Abstract

Cardiovascular disease continues to be a major health concern globally. Developments in genomic discovery have yielded valuable new candidates in the quest for better biomarkers and novel therapeutic targets. This brief perspective focuses on recent trends in this field. DNA microarrays, single nucleotide polymorphism chips, linkage analysis, genome-wide association studies, and other strategies have increased our knowledge of metabolic diseases of the heart. There are many benefits from these approaches, but one must remain cognizant of the importance of patient phenotyping. The integration of new and old tools and technologies promises the discovery and validation of better markers of the presence of cardiovascular disease, its progression, and the response to treatment.

Introduction

Trends in the incidence of cardiovascular disease (CVD) continue upward globally, yielding a significant impact on morbidity and mortality in both developed and developing societies. As the number of patients suffering from CVD mounts, alongside an aging demographic, the economic and social burdens of these diseases will continue to grow, with tremendous consequences for overstretched health-care systems. The search for new and better biomarkers of the presence and progression of disease, risk stratification, and response to treatment has become a matter of urgency. Fortunately, technological advances have facilitated high-throughput assessment and mining of the human genome, proteome, and metabolome. In this context, molecular signatures (biomarkers) will be increasingly useful in the prediction, diagnosis and management of heart disease.

Gene expression analysis

With the rise of high-performance technologies such as DNA microarrays, analyses of gene expression have been applied in the setting of various cardiovascular diseases. The level of transcribed genes and the related mRNAs detectable by the microarrays are often examined in an attempt to discover correlations with the presence or absence of disease, clinical outcome, disease progression, and therapeutic responses [1].
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Microarray analysis comparing the expression of genes in non-failing hearts and failing hearts (ie, ischemic or non-ischemic cardiomyopathy) has revealed substantial differences at a molecular level. In a study by Kittleson et al [2], 288 genes were identified as differentially expressed between groups with non-failing and failing hearts. Although none of the genes is currently used clinically, these genetic biomarkers can still provide therapeutic insights into the metabolic dysregulation underlying the disease conditions. As described by Kittleson and Hare [2] and Tan et al [3], many of the genes upregulated in failing hearts, relative to those in the non-failing hearts, were associated with fatty acid metabolism, whereas those downregulated were linked to glucose metabolism. This has triggered an investigation into the use of drugs such as trimetazidine and ranolazine, which can shift the lipid and glucose metabolic states in myocardial cells, as a potential treatment for failing hearts [2,4].

In the context of atherosclerosis, gene expression studies have also underscored the importance of regulation of lipid metabolism. Using mouse models, Karr et al [5] identified numerous genes involved in lipid metabolism that are differentially expressed during early stages of progression of the atherosclerotic lesion. In cardiovascular diseases such as ischemic and non ischemic cardiomyopathy and atherosclerosis, it is unlikely that a single biomarker can serve sensitively and specifically as the therapeutic or diagnostic biomarker for the disease. Biomarkers of the future are expected to be multi-marker panels characteristic of the complexity of the underlying pathophysiology of the disease process. In fact, only a small portion of familial and sporadic atherosclerosis results from single-gene defects in lipid metabolic pathways [6,7].

Genome-wide association studies

Beyond microarray-based expression studies, genome-wide association studies provide an effective approach to discovering genetic biomarkers. Genetic variants, such as those on chromosome 9 (interval 9p21) and chromosome 4 (4q25), have been linked to increased risk for CVD [8]. McPherson et al [9] applied genome-wide association scanning and discovered a 58 kb interval on chromosome 9p21 that was consistently associated with coronary heart disease in six independent cohorts, containing more than 23,000 participants, from more than four white populations. A similar finding was demonstrated by the Wellcome Trust Case Control Consortium, which found an association between a similar region on chromosome 9p21 and coronary artery disease [10]. In the study by Gudbjartsson et al [11], two sequence variants on chromosome 4q25 were found to be strongly associated with atrial fibrillation in three populations of European descent and in a Chinese population from Hong Kong.

In certain cases, the risk locus identified via genome-wide association studies contains genes that have yet to be annotated and characterized (eg, the 58 kb interval on chromosome 9p21). It may also be unclear what cellular and molecular differences are induced by these genetic variants. Certainly, many of the newly identified susceptibility loci or SNPs require further studies to determine their involvement in the pathogenesis of CVD and potential therapeutic targets for testing. It is likely that each SNP may have a modest influence on the concentrations or function of translated protein products, whereas a specific set of SNPs can have a major impact on the pathobiology of a particular CVD [1]. Nonetheless, just as with genes identified in microarray studies, SNPs may also contain valuable information on the mechanisms of CVD and potential new therapeutic targets.

Linkage analysis

Linkage analysis is another approach to finding genetic biomarkers of cardiovascular diseases. It allows the identification of disease DNA markers by examining the patterns of heredity in large high-risk families and the occurrence of disease phenotypes among family members [1,12]. Using linkage analysis to look at families with early-onset coronary artery disease, Connelly et al [13] have demonstrated an association between GATQA2, a transcription factor, and susceptibility for coronary artery disease. Recent studies by the Genetics of Early Onset Coronary Artery Diseases (GENCARD) investigators also revealed novel gene candidates, such as LSAMP, a tumor suppressor gene, and KALRN, a gene involved in the Rho GTPase-signaling pathway, to be associated with coronary artery disease [14,15].

Discussion

It is not uncommon, in observing different genomic and genetic biomarkers studies using differing technologies – microarrays, SNP chips, or linkage analysis – that different genes or polymorphic loci are found to be associated with the same cardiovascular pathology. Certainly, an important factor to consider when comparing different genetic biomarkers studies is the selection of patient cohort. Depending on the heterogeneity or the size of the population being analyzed, the genetic biomarkers detected may be significantly different. Ideally, a larger, more
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heterogeneous cohort can result in a more widely applicable biomarker discovery. However, this increase in heterogeneity may also compromise the ability to find potentially more specific biomarkers that are associated with particular extreme phenotypes. Ultimately, the key to success in genotypic characterization and expression studies will be the exquisite phenotyping of groups of patients of interest.

The potential genetic basis of cardiomyopathies and therapeutic targets of heart failure have been discussed in detail by Liew and Dzau [16], Kittleson and Hare [2] and Heidecker et al [17]. The genetics with respect to specific types of cardiomyopathies and channelopathies was reviewed in great detail by Bezzina [18], in the previous issue of Heart and Metabolism. In the context of atherosclerosis, relevant genetic biomarkers have also been discussed by Miller and colleagues [6].

Ultimately, the genetic biomarkers identified using various technologies may be complementary to one another. Future systems biology studies may shed light in this regard, and provide a more complete picture of the genetic mechanisms underlying each CVD. It is possible that complex, multifactorial CVDs result from a combination of effects attributable to the presence or absence of specific genetic mutations, polymorphisms, or differential expression [19].

There are probably many effective therapeutic targets that have yet to be discovered. Genetic biomarkers may also help uncover these nuggets of gold. Just to put things into perspective, the human genome contains more than 22,000 genes, but it has been suggested that current medication targets only about 2.3% (approximately 500) of them [6,20].

Developments in the technical capabilities underlying high-throughput genomic approaches, coupled with a focus on patient phenotyping and advanced computational strategies, will continue to add incremental value to our current understanding of heart diseases, and have the potential to revolutionize the management of patients through earlier intervention and more effective interdiction on the processes of disease progression.

REFERENCES
10. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–678.