics to enter a next phase of MS applications.

State-of-the-art mass spectrometric proteome evaluation for biomarker discovery purposes is demonstrated in a recent *EBioMedicine* study by Zhou and co-workers, in which cancer tissue material from pancreatic cancer patients was compared to pancreas tissue from healthy individuals [3]. Their resulting list of up- and downregulated proteins was used as input for a targeted MS-method (parallel reaction monitoring) and converged into the identification of brain acid soluble protein 1 (BASP1) as a candidate marker. Immunohistochemistry was applied for further validation using a biobank of tissue microarrays and identified BASP1 as a prognostic marker for pancreatic cancer. With this approach the authors present a prime example of the technical feasibility of MS-based protein biomarker discovery including validation with an orthogonal method. Clearly, additional development is needed to evaluate the performance of this marker when aiming for future implementation as a clinical test. Furthermore, with regard to discoveries in cancer tissues and anticipated translation of oncomarkers, it should be kept in mind that tumours exhibit a heterogeneous character due the various cell types within their microenvironment, and that clonal evolution can lead to various cellular subpopulations.

Single biomarkers are an attractive starting point due to their straightforward cut-off values. Although a single concentration may seem unambiguous, a multimarker readout is a more accurate description of an individual's disease state and potentially provides a tool for personalised medicine. Currently, the creation of such multimarker panels is being pursued in different ways. The first one is a multiprotein approach that reports a proteotype, which can be obtained from multiplexed MS measurements or alternative strategies based on antibodies or aptamers. In the second approach, data is combined from different -omics technologies, with proteogenomics as a growing example [4]. A third way to obtain a multimarker panel involves mapping proteoforms of one specific protein that is measured in a clinical immunoassay-based test [5]. For example, detailed MS analysis of prostate-specific antigen revealed that this widely used prostate cancer marker actually consist of many isoforms with varying *N*-glycan structures. The measurement of specific glyco-proteoforms next to the overall protein content may render patient stratification feasible as an add-on metric. In conclusion, with lessons learned from the past and with proper cohorts and study design, MS-based -omics strategies continue to be key-players in the discovery of protein biomarkers and could finally provide the long awaited step forward into future diagnostics.

Author disclosure

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E-mail address: yubu@lumc.nl.

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