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Journal of Thoracic Disease and Cardiothoracic Surgery
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Review Article

Current Progress in Multi-Omics Studies of Aortic Dissection

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Received date: April 23, 2023; Accepted date: May 07, 2023; Published date: May 19, 2023

Citation: Qijun Zheng, Xiaoying Zhu, Xiong Jia, Yayu Wang, (2023), Current Progress in Multi-Omics Studies of Aortic Dissection, *J Thoracic Disease and Cardiothoracic Surgery*, 5(1); **DOI:**10.31579/2693-2156/056

Abstract

Aortic dissection (AD) is a cardiovascular disease with a high mortality rate. With the rapid development of genetic testing technology, genomics can be used to predict, diagnose and treat AD. In this review, we summarize studies on AD using the genome, epigenome, transcriptome, proteome and metabolome. Multi-omics analysis can further clarify the mechanisms of AD and provide risk assessment techniques. Although related studies on the different omics of AD have been conducted, the combined analysis of multiple omics has not been studied in depth. In this paper, we will conduct an in-depth discussion of AD research using multiple omics.

Keywords: aortic dissection; genomics; epigenomics; transcriptomics; proteomics

Introduction

Aortic dissection (AD) is a rare but life-threatening cardiovascular condition associated with high morbidity and mortality rates and is one of the main diseases affecting the aorta.[1] AD involves the separation of layers that create a false lumen within the aortic wall. The force of blood pumping can split the layers of the arterial wall and, allow blood to leak between them, in a process called dissection, which can disrupt or interrupt the blood supply to vital organs.[2] If the tear occurs in the ascending aorta, in the front of the chest, it is classified as a type A dissection. If it occurs in the descending aorta, it is classified as a type B dissection. According to incomplete statistics, the annual incidence of aortic dissection in 65-75 years old is 17.4/100000,[3,4] and 200000 new cases are diagnosed in China yearly. However, AD patients have a mortality rate of up to 80% within a week in the absence of emergency treatment.[5] The main treatment methods are drug therapy and surgical repair, however, the mortality rate of surgery is as high as 10%-35%, and there are other sequelae. As the clinical manifestation of AD lacks specificity, the rate of initial misdiagnosis of AD is 14.1% in patients diagnosed with this devastating clinical event.[6] Therefore, exploring potential biomarkers of AD is crucial for early detection and treatment to reduce mortality.The etiology and pathogenesis of AD remain unclear. Essential hypertension, hardening external injury, smoking, pheochromocytoma, and inflammatory alterations may increase the susceptibility to major pulse-related diseases in many patients. In addition, poorly controlled high blood pressure is a major risk factor for aortic clamping,[7–9] and approximately 80% of patients with AD have hypertension. Furthermore, genetic factors also play acrucial role in the etiology of AD. Currently, the diagnosis of AD still relies on imaging techniques, of which contrast-enhanced Computed Tomography (CT) is the most widely used.[7] However, patients with AD require braking and sedation, which limits the use of contrast-enhanced CT. Therefore, the assessment of risk factors, detection of biomarkers and identification of inherited gene mutations are of great importance for predicting the risk and reducing the mortality rate of AD. Since the beginning of this century, the development of high-throughput (omics) techniques, including genomics, transcriptomics, proteomics, metabolomics and computational resources has importantly increased our understanding of AD.

Genomics:

An organism's complete set of DNA is called its genome. Virtually every single cell in the body contains a full copy of the approximately 3 billion DNA base pairs, that make up the human genome.[10] Genomics is the study of a person's genes (the genome), including interactions of those genes with each other and with the person's environment.[8] Genomic sequencing technologies mainly include whole-exon sequencing (WES),[11] whole genome sequencing (WGS), and DNA microarray technology.[12] Genomics pioneered the era of omics and is also the foundation of multi-omics.Currently, the pathogenesis of AD from the perspective of gene variation can be divided into two categories: simple nucleotide variations (SNVs) and structural variations (SVs).[13] The SNVs can be further divided into single nucleotide variations and small insertions/deletions (indels). SVs are generally defined as deletions (DELs), insertions (INSs), duplications (DUPs), inversions (INVs), or translocations (TRAs) at least 50 bp in size.[14] Previous studies have shown that the complex genetic background of AD is mostly related to connective tissue diseases, such as Marfan syndrome (MFS) induced by the FBN1 gene[15,16] Ehlers-Danlos syndrome caused by heterozygous mutations in the COL3A1 gene, which encodes type III collagen (COLL III);[17,18] Loeys-Dietz syndrome caused by heterozygous missense mutations in either the TGF-β receptor gene (TGFBR1) or TGFBR2;[19] Shprintzen-Goldberg syndrome caused by SKI (V-Ski avian sarcoma viral oncogene homolog).[20]

Heredity gene in AD

Thoracic aortic dissection (TAD) occurs in the thoracic region, mainly in middle and old age; most of which are sporadic.[21,22] Several studies have reported the importance of inherited factors in the development of non-integrated thoracic aortas, with a heritability of approximately 70%,[23] and 20%-40% of TAD patients have a family history.[24] A study at Yale University, which sequenced 15 genes in 1025 European patients with TAD in the second generation, found that almost half of those with pathogenic or potentially pathogenic variants were non-syndromal and had no family history of AD.[25] In many affected families, AD is inherited in an autosomal dominant manner with decreased penetrance and variable expressivity.[26] Mutations in 13 genes have been confirmed to be related to the disease in approximately 30% of affected families. Wallace et al assessed the effect of MYLK missense mutation on myosin light-chain kinase (MLCK) activation in 60 patients and found that AD developed earlier in the patients with this mutation.[27]The main risk factors for AD are hypertension and underlying genetic alterations. Genetic changes have been found to help identify the pathogenesis, early detection and early treatment of AD.

Related pathogenic genes of AD

To date, at least a dozen genes may be associated with AD, such as *FBN1*,[28] *FOXE3*,[29] *LTBP3*,[30] *PRKG1*,[31] *CDK1*,[32] and *TGFB2*.[33] The extracellular matrix (ECM) glycoprotein encoded by FBN1 is an integral part of the elastic fiber of AD.[34] The loss of microfibers and the damage to elastic fibers lead to thinning and brittleness of the aortic wall, which is one of the most important motile causes of AD. *FBN1* also plays a role in regulating the bioavailability of TGF-β. The loss of *FBN1* promotes the release of a large amount of active TGF-β1 in the ECM, leading to excessive activation of the TGF-β signaling pathway and accelerating the destruction of the ECM.[35] The elastic fibers of aortic wall cells become thinner and more fragile, AD occurrence.

Although many mechanisms have not been identified yet, the pathogenesis of AD will progress with the development and improvement of genomics and sequencing technology, laying a foundation for the development of precision medicine.

Epigenomics

Epigenomics refers to changes in gene expression levels based on non-gene sequence changes, including DNA methylation, histone modifications, chromosomal remodeling, and noncoding RNA regulation;[36] mainly by regulating transcription or translation process, and affecting gene function and characteristics. Individual epigenetic recognition aids in cardiovascular disease diagnosis, prediction, prognosis, biomarkers and drug target selection.[37] *DNA methylation*

DNA methylation is a process in which cytosine is converted to 5-methyl cytosine catalyzed by DNA methyltransferase.[38] It is a direct chemical modification of DNA without changing the DNA sequence and is closely related to gene expression regulation.[39] The aortic tissues of AD patients and healthy individuals as controls were examined by whole-genome bisulfite sequencing (WGBS). Epigenetic regulatory changes related to the vascular system and heart development, causing changes in gene expression, have been found in AD cases. For example, epigenetics changes in the Hox family genes may lead to loss of aortic integrity and AD pathogenesis.[40] Another recent study also identified 28 differentially methylated positions (DMPs) in Marfan syndrome, which were significantly correlated with aortic diameter in patients with MFS. Seven of these DMPs (25%) could be assigned to genes previously associated with cardiovascular disease (*HDAC4, IGF2BP3, CASZ1, SDK1, PCDHGA1, DIO3, PTPRN2*).[41]

Histone modification

Histone modifications include methylation, acetylation and ubiquitination phosphorylation pathways, which affect the occurrence and development of AD by targeted transcriptional regulation of the AD gene at the transcriptional level.[42] In recent years, the intracellular downstream effectors of the TGF-β ligands TGFB2 and TGFB3 and the TGF-β pathways SMAD2 and SMAD3 have been shown to affect cardiovascular connective tissue disease, leading to aortic aneurysms and varicoses.[43] Overexpression of SMAD2 in these vascular smooth muscle cells (VSMCs) was subsequently shown to be regulated by histone acetyltransferase (P300/PCAF).[44]Therefore, abnormal TGF-β signaling frequently observed in gene-triggered AD may be associated with aberrant histone regulation affecting SMAD2 transcription.

Transcriptomics

The term transcriptome implies the complete set of all the ribonucleic acid (RNA) molecules expressed in some given entity, such as a cell, tissue, or organism.[45] This process links the genome, proteome, and cellular phenotype.[46] After genome sequencing, transcriptomics analysis enables understanding genome expression at the transcriptional level, providing information on gene structure, regulation of gene expression, gene product function and genome dynamics.[47] New biomarkers at the transcriptome level may lead to earlier diagnosis time and higher specificity compared to previously known markers and inflammatory factors. Noncoding RNAs (ncRNAs) such as short-noncoding RNAs and long-noncoding RNAs are emerging as new fundamental regulators of gene expression.

microRNA

MicroRNAs (miRNAs) are endogenous ncRNAs that are approximately 20-25 nucleotides long and play essential roles in regulating pathophysiological functions, such as differentiation, proliferation, migration and apoptosis.

The change in miRNA expression level is related to the occurrence of different diseases, such as miR-135a-3p, miR-200c, miR-216a and miR-340, which modulate the invasiveness of ovarian cancer cell[48] and miR-143/145 in cardiovascular diseases.[49] Over the past decade, several miRNAs have been shown to regulate vascular remodeling,[50] and to target endothelial cells, smooth muscle cells and immune cells in the vasculature to alter the pathophysiology of the aorta. miRNA-21 regulates

SMAD7 expression, affects typical TGF-β signal transduction, and participates in the formation of AD.[51] In addition, some experiments have confirmed the decreased expression of miR-145 in ascending aorta specimens of AD.[49] miR-320 can regulate the expression of matrix metalloproteinases (MMP) after transcription. MMP overexpression contributes to ECM degradation, thus affecting AD progression.[52] In a BAPN(3-Aminopropionitrile fumarate)-induced mouse AD model, inhibition of miR-144-3p expression resulted in a reduced incidence of AD from 90% to 50%. In addition to the mouse model, miR-30A expression is significantly upregulated in human AD ascending aorta specimens[53]. Other miRNAs include microRNA-146b (miR-146b)[54], microRNA146a-5p (miR-146a-5p)[55], and microRNA-143/145[56]. They are biomarkers for AD diagnosis, which can predict the risk of AD, assess prognosis, and serve as a basis for choosing the timing of surgery.

Recently, researchers analyzed exosomal miRNAs in the plasma of AD patients and found 283 specific microRNAs.[55] They analyzed the previous ten and lower ten miRNAs and found that the plasma exosomal microRNAs were mainly involved in the pathogenesis of AD with acute lung injury (ALI) by recruitment of immune cells, expanding inflammatory response, breaking cell connections and the framework. For example, miR-206 is related to lung tissue inflammation in ALI and miR-485-5p may participate in AD with ALI by regulating inflammation and promoting lung capillary endothelial injury.

Long non-coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs), generally 200 nt long, are reported to be three-dimensional (3D) regulators of transcription and translation by acting as molecular decoys and scaffolds or by binding guide ribonucleoprotein complexes to their targets. In recent years, lncRNAs have been found to play an important role in the occurrence and development of cardiovascular diseases.[57] Most of these have significant spatiotemporal expression and specificity during tissue differentiation and development, making them good biomarkers for the diagnosing of AD.

Proteomics

The proteome is the whole complement of proteins, including modifications made to a certain set of proteins, produced by the organism. Proteomics stability is required to ensure the proper function of cells and organisms.[58] Proteomics can be defined as a large-scale study of protein properties, aimed at studying the whole proteome or the sum of all proteins from an organism, tissue, cell, biofluid, or a subfraction thereof.[59,60]

In recent years, progress has been made in the study of AD based on proteomics. Deng et al used isobaric tags for relative and absolute quantitation (iTRAQ) and label-free analysis, to compare the differences in protein expression profiles in ascending aortic wall specimens of AD patients and normal individuals as controls.[61] This study identified and validated that Lumican, PI16, MMP9, and FGL1 proteins may be a potential biomarker in patients with AD. The pathogenesis of AD may be related to the lumican-mediated TGF-1 pathway. In addition, in another label-free proteomics study, vinculin expression was significantly increased in aortic tissue samples and the concentration of vinculin increased in both type A and B dissection.[62] In both of these studies, serum samples were used, but aortic wall samples could also be used. Tandem mass tag (TMT) analysis of the aortic arch revealed that integrin alpha 3 (ITGA-3) and ITGA-5 could be the target proteins of AD among 100 down-regulated proteins.[63]

In proteomics, there are findings in MFS also, in addition to the study of AD. MFS is a heritable disorder of the connective tissue whose most life-threatening manifestation is AD. Using proteomic techniques, Pilop et al identified upregulation of the filamin A C-terminal fragment in aortic media of MFS patients suffering from an aneurysm of the ascending aorta.[64] Another study that investigated the glycoproteomics of MFS showed that microfibril-associated glycoprotein 4 (MFAP4) glycosylation was enhanced in advanced aneurysms of MFS compared with control aneurysms of patients without MFS, and its expression was also enhanced.[65] The research team further conducted a retrospective study of the role of MFAP4 in Marfan syndrome. They found that MFAP4 expression is upregulated by TGF-β in MFS.[66]

These proteomic data provide novel biomarkers for diagnosing AD and improving the accuracy of existing diagnostic strategies. However, proteomic research on AD is still in the developmental stage, and many technologies, such as protein separation, need to be improved further.

Metabolomics

Metabolomics is the scientific study of chemical processes that involve metabolites, small-molecule substrates, intermediates, and cellular metabolites. Specifically, it is the study of the metabolic spectrum of small molecules for specific cellular processes.[67] Metabolomics is a relatively recent development in this domain but has already proven its high efficacy in many clinical areas, such as the evaluation and personalization of drug therapy. Recently, several studies have explored the metabolite profiles of AD patients.

Researchers have identified serum metabolomic markers with the potential to diagnose AD and distinguish between the two subtypes of AD through metabolomic approaches. They analyzed the plasma metabolome of different samples by ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry. They found that in patients with AD, lysophosphatidylcholines (LPCs) and sphingolipids were significantly altered, whereas with sphingolipids, such as sphinganine, phytosphingosine, and ceramide significantly reduced in patients with Stanford type A AD group.[68] The combination of these two metabolite families can be used as potential biomarkers for diagnosing AD and distinguishing Stanford A from Stanford B.

Other researchers have studied new pathological mechanisms and potential biomarkers of AD by analyzing the overall metabolic profile of patients with AD. They compared plasma metabolites in AD, AA, and regular groups and found that sphingolipids, especially their core metabolite C18 ceramide, were significantly increased in TAD patients.[69] Then they demonstrated that C18-Ceramide plays an important role in TAD by aggravating aortic inflammation through the NLRP3 pathway in mice and *in vitro*. Conversely, Lian et al also used metabolomics and Seahorse extracellular flux analysis to examine the metabolic status of macrophages involved in AD. Macrophage metabolism is reprogrammed in AD, thereby inducing HIF-1α activation. These experimental results suggest that macrophage HIF-1α may be a potential therapeutic target for AD.[70]

Significant progress has been made in the study of metabolomics in AD, however, there are still shortcomings and deficiencies. The research conducted so far mainly analyzed the differences in lipids in the metabolome in AD, and there is still a lack of research on the mechanism. Future studies should further analyze the signaling pathways of different products in the metabolome, to identify more effective targets for the treatment of AD. Although metabolomics was developed after genomics and transcriptomics, it has become an important supplement to genomics and transcriptomics because of its low cost and wide detection range.

Discussion

Single- and multi-omics datasets have been widely used in aortic dissection research, to find biomarker signatures, discover disease subtypes, predict response to therapy, and for functional omics studies

(Figure.1). However, various mono mics have their limitations. DNA sequencing can clarify the differences and similarities in coding sequences. In addition, RNA expression, protein structure and activity cannot be determined by gene sequencing. An insufficient genetic pool and positive pathological samples also constrain genetic and phenotypic associations. Double-strand RNA-mediated RNAi-specific gene silencing by specific enzymes can block gene expression at transcriptional, post-transcriptional and translational levels. Shortcomings of current transcriptomics technology are that: RNA does not reach protein in a 1:1 ratio after RNA transcription, degradation, translation and post-translational modification, so it is essential to evaluate proteins and their concentrations, interactions and positions. The protein concentration, activity, and compensation effect of similar proteins in proteomics may affect the study results, and small-molecule substances in metabolomics can compensate for this deficiency.

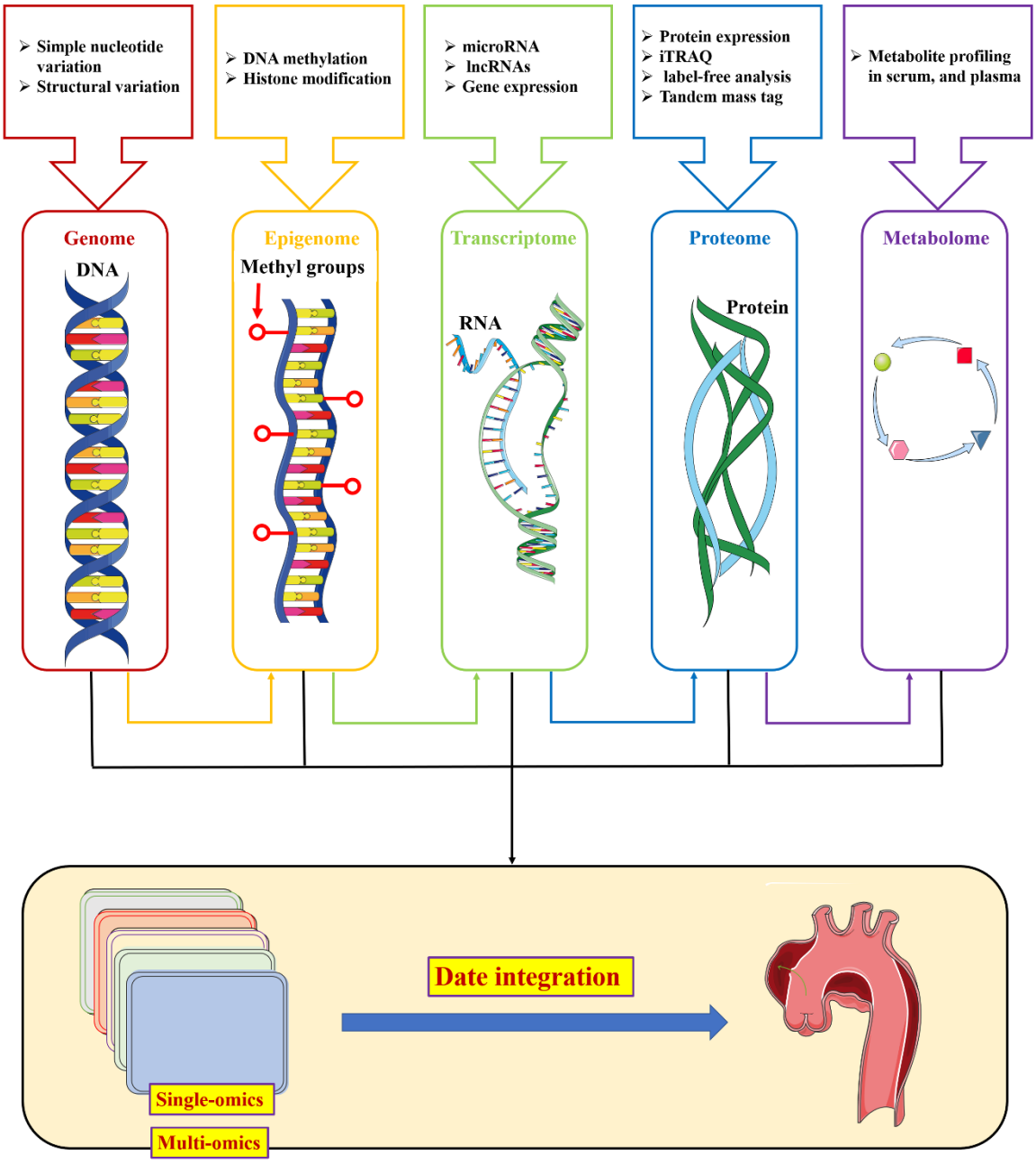

Figure 1: Application of multi-omics research in aortic dissection.

Presently, high throughput sequencing technology has become a popular research topic. Traditional gene expression analysis techniques, such as quantitative polymerase chain reaction, microarrays, and mass RNA sequencing, tend to examine a population of cells that are heterogeneous in their gene expression levels and find the average of their gene expression levels. However, such detection is not appropriate for subsets of cells with relatively low content ignored in conventional RNA sequencing detection and for different individual cells in the cell population.[71] To overcome this constraint, single-cell sequencing, which refers to the sequencing and analysis of genomes and transcriptomes at the single-cell level has been developed. In recent years, studies of AD based on single-cell RNA sequencing have also been

conducted. This method can be used to discover new markers of AD. Liu et al identified Il1rn^{+}/ Trem1^{+} macrophage subsets as cellular targets that slow the progression of thoracic aortic aneurysms and dissections, by sequencing thoracic aortic cells in a mouse model using single-cell technology.[72] In addition, another research group revealed the heterogeneity of experimental AD of smooth muscle cells using single-cell RNA sequencing, and also identified 15 cell clusters and nine cell types.[73]

The pathogenesis of AD is complex. While the idea of single omics is sufficiently mature to obtain definitive analytical results that systematically answer biological questions and explain mechanisms, the introduction of multi-omics is the result of integrating single omics. An in-depth understanding of the pathogenesis of AD will undoubtedly assist in the exploration of new biomarkers for prevention, diagnosis, and treatment as well as promote the development of new drugs, and ultimately, the development of AD research.

It is believed that with the development and maturity of various technologies, the cost will gradually decrease and multi-omics applications will become more widespread. In the future, multi-omics will become a pilot application of AD research and promote progress in precision medicine.

CRediT authorship contribution statement

XYZ, XJ, YYW and QJZ contributed to the revision of the final manuscript. All authors read and approved the final version of the manuscript. XYZ and XJ contributed equally to this work.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We would like to thank all the colleagues in our laboratories (Department of Cardiovascular Surgery, The First Affiliated Hospital, School of Medicine, Southern University of Science and Technology), for their help and support.

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DOI:10.31579/2693-2156/056