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A Genomic Approach to Characterize the Vulnerable Patient – a Clinical Update

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ABSTRACT

Atherosclerosis is the elemental precondition for any cardiovascular disease and the predominant cause of ischemic heart disease that often leads to myocardial infarction. Systemic risk factors play an important role in the starting and progression of atherosclerosis. The complexity of the disease is caused by its multifactorial origin. Besides the traditional risk factors, genetic predisposition is also a strong risk factor. Many studies have intensively researched cardioprotective drugs, which can relieve myocardial ischemia and reperfusion injury, thereby reducing infarct size. A better understanding of abnormal epigenetic pathways in the myocardial pathology may result in new treatment options. Individualized therapy based on genome sequencing is important for an effective future medical treatment. Studies based on multiomics help to better understand the pathophysiological mechanism of several diseases at a molecular level. Epigenomic, transcriptomic, proteomic, and metabolomic research may be essential in detecting the pathological phenotype of myocardial ischemia and ischemic heart failure.

Keywords: coronary artery disease, multiomics, epigenetics, gene sequencing, proteomics

FROM ATHEROSCLEROSIS TO MYOCARDIAL INFARCTION – WHO ARE THE VULNERABLE PATIENTS?

Coronary artery disease (CAD), with its most severe manifestation being acute coronary syndromes comprising acute myocardial infarction and unstable angina, is still the main cause of mortality across the globe.[1,2]

Atherosclerosis is the elemental precondition for any cardiovascular disease and the predominant cause of ischemic heart disease that often leads to myocardial infarction.[3] Atherosclerosis is a chronic, systemic, inflammatory disorder that consists in early and gradual accumulation of lipids and fibrous elements affecting the large and medium-sized arteries.[4–6] These atheromatous or fibrofatty plaques are asymmetric focal thickenings of the intima, which can remain clinically asymptomatic until the surface undergoes erosion or rupture.[7–9] Plaque rupture is the main cause of thrombus formation, obstructing the artery due to cessation of blood flow with subsequent acute ischemia in the affected area.[10]

MULTIFACTORIAL ORIGIN AND HERITABILITY OF ATHEROSCLEROSIS

Systemic risk factors play an important role in the starting and progression of atherosclerosis. The complexity of the disease is caused by its multifactorial origin. Besides the traditional risk factors, such as high plasma lipid concentrations, smoking, alcohol intake, high blood pressure, presence of diabetes and chronic inflammatory disorders, genetic predisposition is also a strong risk factor with an estimated familial inheritance between 30 to 60%, the genetic effects decreasing gradually at older ages.[11–13] These observations drew the attention of researchers to determine the genes involved in the heritability of MI and cardiovascular risk factors.

More recently, the completion of the Human Genome Project and the International Haplotype Map Project has made it possible to perform genome-scale screens for common DNA sequence variants that are associated with phenotypes of interest. This technique has expanded our knowledge of the genetic basis for coronary disease.[14,15]

THE MULTIOMICS APPROACH FOR THE VULNERABLE CARDIOVASCULAR PATIENT

The nomenclature of the disciplines involved in omics research is not absolutely clear; in fact, it is rather chaotic. The main reason for this is that there is no official standpoint on the accurate use of the concepts.

Many studies have intensively researched cardioprotective drugs that can relieve myocardial ischemia and reperfusion injury, thereby reducing infarct size. Similarly to the fight against cancer, drugs that focus mainly on the chromatin-dependent signaling effectors provide a better understanding of the abnormal epigenetic pathways in the myocardial pathology and may result in new treatment options.[16,17] Individualized therapy based on genome sequencing is important for an effective future medical treatment.[18]

Multiomics studies help to understand diseases and disease stages at a molecular level. These analytic technologies provide new insights into the pathogenesis of common diseases, using the detection of biomarkers for disease onset and progression.[19] Epigenomic, transcriptomic, proteomic, and metabolomic research may be essential in detecting the pathological phenotype of myocardial ischemia and ischemic heart failure.[20]

Genomics and transcriptomics

Genomics comprises studying the genome to understand the content of DNA/RNA, as well as their structures, functions, and biological effect. Transcriptomics are similar to genomics studies, studying how the genes are regulated and expressed in different biological settings. Transcriptomics is an inventory of RNAs, examining different RNAs produced by the genome under specific conditions or treatments.[21] Transcriptomic studies are performed through the use of gene expression micro arrays or RNA sequencing (RNA seq) to quantify the abundance of patterns of expression of RNA transcripts across the genome.[21]

The pathogenesis of myocardial ischemia and heart failure triggers microarrays, stress-activated pathways in the nucleus, causing abnormalities in cardiac gene expression. Previous studies have tried to determine the activation of specific DNA-binding transcription factors. Chromatin-dependent signal transduction in cardiac gene control of NFAT, MEF2, NF-κB, GATA4, and C-MYC is significant for cardiac remodeling. These abnormalities in the control of gene expression activated by molecular mechanisms have remained poorly understood.[17] A number of genome-wide linkage studies have been performed and have identified possible chromosomal loci related to myocardial infarction and coronary disease. However, the utility of many of these studies is questionable. Wang *et al.* have studied the mutation in a subcategory of myocyte enhancer family of transcription factors, the human myocyte enhancer factor 2A (MEF2A) gene.[22] The MEF2A has been identified as an autosomal dominant genetic form of CAD.[22]

A few years later, a large follow-up study identified the genes in control subjects without CAD, but they did not find any associations between MEF2A and CAD.[23] The newest study about this gene mutation presents the functional effects of the mutation on the target gene, which is significant and dominant, and therefore may override other risk factors and induce pathological outcomes in subjects with the mutation present.[24] Studies have shown that leukocyte-peripheral blood-based gene expression is changed with stroke, hypertension, and obstructive CAD in non-diabetic patients.[25] Atherosclerosis has a clear inflammatory component; as a consequence, the blood transcriptomics biomarkers of disease are identifiable.[21]

Another source of transcriptome in the plasma, which can be examined, is the microRNA (miRNA). This small type of RNA is an endogenous non-coding RNA, transcriptional and posttranscriptional inhibitors of gene expression, with a negative regulatory function of mRNA translation, which targets the messenger RNAs (mRNAs). They have also been linked to cardiovascular disease and are involved in the pathogenesis of cardiovascular diseases and have become a target for therapeutic intervention.[26]

There is an increasing interest in early changes in microRNA expression as a protective pathway for inducing ischemic preconditioning of the heart, triggered by ischemia, with related cardioprotective mechanisms. Researchers identified potential cardioprotective miR such as miR125b*, miR-139-3p, miR-320, miR-532-3p, and miR-188.[27] Transcriptomic studies have recognized several clusters of miRNA and individual miRs that control cardiomyocyte proliferation and may stimulate effective regeneration processes in the ischemic adult myocardium.[28]

Epigenomics

Epigenomics is the study of gene transcription that is regulated by a complex of epigenetic factors. Studies report that gene expression modulated by epigenetic mechanisms is realized by ATP-dependent chromatin remodeling, ncRNA-based mechanisms, covalent histone modifications, and DNA methylation.[29,30] The interaction between individual genetic properties and cardiovascular risk factors and co-morbidities increase with ageing, which influences expression changes and phenotype.[31]

The complexity of molecular signaling pathways is given by many variations of gene expression profiles and phenotypes, which can directly contribute to disease progression.[20] Many studies have investigated gene transcriptions induced by adverse cardiac remodeling. Gidlof *et al*. have studied the myocardial ischemia-induced genome-wide epigenetic modifications in cardiomyocytes.[32] They performed ChIP-Seq on mice (a combination of chromatin immunoprecipitation followed by sequencing) in the preconditioned cardiac tissue using ischemic preconditioning methods and the microarray transcriptome. They found a strong association between IPC and autophagy-induced proteolysis, which is responsible for the degradation of aggregated and damaged organelles; thus, autophagy seems to have an important role in the cellular stress response. Likewise, they found the Mtor gene, a serine/theonine kinase, which inhibits autophagy.[32]

Proteomics and metabolomics

To better picture the process of how the gene expression profile influences the cardiac phenotype, it is necessary to investigate the global cardiac protein expression and its effect on global cell metabolism.[20] The fundamental difference between the genome and transcriptome/proteome is that while the genome of each cell is the same, the transcriptome and proteome is cell type-dependent.

Proteomics is the study of the complete set of proteins under different circumstances, including post-translational modifications. The study of the proteome includes the characterization of the function of genes influenced by proteins participating in molecular signaling pathways. This cascade is a series of enzymatic reactions, which are initiated by a stimulus that is transduced to the cell interior, resulting in a response to the initial stimulus. Similar to how gene expression can change under pathological conditions, in this case too, at each step of the signaling cascade, many protein-protein physical interactions are involved in regulating cellular actions.[33]

Metabolomics represents the identification and analysis of various metabolite products. A metabolite is the intermediate end-product of a metabolic pathway and enzymatic reaction. Additionally, metabolites participate in the regulation of cellular microenvironments, in which chemical signals can promote changes in gene signal transduction, thereby they can be used to investigate the level of variations.[33]

THE ROLE OF PHARMACOLOGICAL TREATMENTS IN THE MULTIOMIC APPROACH

There is no sufficient human data so far on the effect of cardiovascular risk factors and their pharmacological therapy on the pattern of change in gene expression of the normal or ischemic heart.

Ischemic heart disease and its traditional risks factors induce fundamental alternations in cellular signaling pathways; moreover, some currently applied drugs to treat these comorbidities may also modify the cardiac gene expression pattern.

The excessive use of long-term prophylactic nitrate therapy may induce nitrate tolerance, which leads to the loss of clinical efficacy, also modifying the gene expression profile and aggravating ischemia/reperfusion injury, thus leading to loss of the cardioprotective effect of preconditioning.[31,34]

Statins, a class of drugs frequently used for primary and secondary prevention of vascular disease, show a potential cardioprotective effect. Some statins, depending on the duration of the treatment, present the capacity of modifying the cardiac genetic profile due to interference with the mechanisms of cardiac adaptation to ischemia/reperfusion stress.[31,35] These routinely used cardiovascular medications may have unforeseen cardiotoxic effects, especially on the cardioprotective signaling mechanisms and on the ischemic heart. Multiple clinical studies are examining the mechanisms and long-term effects of statins; however, their effect on cardiac gene expression has not yet been investigated.[20]

CONCLUSION

Coronary artery disease is a multifactorial disease, and previous studies have shown multiple specific genes and their variants directly associated with the presence and prognosis of CAD. New modalities, such as 'omics' approaches, have transformed the fundamentals of clinical diagnostic approaches, risk assessment, prognosis, and future treatment modalities for the vulnerable cardiovascular patient. With genome sequencing on the rise, the use of genomic information in clinical medicine will increase. The integration of genetic methods in clinical practice will help the everyday decision-making and will have a large effect on the development of individualized medicine. The development and description of the cardiac genetic profile may help to recognize key cardioprotective modalities, which can represent a future target of gene therapy. Omics technologies have the capacity to reform our basic understanding of cardiovascular diseases at a molecular level and to open the way to novel research, new therapeutic options and diagnostic modalities of cardiovascular disorders in the post-genomic era.

CONFLICT OF INTEREST

None declared.

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