Advancing Cardiovascular Biology and Medicine via Proteomics
Opportunities and Present Challenges of Cardiovascular Proteomics
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The successful advancement of biology and medicine necessitates a comprehensive and integrative understanding of the proteome in a healthy individual and, through inference, the identification of those proteins considered to be abnormal and to potentially herald disease. Protein markers, complementary to gene markers, constitute the molecular basis for personalized medicine. Given the enormity of the cardiovascular disease burden in modern societies, application of a large-scale protein analysis to cardiac physiology and pathophysiology is important for current and future therapeutic approaches. After nearly a decade of investigation within the realm of cardiovascular proteomics, the daunting question remains: Is proteomics ready to help elucidate normal physiology in health and pathophysiology in cardiovascular disease?

To this end, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health had implemented 2 proteomics programs. The first, the NHLBI Proteomics Initiative, was instrumental in the establishment of 10 multidisciplinary centers to enhance and develop innovative protein-based technologies and to apply them to relevant biological questions to advance our knowledge of heart, lung, blood, and sleep disorders. A parallel second program, the NHLBI Clinical Proteomics Program, was initiated with the goal of promoting a systematic, comprehensive, and large-scale validation of existing and new candidate protein markers that are appropriate for use in the diagnosis and management of heart, lung, blood, and sleep disorders. Additionally, a multimarker approach was encouraged to enhance the sensitivity, specificity, and predictive value of existing and new markers. These programs have been at the forefront of research and technology in cardiovascular medicine, championing the application of proteomic technologies such as mass spectrometry and protein arrays for cardiovascular research, thus paving the way for the translation of proteomic technologies into the clinical arena.

Salient technological advancements resulting from the NHLBI efforts include the construction of a cryogenic Fourier-transform mass spectrometry platform for high-sensitivity mass spectra; microfluidic chips for high-throughput proteomics; annotated gel markup language open source software for 2-dimensional electrophoresis-based proteomics; a transproteomic pipeline for all steps of mass spectrometry-based proteomics; a PeptideAtlas for databasing and statistical validation of mass spectrometry data; high-content, single-cell, phosphospecific flow cytometry; and peptoid-based microarrays for protein high-throughput capture. Furthermore, NHLBI efforts have facilitated the transition of recent biomarker discoveries into the validation pipeline. Highlights include the demonstration that ST2-, a marker for biomechanical stress, complements N-terminal prohormone brain natriuretic peptide in predicting cardiovascular death and congestive heart failure in patients with ST-elevation myocardial infarction; the demonstration that thrombus precursor protein, a marker of activated coagulation, in conjunction with established cardiovascular risk factors, provides complementary information for risk assessment in acute coronary syndromes; and the demonstration in stable coronary artery disease patients that elevated levels of lipoprotein–phospholipase A2 were highly predictive of nonfatal adverse outcomes independently of traditional cardiovascular risk factors.

Although significant progress has been made in the past decade, proteomic research in the cardiovascular field is now presented with new milestones and exciting goals. Cardiovascular proteomics must overcome a number of challenges to fulfill its promises. There is an apparent disconnection between discoveries on the technological front and their effective translation to advances in cardiovascular biology and medicine. Major challenges include an inadequate source of high-quality reagents (eg, high-quality antibodies), insufficient development of standardized protocols/procedures (eg, standard operating procedures for biomarker quantification and validation), and limited infrastructure for data organization and data analyses. Technologies are also pale to discern changes; they are not conducive to inferring real-time protein network information, nor do they facilitate the capture of temporal changes at high resolution in proteomes. The
Can proteomics help elucidate normal physiology in health and pathophysiology in cardiovascular disease?

backbone of the current proteomic instrumentation, the mass spectrometer, has traditionally been more adept at qualitative measurements than quantitative measurements, and significant improvements are essential before proteomics can be adopted in the clinical laboratory. In parallel, there is a demand to optimize reagent design, to provide reproducible quantitative measurements, and to optimize sample consumption/throughput to refine multiplex immunoassay platforms. In a more global sense, additional challenges include our limited understanding of which proteins and their combinations are useful to measure, as well as our inherent need to go beyond correlation to understand biology. Significant barriers for advancing putative biomarkers into clinics are the lack of infrastructure for validation of candidate proteins in well-characterized human samples that are also associated with high-quality clinical data and an insufficient number of investigators with the appropriate expertise.

The current objectives of cardiovascular proteomic research include understanding the proteome at multiple domains and at multiple levels of the cardiovascular system. These efforts are as diverse as the physiological effects and signaling networks that operate in response to environmental factors, the reflection of environmental influences in protein compartmentalization, and the ability to detect pathologies before decompensation and eruption into symptoms and illness. The ever-growing technological capability to characterize the proteotype of cells and organs (eg, defining protein posttranslational modifications, quantifying protein abundance, and determining protein interactions) affords new opportunities to advance our understanding in molecular phenotypes (see Figure). The NHLBI-supported technological developments have vastly increased the capacity for discovery of novel candidate biomarkers or a panel of biomarkers to formulate a “disease fingerprint.”

The accomplishment and experience gained through the NHLBI proteomics programs have helped us identify critical issues in cardiovascular proteomics that we must address. First, proteomic technologies should be applied to enhance our current understanding of cardiovascular biology, function, and molecular phenotypes to help us understand causes of heart disease that cannot be explained by known risk factors. Second, proteomic technologies are developed to address the dynamics and temporal features with respect to disease pathogenesis; which stage of cardiovascular disease should we be targeting for biomarker discovery? Early detection, diagnosis, risk stratification, and therapy monitoring are a few windows of time that would benefit from reliable markers, but the implementation of these markers needs to be balanced with practical issues. Third, advancement in cardiovascular medicine would be greatly facilitated by a more rigorous examination of the existing biomarkers, in addition to the discovery of those that are novel.

We are confident, however, that through the continued development of proteomic technologies and validation/implementation of easily accessible platforms, a proteomic knowledge base supporting biological and medical advances will emerge. This knowledge base will drive the successful integration of cardiovascular proteome biology into the clinical setting and will enable the community to reliably and reproducibly link proteins with specific stages of molecular phenotypes in cardiovascular disease. Our ability to achieve the next phase of goals is supported by the continuation of fruitful partnerships that the NHLBI has nurtured, including investigators; professional scientific societies; voluntary health organizations; patient advocacy groups; community organizations; foundations; corporations; federal, state, and local agencies; and international organizations. This collaborative effort drives productivity and propels innovation as we move forward, ensuring success in an ever-evolving environment.
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