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Proteomics and Cardiovascular Biomarker Discovery

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Circulating biomarkers aid in determining both the diagnosis and prognosis of cardiovascular disease (CVD). Most of the currently used biomarkers were developed out of studies of known proteins. For example, cardiac troponin I and T were known to be specific structural proteins found exclusively in the heart and thus became candidate biomarkers of myocyte injury.[1] C-reactive protein (CRP), an acute phase reactant protein synthesized by the liver, dates back to the 1930s when it was defined as a protein that reacted to the C-polysaccharide on *Streptococcus pneumoniae*. With the growing appreciation of the role of inflammation in atherosclerosis and the advent of high-sensitivity CRP assays, CRP was then utilized as a biomarker of inflammation.[2-6] B-type natriuretic peptide (BNP) was known to be a vasoactive hormone synthesized and secreted by the heart in response to increased left ventricular (LV) wall tension.[7] BNP was therefore adopted as a non-invasive biochemical marker to determine LV hemodynamic stress and a prognostic biomarker in heart failure[8] and acute coronary syndromes.[9]

Although the above approach has been fruitful, recent advancements in protein display and identification technologies now permit the characterization of global alterations associated with disease conditions. In particular, plasma proteomics – through an unbiased survey of all proteins associated with a given cardiovascular pathology – has the potential to lead to the discovery of novel biomarkers. By tailoring the experimental process, proteomics can target the discovery of biomarkers to fill current unmet needs (eg, very early markers of injury, markers of myocardial ischemia in the absence of infarction, etc.). In addition, the biomarkers discovered using proteomics may provide insight into cellular mechanisms of disease and uncover new proteins to serve as targets for therapeutic intervention. The research, development, and future of proteomics are discussed in this issue of *Cardiology Rounds*.

What is proteomics?

First introduced in 1995,[10] the term "proteome" refers to the entire group of proteins associated with a given genome (Figure 1). However, the concept of cataloguing all human proteins actually dates back to the late 1970s when Congress was considering the Human Protein Index project proposed by Norman G. Anderson and N. Leigh Anderson. The goal of that project, conceived at a time before high-throughput DNA sequencing was possible, was to enumerate all human proteins as a stepping-stone to defining all human genes. As it turned out, genomics technology leaped ahead of proteomics technology and, thus, the Human Genome Project took the spotlight.

In fact, proteomics is far more complex and ambitious than genomics. All cells of a given organism contain an equivalent genomic content. In contrast, the proteome does not represent all possible proteins the genome can express; there is selective gene expression during development

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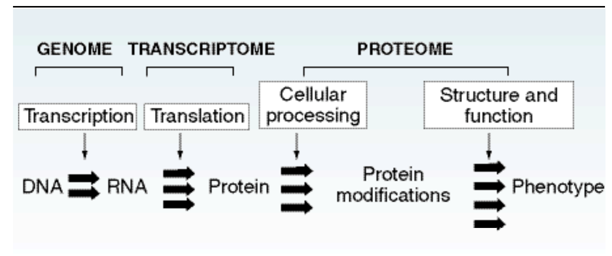
and differentiation, as well as in response to external stimuli. As a result, each cell expresses only the fraction of encoded proteins relevant to its functional state at any given time. Thus, one can discuss not only the general human proteome, but also, more specifically, the proteome of particular cells (eg, cardiomyocytes), and even the proteome expressed by these cells under specific physiologic or pathophysiologic conditions. To that end, proteomics can be broadly defined as "the study of the identities, quantities, structures, and biochemical and cellular functions of all proteins in an organism, organ, or organelle, and how these properties vary in space, time, or physiological state."[11]

Conversely, the proteome extends beyond the expression profile of a particular genome. A number of studies suggest that gene expression often correlates poorly with protein levels.[12,13] Although protein expression is influenced by the rate of transcription, nucleotide and protein half-lives vary, such that the presence or absence of messenger ribonucleic acid (mRNA) may not accurately reflect the presence or absence of the corresponding protein. Additional co- or post-translational events may affect protein stability. Thus, mRNA sometimes reveals surprisingly little information about protein abundance and is an imperfect predictor of post-translational regulation.

The proteome associated with a particular gene set includes all variants of the same protein that result as a consequence of differential cellular processing (Figure 1). Transcription initiation sites may vary for the same protein. Subsequently, as many as one-quarter or more of higher eukaryotic genes can be alternatively spliced, resulting in multiple transcripts. Following transcription, the protein may undergo (often on multiple sites) 1 or more of >200 potential post-translational modifications (eg, phosphorylation, glycosylation, acetylation, and sulfation). Subsequent additional enzymatic and non-enzymatic alterations culminate in a greatly expanded number of simultaneously existing molecular species. The one gene-one protein dictum, now no longer tenable, allowed few to anticipate the immense magnitude and complexity of the resulting proteome.

Proteomics is uniquely positioned to offer insights into disease because proteins and their bio-enzymatic functions largely determine the phenotypic diversity that arises from a set of common genes. Because the entire complement of expressed proteins in their various forms can rapidly change in response to environmental cues, the proteome represents the unique ensemble of proteins that reflects the state of the cell or group of cells at a given time, in a particular context, under particular stimuli. Thus, the proteome is highly dynamic, in contrast to the stability of the genome. This complexity is the basis of both its great informative potential and analytical challenge. Since the majority of pathologies results from protein alterations, either as cause or effect, whether by genetic disposition or environmental/pharmacological factors, just as the proteins serve as natural biomarkers and potential therapeutic targets.

Figure 1: Relationship between the genome and proteome



Technologies for biomarker discovery

Prerequisites for proteomic analysis

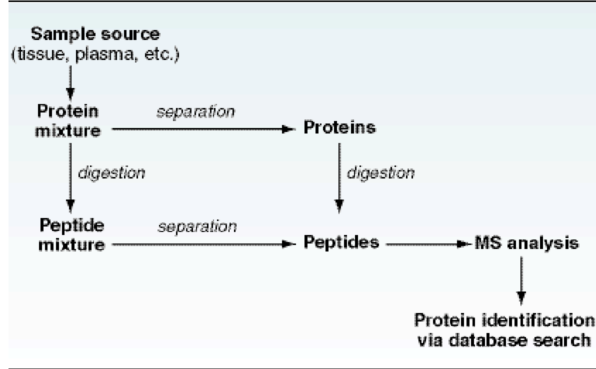
A diverse and increasing set of techniques falls under the rubric of proteomics, the goal of which is to define the quantitative protein profile of a well-defined system. Broadly, there are several features critical for the success of proteomic technologies.

- Techniques must be able to identify a wide breadth of proteins within complex biological samples and across a broad range of physical characteristics, including size, charge, etc.
- The technology must be sensitive enough to probe the proteome to adequate depths. Often the least abundant proteins play critical regulatory roles in the response to physiological stressors. For example, concentrations of the interleukins, central to many inflammatory and immune responses, fall in the low nanomolar range. In contrast, the concentration of albumin, typically the most abundant circulating protein, is approximately 8 orders of magnitude greater.
- Tools must also work across a broad dynamic range, meaning that they must be able, simultaneously, to identify both more abundant and less-abundant proteins in the same complex mixture. The ability to analyze unfractionated specimens becomes even more critical with the realization that attempted removal of high abundance proteins, such as albumin in plasma samples, almost always risks removal of the lower abundance proteins as well.
- Crucial support for proteomics experiments is offered by robust databases that can be searched for validation of identified proteins. Essential to the interpretation of the data is software that can search through databases for candidate identification. Much of this software has been made available on the Internet.

Components of a proteomics experiment

The essential elements of a proteomics approach are summarized in Figure 2. Most biological samples consist of a complex mixture containing proteins of varying molecular weights, modifications, and solubilities. Therefore, samples must be fractionated to create more homogeneous and less complex sub-samples for analysis. This process has been compared to printing a book:[14] you could cram all the contents of the book onto 1 page, but that page

Figure 2: **Overview of a proteomics experiment**



would be illegible. By dividing the text onto multiple pages organized into logical sections, a comprehensible text emerges. The proteins in each of these fractions are then separated and quantified using gel electrophoresis or, more commonly, mass spectrometry (MS) (Figure 3). Individual proteins must eventually be digested to their peptide components in order to obtain sequence information by mass fingerprinting or tandem MS. The sequences are then matched to a protein database to verify the identity of the proteins of interest.

Research applications

Considerations for experimental design

Certain features unique to cardiovascular conditions will influence the choice of proper experimental design. Whereas chronic conditions might lead to altered gene expression and changes in protein levels, acute insults will more likely induce rapid post-translational modifications of pre-existing proteins. The need for capturing these modifications would also favor the use of certain analysis techniques. Similarly, the short time frame of evolution for acute cardiac conditions and the rapidity of proteome modulation must be considered and both argue for serial observations in subjects at specific time points in relation to their disease. Moreover, if possible, samples should be obtained before and after the perturbation of interest. This approach allows each subject to serve as his or her own control and greatly simplifies the search for proteins related to the perturbation of interest (Figure 4).

Figure 3: **Schematic of tandem mass spectrometry**

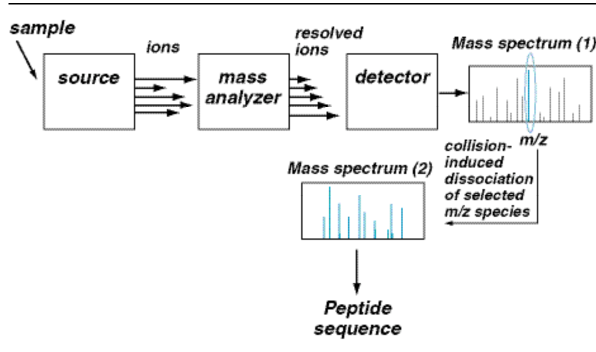
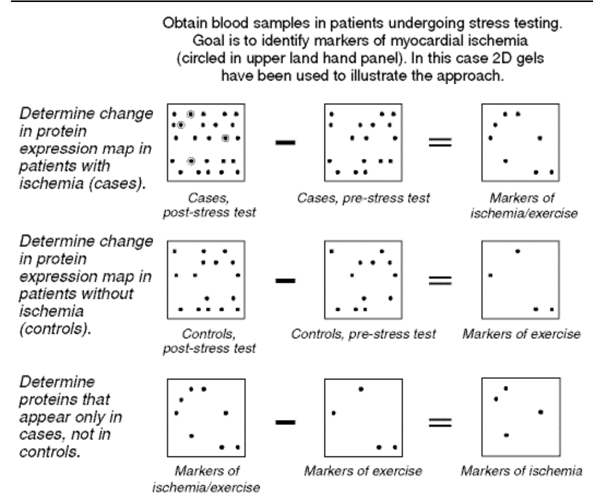


Figure 4: **Advantage of obtaining serial samples**

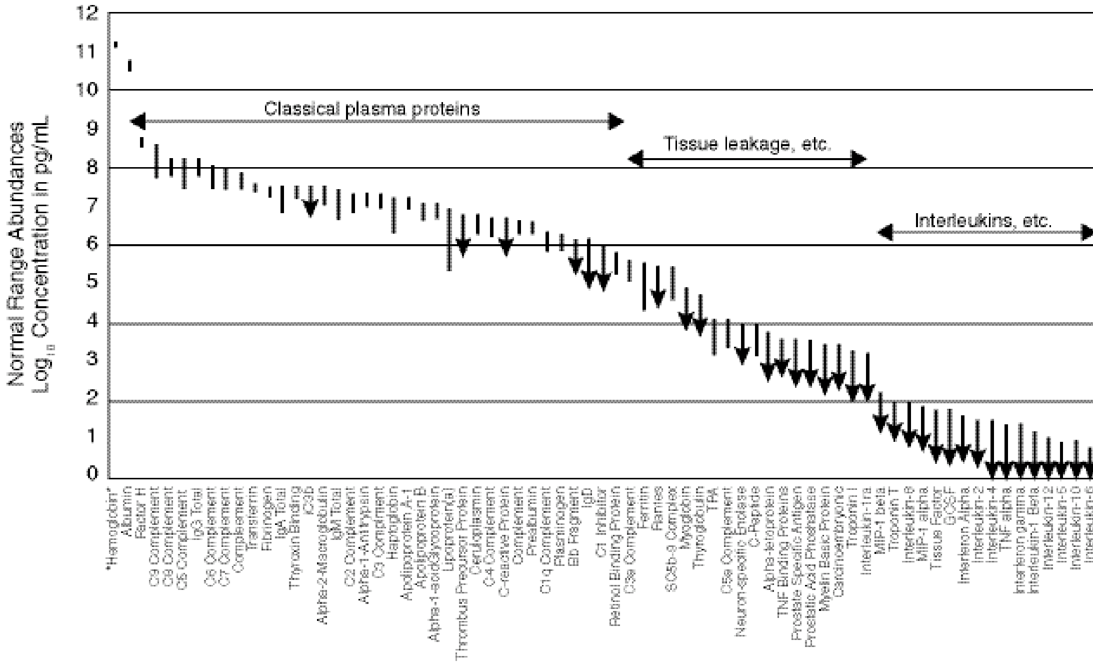


Plasma proteomics in CVD

The plasma proteome is unique in that it does not represent a particular cellular genome, but instead reflects the collective expression of all cellular genomes. Twenty-two of the most abundant circulating proteins, including albumin and the immunoglobulins, comprise 99% of the plasma proteome mass. Many of the biologically interesting molecules relevant to CVD are low abundance proteins. For example, cardiac markers such as troponin are found in the nanomolar (10^{-9}) range, insulin in the picomolar range (10^{-12}), and tumor necrosis factor (TNF)-α in the femtomolar (10^{-15}) range. In all, there are an estimated 10,000 unique proteins in plasma, with concentrations spanning a dynamic range over 9 orders of magnitude (Figure 5). However, some researchers hypothesize that the entire set of >300,000 estimated human polypeptide species resulting from splice variants and post-translational modifications is potentially represented in the plasma proteome. This is possible because plasma contains not only expected circulating proteins (eg, albumin and immunoglobulins), but also less-expected proteins from all functional classes and cellular localizations (Figure 6). A surprising majority of the lower abundance proteins in plasma actually consists of intracellular or membrane proteins that are present in plasma because of cellular signaling, apoptosis, or necrosis. Efforts to catalogue the human serum proteome using multidimensional separation strategies coupled with tandem mass spectrometry (MS/MS) have led to the identification of >1000 unique proteins in human plasma.

In theory, all diseases lead to perturbations detectable in plasma because almost all cells communicate using plasma, which is the common transport conduit of cellular secretions, tissue leakage products, and waste. This potentially makes plasma the most informative proteome from a diagnostic viewpoint. There are also substantial practical advantages to analyzing human plasma for proteomics-based biomarker discovery. The blood represents an easy,

Figure 5: Complexity of human plasma



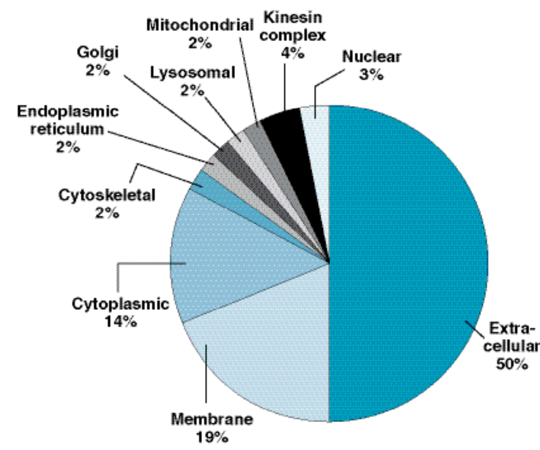
inexpensive, and rapidly sampled source for study, and may have particular relevance to CVDs, in which the blood itself is the site of pathology. Blood is also suitable for repeated sampling, both in greater quantity and with less tissue heterogeneity and sampling error than with biopsy. Because multiple tissues ultimately contribute to the pool of circulating proteins, changes in the plasma proteome can also reflect disease involvement of other organs, as well as associated pathophysiology at distant sites. For example, cardiac troponin (released from the heart) and CRP (derived from the liver) arise from different tissues, but contribute jointly as complementary markers of cardiac status.[15] Other yet-to-be discovered molecules, perhaps those reflecting hemodynamic compromise, might be generated by organs such as the kidneys. Thus, while analysis of specific proteomes (eg, from cardiomyocytes or endothelial cells) provides clues on individual components of the disease process, the study of plasma proteomic patterns offers a more comprehensive framework for biomarker discovery by providing global measurements of all system constituents.

Plasma proteomic signatures

Perturbations of the proteome that arise either as a cause or consequence of disease manifest as particular patterns or "signatures" of proteins in plasma. Mass spectrometers can rapidly generate well-defined sets of proteomic peaks from a sample across a broad range of mass/charge. Some have advocated using these signatures of unidentified peaks as the biomarker, skipping the far more laborious task of unambiguously identifying the proteins that underlie the peaks. In one highly publicized effort, it was demonstrated that mass spectrometry, coupled with an artificial intelligence algorithm, could distinguish ovarian cancer from normal controls with an unprecedented 100% sensitivity and 95% specificity.[16]

Using a pattern of peaks to diagnose disease without knowing the represented proteins, however, raises some concerns. One issue is that of reproducibility. Because most mass spectrometers were not designed as clinical tools, it is hard to generate consistent results from machine to machine or from operator to operator. Some contend that the patterns are mostly "noise" and do not discriminate biologically meaningful information. Independent reanalysis of cancer

Figure 6: Constituents of human plasma



proteomic data has cast some doubt on the bias and validity of the data. Without unequivocal protein identifications, one cannot independently confirm findings with complementary technologies such as ELISA. Moreover, by not unequivocally identifying proteins, little insight is gained into the biology, either to understand disease pathways through basic cellular mechanisms or as a check on the biological consistency and reasonableness of the data.

Cardiovascular disease

Researchers have begun to apply protein profiling to CVD, specifically investigating serum signatures of myocardial infarction (MI). One team of researchers has attempted to identify patterns in the plasma of MI patients.[17] They reported a diagnostic series of peptide peaks differentially expressed in diseased sera. Ultimately, several peaks were found to relate to complement and fibrinogen products. The researchers acknowledged that the reported patterns were influenced by storage and handling conditions, thus underscoring the importance of sample quality in proteomics studies. Again, prospective validation of such findings in new epidemiological cohorts is critical.

Another group of researchers obtained plasma samples from patients with acute MI, unstable angina (UA), and healthy controls. Using 2D gels, they identified 400 distinct spots and 4 defined areas on the gels that appeared to differ consistently between patients with acute coronary syndrome (ACS) and controls. In particular, certain isoforms of α1-antitrypsin were higher in patients with ACS than in controls, whereas others were lower. The fibrinogen γ chain was elevated in patients with ACS. Perplexingly, levels of apolipoprotein A-I were higher in patients with UA than in controls, but were lower in patients with MI than in controls. Finally, and not unexpectedly, immunoglobulin levels were higher in patients with ACS.

Recently, we have employed metabolomics (analogous to proteomics, but using metabolites rather than proteins) to examine patients enrolled in PROMPT-TIMI 35, a dedicated myocardial ischemia biomarker discovery study in patients undergoing exercise stress testing for suspected coronary artery disease. For in-depth metabolic profiling, we selected 36 patients, 18 of whom demonstrated inducible ischemia (cases) and 18 of whom did not (controls), and examined blood samples obtained before and after stress testing. As noted above, this feature allowed each patient to serve as his or her baseline control and markedly simplified data analysis. Plasma was fractionated by high-performance liquid chromatography. A triple quadrupole mass spectrometer was operated in an automated switching polarity mode using a turbo ion spray liquid chromatography/mass spectrometry (LC/MS) interface under selected reaction monitoring (SRM) conditions. A total of 477 parent/daughter (P/D) ion pairs were monitored through 6 SRM experiments on each sample. We found 6 metabolites that exhibited significant discordant regulation in cases vs. controls, including GABA ($P=0.0005$), uric acid ($P=0.0006$), citric acid ($P=0.0082$), and unknown metabolites MET288 ($P=0.0056$), MET200 ($P=0.0082$), and MET193 ($P=0.0068$). Using ROC curve analysis, cutpoints were selected for the change in each of these 6 metabolites. A metabolic risk score was created by assigning patients 1 point for each metabolite for which the change with exercise exceeded the cutpoint for ischemia. Using this score we were able to differentiate cases from controls with a high degree of accuracy ($P<0.0001$, c-statistic$=0.95$).

Challenges and perspectives

Clinical proteomics is currently undergoing a revolution. Advancing instrumentation and computational methodologies are allowing not only exploration, but also quantification of the proteomes of biological tissues and fluids on a wide scale. Fueling these advances is the notion that every disease will create characteristic changes reflected in the tissue or serum proteome. This is a systems biology approach, where all concurrent processes of a cell or tissue can be monitored in defined physiological states. The remarkable degree of information made accessible by proteomics moves the field closer to more individualized forms of medicine and offers more awareness, not only of disease perturbations, but also the even greater normal biologic variations within – and between – healthy individuals.

However, the field is still in its infancy. There is lack of consensus and standardization in technology and techniques. Several fundamental issues remain unresolved regarding the best way to collect and store samples, in part, because it is difficult to anticipate all future needs from the samples presently stored. Currently, bioinformatics is perhaps the biggest bottleneck. Identification of proteins continues to be a slow process. Finally, the high sensitivity of mass spectrometry and the present lack of bioinformatic standardization make it critical that any suspected proteomic changes be thoroughly reviewed and verified, addressing any inadvertent biases or artifacts of collection, handling, storage, or analysis.

The search for novel biomarkers begins with broad-based screening often because little is known about the pathways involved. Whether these findings translate into clinical utility will ultimately depend on the ability to develop high throughput assays. The overarching goal, however, is to relate findings back to biology for characterizing the molecular mechanisms of disease. Proteins, their functionally relevant modifications, and their binding partners must all be placed

in cellular pathways in order to generate new hypotheses leading to future therapeutics. Identifying dynamic changes in proteins, in the setting of specific diseases, should be particularly informative. The scope of expertise relevant to such endeavors will necessarily involve increasing collaborative efforts between clinical investigators, laboratory scientists, and bioinformatic specialists, all with the promise of providing new relevant diagnostic and therapeutic information for clinicians.

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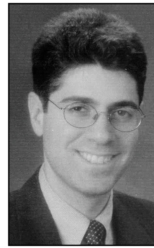

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