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Research Report

Inner ear proteomics: A fad or *hear* to stay

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ARTICLE INFO

Article history:
Accepted 26 January 2006
Available online 15 March 2006

Keywords:
Proteomic
Inner ear
2-DE
Systems analysis

ABSTRACT

Proteomics, the large-scale analysis of the structure and function of proteins, as well as of protein–protein interactions, has evolved into a major component of 'systems analysis'. This requires the integration of information from different sources and at multiple levels, and involves two distinct parameters, (1) high-throughput protein separation, identification, and characterization, and (2) the extension of the obtained analytical data for the determination of the physiological function. The inner ear poses exceptional challenges to the study of proteomics because of its minute size, poor accessibility, association with complex fluid spaces, and diversity of cell types. Various approaches to the study of proteomics of the inner ear are presented, and success stories, noteworthy failures and what lies ahead, will be discussed.

1. Introduction

A year ago we celebrated the 50th anniversary of the discovery of the DNA double helix. After a 40-year gap the first genome of *Haemophilus influenzae* was completed. While already some 20 years ago the concept of global mapping of expressed proteins was proposed by the Anderson father and son team (Anderson and Anderson, 1982), the term 'proteome' was coined only in 1996 by an Australian Team and defined as the 'protein complement of a genome' (Wilkins et al., 1996). Recently, the definition of proteomics was extended to "effort to establish identities, quantities, structures, biochemical and cellular functions of all proteins in an organism, organ or organelle and how these properties vary in time and physiological function" (Workshop Report, Nat. Acad. Sci., Kenyon et al., 2002)—a daunting endeavor. Ultimately the information obtained from transcriptomics and the systematic study of global protein properties, integrated with experimental and theoretical physiological data, will assure transformation of biology and medicine.

2. From genome to proteome

Genomics will undoubtedly remain at the top of the list of revolutionary scientific developments. Transcriptomics, the global expression of mRNA, based on powerful techniques, such as DNA microarrays and serial analysis of gene expression (SAGE), has resulted in valuable information; however, neither genomics nor transcriptomics allow the study of dynamic processes. mRNA frequently does not correlate with protein expression (and hence function) (Zheng et al., this issue). Significantly, neither abundance of a protein, changes in abundance, nor types of post-translational modifications can be predicted at the message level, all factors playing a vital role in pathology. In addition, it cannot be determined which splice variants are translated and/or are functional.

It is obvious that the functional complexity of an organism goes beyond the genome sequence alone. At least in eucaryotes, the number of functional gene products that can be expressed by an organism far exceeds the

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URL: http://oto.wustl.edu/thc/innerear2d.htm.

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doi:10.1016/j.brainres.2006.01.099

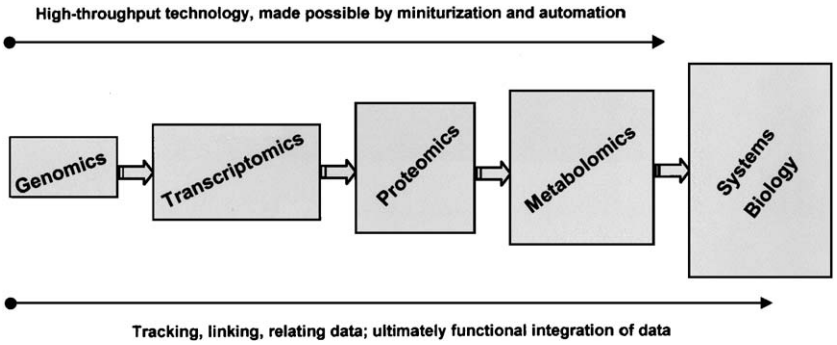

Fig. 1 – Schematic representation of the progression from information contained in the genome through the various 'omics' and integrated to ultimately lead us by means of systems biology to the whole organism.

number of genes that encode them. Whereas the number of coding genes in humans lies between 30,000 and 40,000, the number of gene products is estimated to be 500,000, considering post-translational modifications, splice variants, and cleavage products. In the case of plasma, the number rises by another order of magnitude when the immunoglobulin class containing an estimated 10,000,000 different sequences is included (Anderson and Anderson, 2002).

A recent Editorial in Nature (Vol. 437, 2005), presents a dismal picture of the present status of proteomics; fortunately the Editorial offers a solution (see below). Admittedly, the deluge of data reported in the literature resulting from the discovery of new high-throughput techniques often proved difficult to reproduce, which made comparisons between the various laboratories arduous. According to the Editorial "the proteomics community needs to clean up the house." This became the task for HUPO, the Human Proteomics Organisation, launched in 2001. The society is developing standards for data generation, including standardized formats for databases. At the present time 38 laboratories from 13 countries are signed up (Omenn et al., 2005).

If the goal of proteomic research is to understand the expression and function of proteins, a systems-based approach must be applied (Weston and Hood, 2004; Sauro, 2005; Murphy, 2005). A high-throughput approach, made possible by the refinements in miniturization and automation technology, combined with the developments in informatics enabled a shift from the level of each "omic" approach to an integrative approach, so to speak from genes to metabolites (Fig. 1) (Hocquette, 2005). Ultimately, integration of experimental and theoretical biological data will help us understand biology as a whole, going from gene to molecule to cell, to organ, to an individual, and finally to ecosystems. While proteomics research has been accused of being 'discovery-driven', this integrative approach appears more like the time-honored hypothesis-driven approach.

3. Requirements for successful proteomics studies in general

There are three basic requirements, each of which has to be optimized for the species, organ, cell, or organelle to be studied (Fig. 2).

(a) Adequate spatial and temporal resolution of the sample to be analyzed;
(b) High-throughput protein separation, identification, and characterization; and
(c) Meaningful extension of the obtained analytical data to the elucidation of the molecular/physiological function.

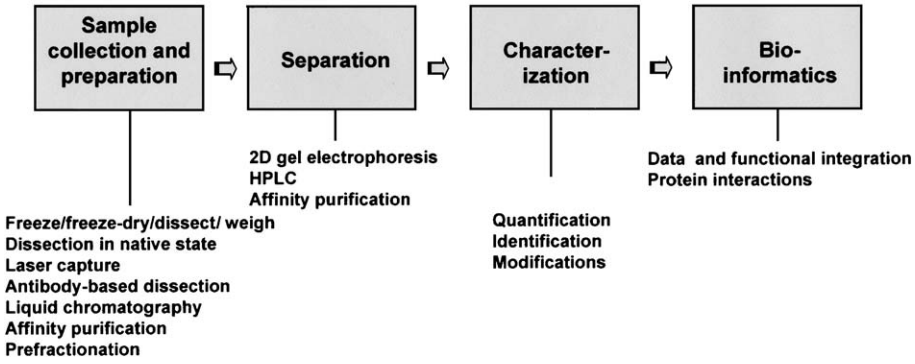

Fig. 2 – Schematic diagram of the basic steps involved in proteomic analysis. For each step, several possible techniques are given.