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Review

Gene expression studies in human abdominal aortic aneurysm

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ABSTRACT

Abdominal aortic aneurysm (AAA), defined as a dilatation of the aorta (> 3 cm) below the renal arteries, has a complex etiology and it is associated with a risk of rupture. Surgical repair, open or endovascular, is the only available treatment option. Genome-wide studies using microarrays with the purpose of identifying mRNAs and microRNAs involved in the pathogenesis of AAA have been published recently. They provided strong evidence that genes involved in immune and inflammatory pathways and a wide range of other biological functions, such as calcium signaling, cell adhesion or regulation of apoptosis differ in expression when comparing aortic tissue taken from AAA and non-aneurysmal controls. MicroRNAs that control gene expression were also found to be up or down regulated providing a potential mechanism for differences in mRNA levels in the AAA tissue. Future studies to confirm these findings and to elucidate the molecular mechanisms of pathophysiology are needed to develop better diagnostic tests, using biomarkers, and to identify new therapeutic targets for AAA.

Contents

Abbreviations: AAA, abdominal aortic aneurysm; ANGPTL4, angiopoietin-like 4; C1QA, complement component 1, q subcomponent, A chain; C1QC, complement component 1, q subcomponent, C chain; C2, complement component 2; C3AR1, complement component 3a receptor 1; C5AR1, complement component 5a receptor 1; CAM, cell adhesion molecules; CD59, CD59 molecule, complement regulatory protein; CFH, complement factor H; FA, focal adhesion; FDR, false discovery rate; GEO, Gene Expression Omnibus database; GO, Gene Ontology; HBB, hemoglobin, beta; HBD, hemoglobin, delta; HBQ1, hemoglobin, theta 1; HOX, homeobox gene; HOXA4, homeobox A4; HRG22, hypermethylated in cancer 2 (HIC2); IL8, interleukin 8; ILT, intraluminal thrombus; INFγ, interferon, gamma; IPA, Ingenuity Pathway Analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes; LRP5, low density lipoprotein receptor-related protein 5; LTEM, leukocyte transendothelial migration; MAPK, mitogen-activated protein kinase; miRNA, microRNA; NK cell, natural killer cell; PCA, principal component analysis; PROK2, prokineticin; Q-RT-PCR, quantitative reverse-transcription - polymerase chain reaction; RAC, regulation of actin cytoskeleton; RT-PCR, reverse transcription - polymerase chain reaction; rVISTA, regulatory VISTA, a computational tool for comparative genomics; SAM, significance analysis of microarray; SERPING1, serpin peptidase inhibitor, clade G (C1 inhibitor), member 1; SNP, single nucleotide polymorphism; STAT5A, signal transducer and activator of transcription 5A; VEGF, vascular endothelial growth factor A

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Introduction

Abdominal aortic aneurysm (AAA) is defined as a dilatation in the infrarenal aorta with a diameter greater than 3 cm [1]. AAA is four times more common in men than women and the prevalence increases with age [2]. Smoking is the most important risk factor for the development of AAA and people who continue to smoke also have higher AAA growth rates [3]. Other risk factors include family history of AAA and coronary artery disease [4]. Interestingly, diabetes has a negative relationship with AAA which contrasts with its role in occlusive vascular disease and provided a challenge to the traditional view of AAA as a manifestation of atherosclerosis [5]. The options for a patient with an asymptomatic AAA include observation with follow-up or a surgical treatment using open surgical repair or endovascular stenting [1]. Medical therapy may be helpful in patients with small- to medium-sized aneurysms that are not surgically treated and should include: cessation of smoking and antihypertensive treatment [1]. There is, however, no medication proven to slow AAA progression [6]. It is, therefore, important to study the mechanisms of AAA development and progression to help design drugs to interfere with the processes and develop medical treatment options [6,7].

AAA has a strong genetic component, although the pathobiology of AAA is not well understood [1,6–12]. Genetic studies on AAA have included candidate gene studies, DNA linkage studies and genome-wide association studies [7–12]. Another approach to study disease pathogenesis at the molecular level is to perform a genome-wide mRNA expression analysis to identify genes actively transcribed in AAA and non-aneurysmal infrarenal aortic tissue and look for changes in mRNA levels introduced by the disease [7–9,11,13]. In the current article we review and summarize the results of the published genome-wide mRNA and microRNA (miRNA) expression studies on AAA, discuss methodological considerations and highlight future research opportunities.

Methodological considerations in genome-wide expression studies in human AAA

To carry out large-scale gene expression studies, DNA microarrays were developed in the 1990s. They allow the RNA products of thousands of genes to be monitored simultaneously, revolutionizing the way in which gene expression is now analyzed (Fig. 1). The investigation starts with collecting samples in a way that minimizes RNA degradation and trying to match cases and controls for sex, age and ethnicity. It is also important to obtain the control samples from the infrarenal region of aorta, since this is the most common site of AAAs and regional variation in gene expression along the length of the aorta has been reported [14]. Strict quality control steps are required to make sure the isolated RNA is intact. cDNA is then synthesized from the RNA, labeled with a fluorescent dye and used for hybridization against probes located in the microarray [9]. After washing and scanning, the results are analyzed. Special attention is required on statistical analysis to correct for multiple testing. Finally, *in silico* analyses to classify the genes found to be significantly different between cases and controls are carried out. These analyses might include using Gene Ontology (GO; http://www.geneontology.org/) [15] and Kyoto Encyclopedia of Genes and Genomes (KEGG; http://www.genome.jp/kegg/) [16] for categorizing the differentially expressed genes into functional groups and biological pathways. Additional *in silico* analysis includes a network analysis, such as Ingenuity Pathway Analysis (IPA; Ingenuity Systems, Mountain View, Calif., USA;

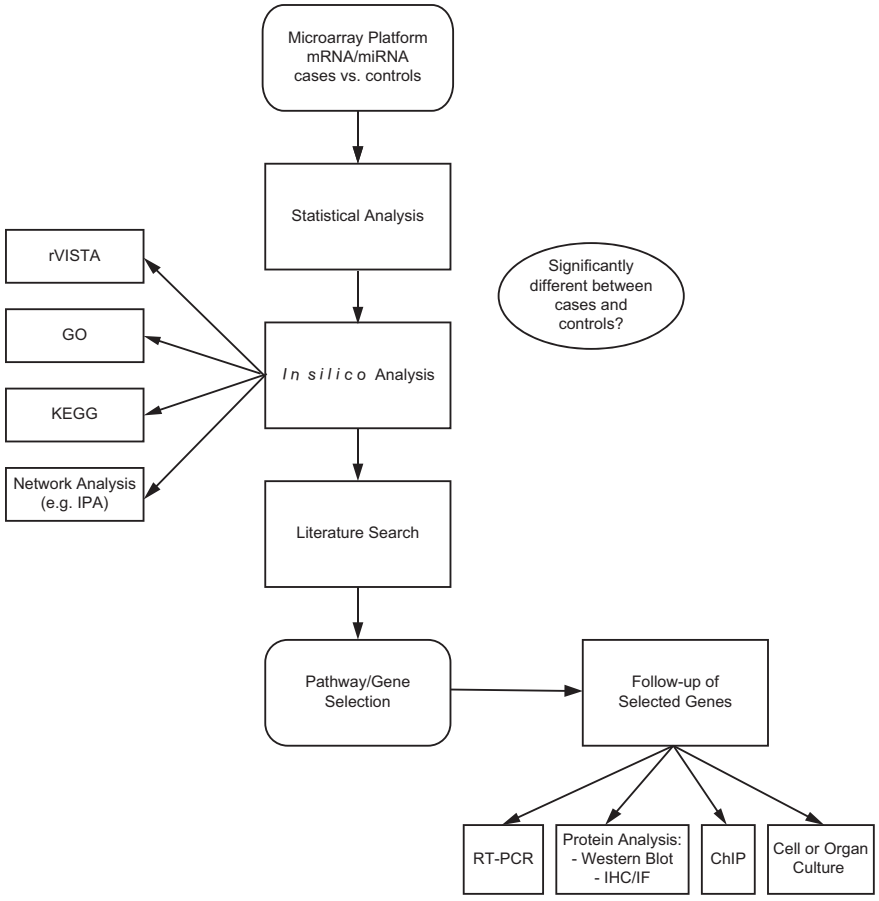

Fig. 1. Summary of microarray-based gene expression and follow-up studies in AAA. See text for details on the different steps.