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Review

Understanding different facets of cardiovascular diseases based on model systems to human studies: A proteomic and metabolomic perspective☆

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ABSTRACT

Cardiovascular disease has remained as the largest cause of morbidity and mortality worldwide. From dissecting the disease aetiology to identifying prognostic markers for better management of the disease is still a challenge for researchers. In the post human genome sequencing era much of the thrust has been focussed towards application of advanced genomic tools along with evaluation of traditional risk factors. With the advancement of next generation proteomics and metabolomics approaches it has now become possible to understand the protein interaction network & metabolic rewiring which lead to the perturbations of the disease phenotype. Further, elucidating different post translational modifications using advanced mass spectrometry based methods have provided an impetus towards in depth understanding of the proteome. The past decade has observed a plethora of studies where proteomics has been applied successfully to identify potential prognostic and diagnostic markers as well as to understand the disease mechanisms for various types of cardiovascular diseases. In this review, we attempted to document relevant proteomics based studies that have been undertaken either to identify potential biomarkers or have elucidated newer mechanistic insights into understanding the patho-physiology of cardiovascular disease, primarily coronary artery disease, cardiomyopathy, and myocardial ischemia. We have also provided a perspective on the potential of proteomics in combating this deadly disease.

Biological significance
This review has catalogued recent studies on proteomics and metabolomics involved in understanding several cardiovascular diseases (CVDs). A holistic systems biology based approach, of which proteomics and metabolomics are two very important components, would help in delineating various pathways associated with complex disorders like CVD. This would ultimately provide better mechanistic understanding of the disease biology leading to development of prognostic biomarkers.
This article is part of a Special Issue entitled: Proteomics in India.

Contents

Abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; MI, myocardial infarction; WHO, World Health Organization; SNPs, single nucleotide polymorphism; GWAs, genome wide association studies; MRM, multiple reaction monitoring; ELISA, enzyme-linked immunosorbent assay; PTMs, post translational modifications; DCM, dilated cardiomyopathy; ER, endoplasmic reticulum; HF, heart failure; HDL, high density lipoprotein; LDL, low density lipoprotein; 2D, 2-dimensional; LV, left ventricle; PCA, principal component analysis.

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1. Introduction

Cardiovascular disease (CVD) is the most alarming complex disorder with increasing incidence every year across the world [1,2]. Since it is one of the largest causes of morbidity and mortality worldwide till date, the impact of this disease on public health is of high importance [3,4]. CVD is generally used as a broad term that encompasses a plethora of pathophysiological conditions of heart, blood and vasculature of the body. This includes coronary artery disease (CAD), myocardial infarction (MI), heart failure, cardiomyopathy, arrhythmias, aortic stenosis, etc. [5]. Most importantly, incidence of CVD is rising at an alarming rate in the developing countries. WHO reports indicate that CVD is the leading cause of mortality in the developing countries. An enormous amount of clinical and basic research has been undertaken to identify pre-diagnostic markers for better management of CVD. Studies leading to molecular understanding of the disease process have helped in combating these diseases to a certain extent. Several biochemical and molecular biology based approaches led to the discovery of key mechanisms in different heart diseases. Numerous classical markers (HDL, LDL, etc.) and risk factors (diabetes, hypertension, etc.) have been identified that could play a role in the development of heart diseases. However, taken together all these risk factors lack the desired predictive accuracy in terms of the prognostic value. Thus, a holistic understanding of the disease process and identification of better prognostic biomarkers remained a challenge to researchers for decades.

After the human genome sequencing project, single nucleotide polymorphism (SNPs) screening remained a major thrust in identifying the markers for CVD. However, even with the advancement of next generation sequencing and Genome Wide Association Studies (GWAS) undertaken in different populations across the world these genetic markers could only explain a very low percentage (about 10%) of the disease heritability. Further the associations of several genetic polymorphisms could not be replicated across populations. Apart from these, the gene expression profiling methods were developed and it was felt that the expression of mRNA could potentially identify key genes in several CVD. However, recent understanding points towards the fact that global transcriptome may not necessarily correlate with the protein complement in a biological system [6]. This limits the potential of global gene expression based studies in terms of understanding disease process; as proteins remained the functional element for any cell.

During the late 90s mass spectrometry started developing as a potential source to characterise biomolecules in a robust way. The advancement of soft ionisation techniques and development of several algorithms for proteome analysis led the development of an emerging field for biological research termed as “Proteomics”. The concept to characterise all the proteins present in a specific tissue or cell type was put forth by Mark Wilkins in 1994 who coined the term “proteome” as the total protein complement of any cell type or tissue. Over the last 15 years “proteomics” has emerged as a fascinating tool to probe the biological perturbations occurring at a specific system in a given time scale. It has contributed enormously to understanding the molecular changes during several disease processes and helped in identifying several potential biomarkers for disease prognosis [7]. Recently, “Metabolomics” has emerged as the new apogee to the “omics” based studies and have enormous potential to probe biochemical changes. Application of metabolomics has been also used in CVD to unravel novel metabolic biomarkers.

This review is an attempt to address the progress in identifying biomarkers for CVD and mechanistic understanding of these diseases led by proteomic and metabolomic research. We have focussed our attention towards CAD, MI and cardiomyopathy that converge leading to HF.

2. Application of quantitative proteomics for the discovery of biomarkers

Biomarkers are quantifiable molecules which must provide accurate, reliable and cost-effective information about disease either to aid in prognosis, diagnosis, or in monitoring of therapy. Identification of novel biomarkers holds the key to the development of better disease management strategies. Biomarkers are sought to be discovered in minimally invasive, easily accessible samples such as urine or plasma keeping in mind the ease of translation. In this section, we discuss various aspects of existing biomarkers for MI, cardiomyopathy and CAD.

The classical marker with high predictive value for MI remains Troponin T. An elevated level of Troponin T is considered to be the gold standard method for detection of MI. However, Troponin T is elevated only during MI and hence has little prognostic value. Thus, several proteomics based studies have been undertaken to discover novel prognostic markers for MI. Such studies led to the identification of cardiac troponin I as another potential biomarker [8–10]. Apart from this several other proteins like h-FABP and CK-MB have also been identified as potential markers for MI [11–13]. Recently, Rezeli et al. have undertaken a multiple reaction monitoring (MRM) based study to show that the levels of APOC1, APOC2 and APOE were strongly associated with ST segment elevated MI [14–17]. Plasma proteomic analysis of large number of proteins in 135 MI patients revealed 7 markers (cyclophilin A, cluster of differentiation 5 molecule [CD5] antigen-like, mucin cell surface associated protein 18 [MUC-18], a cell-surface glycoprotein, collagen-α 1 [XVIII] chain, salivary α-amylase 1, C-reactive protein, and multimerin-2) to be strongly associated with the disease [18–23]. Applying discovery proteomics along with validation using orthogonal techniques like ELISA, Cubedo et al. have recently identified that lower level of retinol binding 4 (RBP4) is associated with onset of MI [24,25]. Apart from patient samples, model system based biomarker discovery for MI has also been undertaken. Jacquet et al. has identified myosin binding protein C, using a mice model of acute MI, as a candidate biomarker [26,27].

For the discovery of biomarkers in cardiomyopathy induced HF similar approaches have been undertaken by several groups either using animal models or by analysing patient samples. Classically using 2D electrophoresis followed by mass spectrometry analysis several studies have been published identifying different markers for HF. Peroxiredoxin 2, alpha crystalline, HSP 27, MMP-10 and MMP-7 were identified from human HF samples [28–34]. Chugh et al. have recently identified myosin heavy chain 7, desmin, insulin-like growth factor 7, and annexinA2 as circulating biomarkers of HCM induced HF using a transgenic mouse model and validated in human HF samples [35–38]. Interestingly, oxidation of alpha-1-antitrypsin and fibrinogen in plasma of cardiomyopathy patients by mass spectrometry has been documented [39]. Although B-type natriuretic peptide (BNP) has been so far the gold standard biomarker for HF, there is huge scope for identifying newer markers which could eventually help in the treatment. Recently, Quiescin Q6 (QSOX1) has been identified as a biomarker for decompensated HF. This protein plays a pivotal role in the formation of disulphide bridges. This protein was also tested in a prospective cohort and combining with BNP; the predictive accuracy improved to 0.95 area under the curve [40,41].

Atherosclerosis, the underlying cause for CAD, is another major form of CVD, which has been studied in great detail. The classical risk factors