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EDITORIAL

Multi-Omics Approaches in Research of Cardiovascular Diseases

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Abstract

Cardiovascular diseases remain number 1 killer world-wide. New technologies, particularly the novel approaches at genetics, transcriptomics, proteomics and metabolomics levels have provided new insights into the disease aetiology, pathophysiology and diagnosis, as well as therapeutics from molecular level. These omics by integrating the nuclear, cellular components, proteins, enzymes generate large data sets gather the information with support of organised and systematic computational methods. The integrated analyses may give deeper view on the development, treatment and prevention of the disease. In recent years, multi-omics technologies have been used in research on cardiovascular diseases including coronary artery disease, heart valve disease and congenital heart disease. These studies help in understanding the aetiology and pathophysiology of the disease and facilitate the precision diagnosis, therapy and prognosis.

Key words: Omics; Cardiovascular; Coronary artery disease; Heart valve; Congenital heart.

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Introduction

Cardiovascular diseases remain number 1 killer world-wide. New technologies, particularly the novel approaches at genetics, transcriptomics, proteomics and metabolomics levels have provided new insights into the disease aetiology, pathophysiology and diagnosis, as well as therapeutics from molecular level. These omics by integrating the nuclear, cellular components, proteins, enzymes generate large data sets gather the information with support of organised and systematic computational methods. The integrated analyses may give deeper view on the development, treatment and prevention of the disease. In recent years, the multi-omics approach has become very useful tool for medical research. This review will briefly describe our multi-omics studies in cardiovascular research.

Coronary artery disease (CAD)

Proteomics of multi-vessel disease in CAD

World Health Organisation has indicated that the world's biggest killer is CAD (ischaemic heart disease), responsible for 16 % of the world's total deaths. Since 2000, the largest increase in deaths has been for CAD.[1]

We have focused the multi-omics studies on coronary artery bypass grafting (CABG) related issues. First, a study to identify the protein profiling in patients with triple vessel coronary artery disease (CAD) undergoing CABG, in order to detect CAD-related differential proteins (DPs) in these patients was designed. Plasma samples of 20 males and 20 females in each group were analysed with iTRAQ technique. ELISA test was used

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to test the chosen proteins from iTRAQ results in plasma samples from a new cohort of the CABG group (n = 120) and control (n = 120). iTRAQ detected 544 proteins with 35 up-regulated and 41 down-regulated. Three proteins including platelet factor 4 (PF4), coagulation factor XIII B chain (F13B), and secreted frizzled-related protein 1 (sFRP1) were selected for validation by using ELISA that demonstrated significant up-regulation of PF4 and sFRP1. There was a positive correlation between these proteins and CAD and myocardial infarction history. Thus, the thrombotic disease/inflammation progress-related protein PF4 and sFRP1, a member of the Wnt/fz signal-transduction pathway and related to myocardial repair, are significantly up-regulated in triple-vessel disease with/without left main stenosis. PF4 may be developed as a biomarker for the diagnosis of the severity of CAD requiring CABG procedure.[2]

Proteomics and metabolomics of postoperative atrial fibrillation (POAF)

POAF is a common complication in CABG. A prospective study aimed to investigate predisposition of proteins and metabolites correlated to POAF after CABG and related cellular pathways was performed. Preoperative plasma samples from CABG patients were prospectively collected. After CABG, the patients were grouped to POAF or sinus rhythm. The plasma samples were analysed using proteomics, metabolomics and bioinformatics to identify the differential proteins (DEPs) and metabolites (DEMs). The correlation between DEPs and POAF was also investigated by multivariable regression analysis and receiver operator characteristic (ROC) analysis. It was found that in POAF(+) group, 29 DEPs and 61 DEMs were identified compared to POAF(-) group. The analysis of integrated omics revealed that preoperative alteration of PPAR-alpha and glutathione metabolism pathways increased the susceptibility of POAF after CABG. There was a correlation between plasma levels of APO-CIII, PLTP, GPX3, CETP and POAF. It was then concluded that at multi-omics levels pre-existing DEPs and DEMs in the plasma of patients prone to POAF after CABG. Dysregulation of PPARα and glutathione metabolism pathways related to metabolic remodelling and redox imbalance-associated electrical remodelling may play a key role in the pathogenesis of POAF. Lower plasma PLTP, APO-CIII, higher CETP and GPX3 are linked with POAF. These proteins/metabolites may be developed as biomarkers to predict POAF.[3]

Transcriptomics, proteomics and metabolomics in heart valve disease (HVD)

Plasma proteomics in HVD

A proteomic study was conducted to exam the hypothesis that certain proteins may be associated with the pathological changes in the plasma of HVD patients. Differential protein analysis in the plasma identified 18 differentially expressed protein spots and 14 corresponding proteins or polypeptides by two-dimensional electrophoresis and mass spectrometry in 120 subjects. Two up-regulated (complement C4A and carbonic anhydrase 1) and three down-regulated proteins (serotransferrin, alpha-1-antichymotrypsin and vitronectin) were validated by ELISA in enlarging samples. The plasma levels (n = 40 for each) of complement C4A in RVD and carbonic anhydrase 1 in DVD patients were significantly higher and that of serotransferrin and alpha-1-antichymotrypsin in RVD patients were significantly lower than those in controls. The plasma vitronectin level in both RVD and DVD was significantly lower than those in normal controls. This study identified alterations of 14 DPs or polypeptides in the plasma of patients with various HVD. The elevation of plasma complement C4A in RVD and carbonic anhydrase 1 in DVD and the decrease of serotransferrin and alpha-1-antichymotrypsin in RVD patients may be useful biomarkers for these valvular diseases. The decreased plasma level of vitronectin – a protein related to the formation of valvular structure – in both RVD and DVD patients might indicate the possible genetic deficiency in these patients.[4]

Transcriptomics and proteomics in atrial tissue in atrial fibrillation (AF) associated with HVD

In this study, multi-omics approach with combined transcriptomic and proteomic technologies in the human atrial tissue was used to investigate the correlation between electrical and structural remodelling processes in HVD patients with AF. Human atrial tissues from the patients with rheumatic mitral valve disease in either sinus rhythm or persistent AF were analysed. An up-regulation in chloride intracellular channel (CLIC) 1, 4, 5 and a rise in type IV collagen were revealed. Combined with the results from immunohistochemistry and electron microscope analysis, the distribution of type IV collagen and effects of fibrosis

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on myocyte membrane indicated the possible interaction between CLIC and type IV collagen, confirmed by protein structure prediction and co-immunoprecipitation. These results indicate that CLICs play an important role in the development of AF and that CLICs and structural type IV collagen may interact on each other to promote the development of AF in rheumatic mitral valve disease.[5]

Transcriptomics and proteomics in human atrial tissue identified PPAR pathway in AF associated with HVD

In this study, human atrial tissues from patients with HVD in persistent AF preoperatively for at least 6 months or remaining sinus rhythm (as a control) undergoing heart valve replacement surgery were studied by combined transcriptomics and proteomics analyses. The total RNA of the

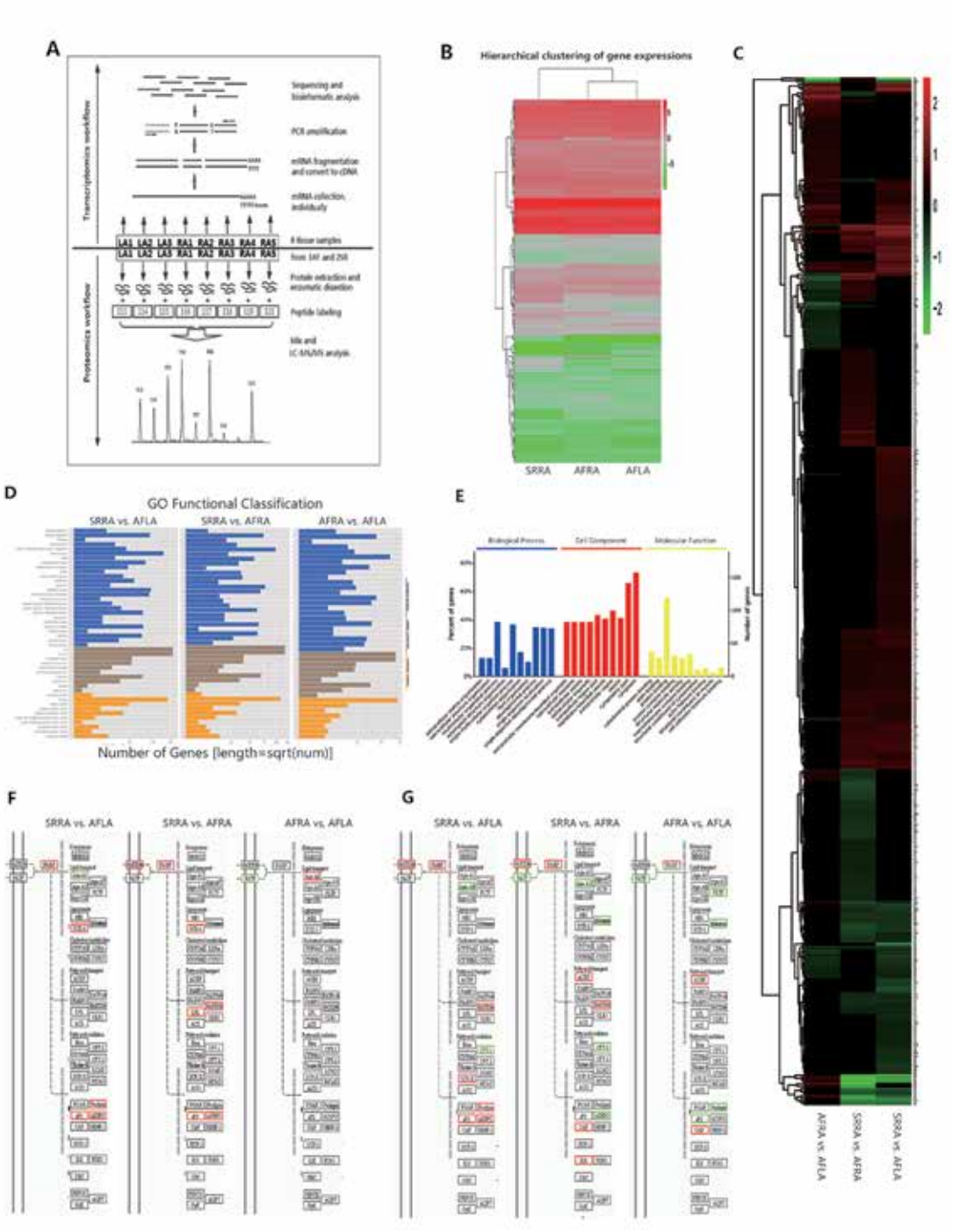

Figure 1: Integrated transcriptomics and proteomics in human atrial tissue identified PPAR pathway in atrial fibrillation (AF) associated with heart valve disease (HVD) (reproduced from reference 6 with permission)

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left and right atrial tissue samples (AFLA and AFRA) from the same AF patients and right atrial tissue from SR (SRRA) patients was extracted. cDNA library was sequenced in a single lane of the Illumina HiSeq™ 2000 system using paired end protocols according to the manufacturer's instructions. The total protein from each sample was extracted and labelled with a unique iTRAQ tag. Big data obtained from the omics studies were analysed by bioinformatics tools. This study provides an integrative analysis of transcriptomics and proteomics in the human atrial tissues of AF-associated HVD patients and reveals that the PPAR signalling pathway plays an important role in the pathogenesis of AF and that some proteins may serve as biomarkers for AF. Owing to the importance of the PPAR pathway in the pathology of AF found in HVD in this study, targeting differential proteins in the PPAR pathway may become new diagnostic and therapeutic methods in the future (Figure 1).[6]

Plasma biomarkers in AF associated with HVD identified by multi-omics methods

Further, the molecular mechanisms and possible biomarkers for chronic AF in HVD was investigated by using multi-omics methods with combined proteomics and metabolomics technologies. This prospective study enrolled patients with mitral valve disease (n = 100) undergoing mitral valve replacement surgery. The patients were allocated into chronic AF and sinus rhythm (SR) groups. Plasma samples were collected preoperatively. Proteomics was performed with iTRAQ to identify DEPs between the two groups. The selected DEPs were then validated in a new cohort of patients by ELISA. A gas chromatography-mass spectrometer was used in the metabolomics study to identify differential metabolites (DEMs). Bioinformatics analyses were performed to analyse the results. Among the 447 plasma proteins and 322 metabolites detected, 57 proteins and 55 metabolites, including apolipoprotein A-I (ApoA-I), apolipoprotein A-II (ApoA-II), LIM domain only protein 7 (LMO7), and vitronectin (VN) were differentially expressed between AF and SR patients. Bioinformatics analyses identified enriched pathways related to AF, including peroxisome proliferator-activated receptor alpha (PPARα), the renin angiotensin aldosterone system (RAAS), galactose, biosynthesis of unsaturated fatty acids and linoleic acid metabolism. Using integrated multi-omics technologies in HVD-associated AF patients, this study revealed important signalling pathways, such as PPARα, as well as possible roles of other signalling pathways, including the RAAS and galactose metabolism to understand the molecular mechanism of MVD-associated AF. It also identified a large number of DEPs and DEMs. Some identified proteins and metabolites, such as ApoA-I, ApoA-II, LMO7 and VN, may be further developed as biomarkers for MVD-associated AF.[7]

Congenital heart disease (CHD)

CHD is the most prevalent primary type of congenital anomalies.[8] Genetic studies may reveal the aetiology of the CHD. Under most circumstances, genomic and genetic studies are useful to identify the genetic variants of CHD. However, proteomics studies are also important in identifying the most important protein changes during disease progress. This was the aim in the present studies on CHD.

Genetic studies on 22q11.2 deletion syndrome

The 22q11.2 deletion syndrome is considered the most frequent chromosomal microdeletion syndrome in humans and the second leading chromosomal cause of CHD. The aim was to identify the prevalence and the detailed genetic characterisation of 22q11.2 region in children with CHD including simple defects and to explore the genotype-phenotype relationship between deletion/amplification type and clinical data. Patients with CHD were screened by multiplex ligation-dependent probe amplification and capillary electrophoresis methods. Universal Probe Library technology was applied for validation. In 354 CHD patients, 40 (11.3 %) carried different levels of deletions/amplifications at the 22q11.2 region with various phenotypes. The affected genes at this region include CDC45 (15 patients), TBX1 (8), USP18 (8), RTDR1 (7), SNAP29 (6), TOP3B (6), ZNF74 (4) and other genes with less frequency. Among those, two patients carried 3 Mb typically deleted region from CLTCL1 to LZTR1 (Low Copy Repeats A-D) or 1.5 Mb deletions from CLTCL1 to MED15 (Low Copy Repeats A-C). Clinical facial manifestations were found in 12 patients. This study revealed an unexpected high prevalence of chromosome 22q11.2 variations in CHD patients

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even in simple defects. The genotype-phenotype relationship analysis suggests that genetic detection of 22q11.2 may become necessary in all CHD patients and that detect of unique deletions or amplifications may provide useful insight into personalised management in CHD patients.[9]

Complex CHD with polydactyly

CHD associated with polydactyly involves various genes. In this study, it was aimed to identify variations from genes related to complex CHD with polydactyly and to investigate the cellular functions related to the mutations. Blood was collected from a complex CHD case with polydactyly and whole exome sequencing (WES) was performed. The CRISPR/Cas9 system was used to generate human pluripotent stem cell with mutations (hPSCs-Mut) that were differentiated into cardiomyocytes (hPSC-CMs-Mut) and analysed by transcriptomics on day 0, 9 and 13. Two heterozygous mutations, LTBP2 (c.2206G>A, p.Asp736Asn, RefSeq NM_000428.2) and TCTN3 (c.1268G>A, p.Gly423Glu, RefSeq NM_015631.5) were identified via WES but no TBX5 mutations were found. The stable cell lines of hPSCs-LTBP-2^{mu}/TCTN3^{mu} were constructed and differentiated into hPSC-CMs-LTBP2^{mu}/TCTN3^{mu}. Compared to the wild type, LTBP2 mutation delayed the development of CMs. The TCTN3 mutation consistently presented lower rate and weaker force of the contraction of CMs. For gene expression pattern of persistent up-regulation, pathways in cardiac development and CHD were enriched in hPSCs-CM-LTBP2^{mu}, compared with hPSCs-CM-WT. Thus, the heterozygous mutations in TCTN3 and LTBP2 affect contractility (rate and force) of cardiac myocytes and may affect the development of the heart. These findings provide new insights into the pathogenesis of complex CHD with polydactyly.[10]

Genetic studies in CHD

The DNA on a series of CHD was sequenced and genetic variants of ventricular septal defect (VSD) were identified.[11-14]

Proteomics studies in CHD

Owing to the importance of protein profiling in CVD, a series of studies on proteomics in CHD was also performed.

Plasma proteomics in CHD

In this early study, the hypothesis that plasma proteins may be altered and related to the pathological changes of CHD was examined. Differential protein analysis was performed in the plasma of patients with tetralogy of Fallot (TOF), isolated VSD and normal controls by using two-dimensional electrophoresis and mass spectrometry. Candidate proteins that might be related to disease processes were further confirmed by ELISA in the new samples. Eighteen differentially expressed protein spots and 10 corresponding proteins or polypeptides were identified. Among those, two down-regulated proteins (gelsolin, ficolin-3) with significant clinical relevance were further analysed for validation. The plasma gelsolin and ficolin-3 levels in TOF patients were significantly lower than those in normal controls. This proteomic study demonstrated the plasma protein changes in CHD patients.[15, 16]

Plasma proteomics in CHD after repair surgery

The final goal for treatment of CHD is to resume not only the normal heart structure but also physiology. This study was designed to evaluate surgical results at molecular basis on the proteomic pattern in the pre- and post-operative period in TOF and VSD in order to find whether structure repair is associated with clinically important molecular changes in CHD. Differential protein analysis by using two-dimensional gel electrophoresis and mass spectrometry followed by ELISA validation was performed in the plasma samples of patients with TOF (n = 82) or VSD (n = 82) preoperatively, 6-month postoperatively and in normal controls (n = 82). A total of 473 protein spots in preoperative patients and 515 in postoperative patients were detected. Significantly downregulated or upregulated proteins were detected. Validation of proteins in the new cohort of patients demonstrated that in VSD patients, postoperative complement component C3c was partially and serum amyloid P-component was completely recovered. In TOF patients, postoperative gelsolin was partially recovered. In contrast, the elevated fibrinogen gamma chain level in preoperative patients became normal postoperatively. Thus, it was for the first time demonstrated by using proteomic methods that repair surgery for CHD not only corrects the structure malformation but also resumes the normality of certain altered proteins at molecular level. Identification of the recovered or unchanged proteins may facilitate the evaluation of the surgical results and the personalised management in postoperative period and long-term.[17]

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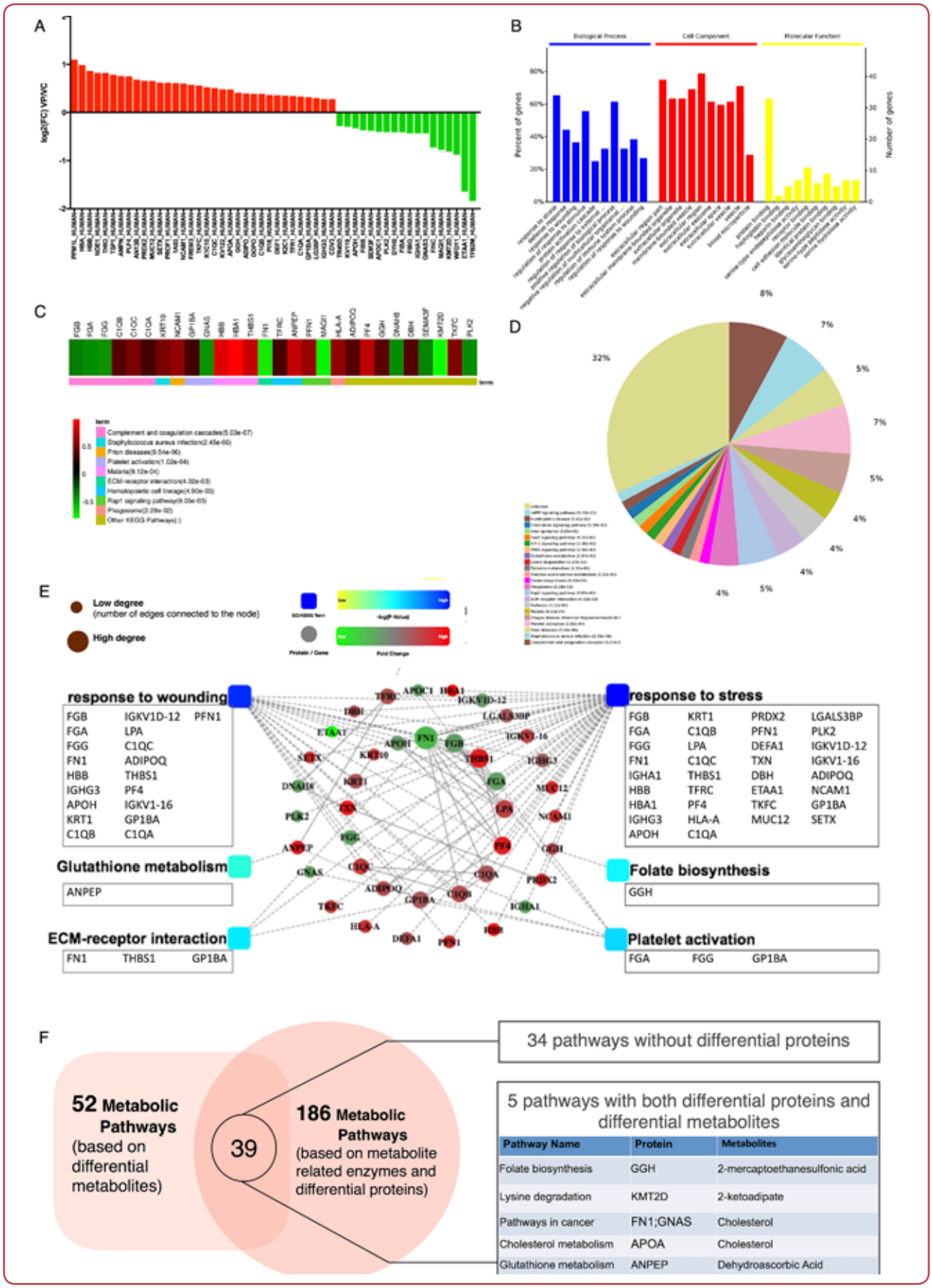

Figure 2: Multi-omics study on CHD-PAH to identify biomarkers (reproduced from reference 20 with permission)

Proteomics in patent ductus arteriosus (PDA) patients

PDA is the third most common congenital heart disease and resulted from the persistence of ductal patency after birth. Ductus arteriosus closure involves functional and structural remodelling, controlled by many factors. The changes in plasma protein levels associated with PDA closure are not known. Here, there were for the first time demonstrated six key differential plasma proteins in human PDA patients using proteomic technology and present a model to illustrate the constriction and closure of ductus arteriosus. Differentially expressed proteins were analysed by using isobaric tags for relative and absolute quantification and validated by enzyme linked immunosorbent assay in new samples. There were 74 up-regulated and 98 down-regulated proteins in the plasma of PDA patients. Five decreased proteins (platelet factor 4, fibrinogen, von Willebrand factor, collagen and mannose binding lectin-associated serine protease-2) and one increased protein (fibronectin) may increase the risk of PDA. Those proteins are closely related to platelet activation and coagulation cascades, complement mannan-binding-lectin and other systemic signalling pathways. These findings for the first time indicate that the differential proteins involved in different pathways may play key roles in the non-closure of the ductus arteriosus in humans and may be developed as biomarkers for diagnosis. All those findings may be served as the basis of understanding the aetiology and pathogenesis of PDA.[18]

Plasma proteomic study in pulmonary arterial hypertension (PAH) associated with CHD

Pulmonary arterial hypertension associated with congenital heart disease (CHD-PAH) has serious consequence and plasma protein profiles in CHD-PAH are unknown. It was aimed to reveal the differential plasma proteins in 272 CHD patients with or without PAH. Various types of CHD-PAH were studied. Differential plasma proteins were first detected by iTRAQ proteomic technology and those with significant clinical relevance were selected for further ELISA validation in new cohort of patients. Among the 190 differential plasma proteins detected by iTRAQ, carbamoyl-phosphate synthetase I (CPSI, related to urea cycle and endogenous nitric oxide production) and complement factor H-related protein 2 (CFHR2, related to complement system and coagulant mechanism) were selected for further ELISA validation in new cohort of 152 patients. Both CPSI and CFHR2 were down-regulated with decreased plasma levels. Thus, for the first time in CHD-PAH patients, a large number of differential plasma proteins was identified. The decreased CPSI expression in CHD-PAH patients may reveal a mechanism related to endogenous nitric oxide and the decrease of CFHR2 protein may demonstrate the deficiency of the immune system and coagulation mechanism. The findings may open a new direction for translational medicine in CHD-PAH with regard to the diagnosis and progress of the disease.[19]

Biomarkers in CHD-PAH

Further, a study was designed to investigate the signalling and metabolic pathways and risk scores of protein biomarkers in CHD-PAH by using integrated multi-omics studies. Plasma from 160 children, including 120 VSD patients with/without PAH and 40 healthy children was studied by integrated proteomics, metabolomics and bioinformatics analyses. Proteomics (iTRAQ) identified 107 DEPs between patients with/without PAH including significantly increased ADIPO, DBH, ANPEP, TRF1, GP1BA and decreased GNAS in VSD-PAH. Metabolomics discovered 191 differential metabolites between patients with/without PAH including elevation of 5-HT, taurine, creatine, sarcosine and 2-oxobutanoate and decrease of vanillylmandelic acid, 3,4-dihydroxymandelate, 15-Keto-$PGF_{2\alpha}$, fructose-6-phosphate, L-glutamine, dehydroascorbate, hydroxypyruvate, threonine, L-cystine and 1-aminocyclopropane-1-carboxylate. The DEPs were validated in a new cohort of patients (n = 80). Integrated analyses identified the key pathways including cAMP signalling pathway, ECM-receptor interaction, AMPK signalling pathway, HIF-1 signalling pathway, PI3K-Akt signalling pathway and amino acid metabolisms. Increased plasma protein levels of DBH, ADIPO and ANPEP were found to be independently associated with the occurrence of PAH with a new total risk score from these three proteins developed for clinical diagnosis. In this integrated multi-omics analysis in VSD-PAH patients, it was for the first time found that VSD-PAH patients present important DEPs, metabolites and key pathways. A total-risk-score (based on the plasma concentration of DBH, ANPEP and ADIPO) was developed as a predictor of development of PAH in CHD-VSD patients. Therefore, these proteins may be used as biomarkers and the new total-risk-score has significant clinical implications in the diagnosis of PAH (Figure 2).[20]

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Conclusion

Multi-omics technologies have been used in research on cardiovascular diseases including CAD, HVD and CHD. These studies help in understanding the aetiology and pathophysiology of the disease and facilitate the precision diagnosis, therapy and prognosis. New technologies such as single cell sequencing may also be used in future studies to advance the understanding in the disease aetiology and development.

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Conflict of interest

None.

References

1. World Health Organization [Internet]. [Cited: 1-Jun-2022]. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
2. Guo ZP, Hou HT, Jing R, Song ZG, Liu XC, He GW. Plasma protein profiling in patients undergoing coronary artery bypass grafting surgery and clinical significance. Oncotarget 2017 Mar 18;8(36):60528-38.
3. Li XY, Hou HT, Chen HX, Liu XC, Wang J, Yang Q, et al. Preoperative plasma biomarkers associated with atrial fibrillation after coronary artery bypass surgery. J Thorac Cardiovasc Surg 2021 Sep;162(3):851-63.e3.
4. Gao G, Xuan C, Yang Q, Liu XC, Liu ZG, He GW. Identification of altered plasma proteins by proteomic study in valvular heart diseases and the potential clinical significance. PLoS One 2013 Aug 27;8(8):e72111. doi: 10.1371/journal.pone.0072111.
5. Jiang YY, Hou HT, Yang Q, Liu XC, He GW. Chloride channels are involved in the development of atrial fibrillation - a transcriptomic and proteomic study. Sci Rep 2017 Aug 31;7(1):10215. doi: 10.1038/s41598-017-10590-w.
6. Chen HX, Li MY, Jiang YY, Hou HT, Wang J, Liu XC, et al. Role of the PPAR pathway in atrial fibrillation associated with heart valve disease: transcriptomics and proteomics in human atrial tissue. Signal Transduct Target Ther 2020 Jan 17;5(1):4. doi: 10.1038/s41392-019-0093-2.
7. Li MY, Chen HX, Hou HT, Wang J, Liu XC, Yang Q, et al. Biomarkers and key pathways in atrial fibrillation associated with mitral valve disease identified by multi-omics study. Ann Transl Med 2021 Mar;9(5):393. doi: 10.21037/atm-20-3767.
8. Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet 2013 Mar 23;381(9871):997-1020.
9. Hou HT, Chen HX, Wang XL, Yuan C, Yang Q, Liu ZG, et al. Genetic characterisation of 22q11.2 variations and prevalence in patients with congenital heart disease. Arch Dis Child 2020 Apr;105(4):367-74.
10. Chen HX, Yang ZY, Hou HT, Wang J, Wang XL, Yang Q, et al. Novel mutations of TCTN3/LTBP2 with cellular function changes in congenital heart disease associated with polydactyly. J Cell Mol Med 2020 Dec;24(23):13751-62.
11. Xuan C, Jia KG, Wang BB, Bai XY, Gao G, Yang Q, et al. Identification of two novel mutations of the HOMEZ gene in Chinese patients with isolated ventricular septal defect. Genet Test Mol Biomarkers 2013 May;17(5):390-4.
12. Xuan C, Wang BB, Gao G, Bai XY, Yang Q, Liu XC, et al. A novel variation of PLAGL1 in Chinese patients with isolated ventricular septal defect. Genet Test Mol Biomarkers 2012 Aug;16(8):984-7.
13. Zheng SQ, Chen HX, Liu XC, Yang Q, He GW. Identification of variants of ISL1 gene promoter and cellular functions in isolated ventricular septal defects. Am J Physiol Cell Physiol 2021 Sep 1;321(3):C443-C52.
14. Zheng SQ, Chen HX, Liu XC, Yang Q, He GW. Genetic analysis of the CITED2 gene promoter in isolated and sporadic congenital ventricular septal defects. J Cell Mol Med 2021 Feb;25(4):2254-61.
15. Xuan C, Gao G, Yang Q, Wang XL, Liu ZG, Liu XC, et al. Proteomic study reveals plasma protein changes in congenital heart diseases. Ann Thorac Surg 2014 Apr;97(4):1414-9.
16. Zhang X, Wang K, Yang Q, Wang J, Xuan C, Liu XC, et al. Acute phase proteins altered in the plasma of patients with congenital ventricular septal defect. Proteomics Clin Appl 2015 Dec;9(11-12):1087-96.
17. He GW, Hou HT, Xuan C, Wang J, Liu LX, Zhang JF, et al. Corrective surgery alters plasma protein profiling in congenital heart diseases and clinical perspectives. Am J Transl Res 2020 Apr 15;12(4):1319-37.
18. Hou HT, Xi-Zhang, Wang J, Liu LX, Zhang JF, Yang Q, et al. Altered plasma proteins released from platelets and endothelial cells are associated with human patent ductus arteriosus. J Cell Physiol 2019 May;234(5):6842-53.
19. Zhang X, Hou HT, Wang J, Liu XC, Yang Q, He GW. Plasma proteomic study in pulmonary arterial hypertension associated with congenital heart diseases. Sci Rep 2016 Nov 25;6:36541. doi: 10.1038/srep36541.
20. Yuan C, Chen HX, Hou HT, Wang J, Yang Q, He GW. Protein biomarkers and risk scores in pulmonary arterial hypertension associated with ventricular septal defect: integration of multi-omics and validation. Am J Physiol Lung Cell Mol Physiol 2020 Nov 1;319(5):L810-L22.

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