Title: A myopic perspective on the future of protein diagnostics

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A myopic perspective on the future of protein diagnostics

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Highlights

- Protein leakage markers can allow liquid biopsies that reveal disease processes
- Leakage markers promise diagnosis at early timepoints, but progress has been slow
- Tissue-specific proteins are of special interest as potential leakage markers
- High-quality affinity reagents remain a limiting factor for new assays
- Target recognition by two or more antibodies improves specificity
- Extensive biobanks of dried blood spot could serve to validate markers
- Greatly increased protein assay throughput can be foreseen in research

Abstract

Plasma proteome analyses of the future promise invaluable insights into states of health, not only by measuring proteins whose role it is to ensure blood homeostasis, but increasingly also as a window into the health of practically any tissue in the body via so-called leakage protein biomarkers. Realizing more of this vast potential will require progress along many lines. Here we discuss the main ones, such as optimal selection of target proteins, affinity reagents, immunoassay formats, samples, and applications, with a view from ongoing work in our laboratory.

Introduction

The concept of liquid biopsy attracts interest because of the potential to improve diagnostics by revealing diseases anywhere in the body via a simple blood sampling. Cells, DNA and RNA molecules from otherwise hard-to-reach tissues can all potentially be accessed via blood samples and applied to investigate organ damage, malignancy or fetal health [1,2]. Assays for protein in plasma often target proteins that exert their activities in blood, such as coagulation factors, lipoproteins or cytokines, but liquid biopsies in the form of protein assays that target leakage markers are also well established in routine healthcare. For example, elevated plasma levels of troponin, exclusively expressed in heart muscle cells, signals insults to myocardial tissue in a heart attack [3]. Similarly, S100B is a marker of brain damage [4], possibly superseded in diagnostic value by the more recently identified serum neurofilament light protein [5].

It is likely that many more proteins than currently appreciated could provide a basis for improved diagnostics via protein-based liquid biopsy testing, and exosomes, recognized via their membrane proteins, represent a related class of targets for testing [6-9]. Affinity-based protein detection seems to offer the greatest promise for highly sensitive protein assays, but despite rapidly increasing molecular insights, progress establishing new, clinically useful markers has been surprisingly slow [10,11]. It is worthwhile taking stock of what it may take to develop and apply new protein liquid biopsy markers on a larger scale, with the purpose of assessing states