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Review

Innovations in proteomic profiling of cancers: Alternative splice variants as a new class of cancer biomarker candidates and bridging of proteomics with structural biology☆,☆☆

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ABSTRACT

Alternative splicing allows a single gene to generate multiple RNA transcripts which can be translated into functionally diverse protein isoforms. Current knowledge of splicing is derived mainly from RNA transcripts, with very little known about the expression level, 3D structures, and functional differences of the proteins. Splicing is a remarkable phenomenon of molecular and biological evolution. Studies which simply report up-regulation or down-regulation of protein or mRNA expression are confounded by the effects of mixtures of these isoforms. Besides understanding the net biological effects of the mixtures, we may be able to develop biomarker tests based on the observable differential expression of particular splice variants or combinations of splice variants in specific disease states. Here we review our work on differential expression of splice variant proteins in cancers and the feasibility of integrating proteomic analysis with structure-based conformational predictions of the differences between such isoforms. This article is part of a Special Issue entitled: From Genome to Proteome: Open Innovations.

Contents

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1. Introduction

In February 2001, *Nature* and *Science* simultaneously published now-classic issues devoted to the sequencing results and early biological applications of the landmark Human Genome Project accomplished by the public and private-sector research teams [1,2]. Five days later, the 21 February issue of *The Financial Times* presented the article shown in Fig. 1 "Searching for the Real Stuff of Life" [3]. Note that the double-helix has been moved into the shadows, off-stage, while the robust globular protein has taken center stage! The article referred to the enormous task to "decipher the human protein set", the proteome, as "Biotech's Next Holy Grail".

The Siena Conferences have been in the forefront of the development of the field of proteomics, even the naming of the field with the term suggested by Marc Wilkins of Australia in 1995. Our theme for this 9th Conference is "From Genome to Proteome". The overall drivers are these:

- Proteins are the major action molecules of cells
- Proteins and their isoforms are dynamic
- Proteins play critical roles in gene regulation
- Modern instruments, reagents, and bioinformatics facilitate integration and modeling of data from multiple 'omics platforms
- Proteins are the primary targets of drugs and can be drugs themselves, as well as biomarkers for diagnosis, prognosis, and response to therapy

During the past few months there have been several major science policy reports in the United States that strongly highlighted proteomics:

- Vidal, Chan, Gerstein, Mann, Omenn, Tagle, Sechi. The human proteome. Clinical Proteomics 2012 [4]. This report from the NIH Workshop on Human Proteomics emphasized the interactome and the path from biomarker candidate to diagnostic test.
- Hood, Omenn, Moritz, Aebersold, Yamamoto, Amos, Hunter-Cevera, Locascio. Proteomics technologies, a grand challenge in life sciences. Proteomics 2012 [5]. This report from the Gaithersburg Workshop hosted by the National Institute for Standards and Technology addressed the essential role of proteomics in relizing the goals of the Human Genome Project, identified performance challenges and emerging proteomics technologies, and showed applications for health, agriculture and nutrition, energy and environment, and national security.
- Office of Science and Technology Policy. The National Bioeconomy Blueprint, April 2012[6]. Three "foundational fields" for the coming decade were highlighted: synthetic biology, proteomics, and computational biology.
- Institute of Medicine. Evolution of Translational Omics: Lessons Learned and Path Forward. Micheel, Nass, Omenn (eds). National Academy Press, March 2012 [7]. This report presented a framework for discovery, validation, and clinical utility phases of development of multi-analyte diagnostic tests. Strong recommendations were made for the responsibilities of investigators, lab directors, research institutions, funders, regulators, and journals.

The use of proteomics in cancer biomarker research has two complementary starting points. The first is to directly profile tumor specimens for diagnosis and stratification of patients, for prognosis with or without particular therapies, and for clues to mechanisms and to circulating biomarkers. The second is to profile proteins in the blood plasma to discover and validate biomarkers for earlier or more specific diagnoses and to apply such biomarkers to predict response to treatment and monitor patients for recurrence or metastasis of the tumor.

2. Strategies for biomarker discovery from combined analyses of tumor tissues and plasma

There are now four strategies with high promise for developing tumor-specific and organ-specific biomarkers that can be assayed in the circulation:

1. Start with microarray or next-gen sequencing evidence for carcinogenic pathway mechanisms in tumor and track corresponding protein biomarker candidates to the plasma. This is a major strategy at the Institute for Systems Biology, identifying differentially-expressed transcripts and proteins

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