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A comprehensive analysis of differentially expressed genes and pathways in abdominal aortic aneurysm

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Abstract. The current study aimed to investigate the molecular mechanism underlying abdominal aortic aneurysm (AAA) via various bioinformatics techniques. Gene expression profiling analysis of differentially expressed genes (DEGs) between AAA samples and normal controls was conducted. The Database for Annotation, Visualization and Integrated Discovery tool was utilized to perform Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes analyses for DEGs and clusters from the protein-protein interaction (PPI) network, which was constructed using the Search Tool for the Retrieval of Interacting Genes. In addition, important transcription factors (TFs) that regulated DEGs were investigated. A total of 346 DEGs were identified between AAA samples and healthy controls. Additionally, four clusters were identified from the PPI network. Cluster 1 was associated with sensory perception of smell and the olfactory transduction subpathway. The most significant GO function terms for cluster 2 and 3 were response to virus and defense response, respectively. Cluster 4 was associated with mitochondria-associated functions and the oxidative phosphorylation subpathway. Early growth response-1 (EGR-1), Myc, activating transcription factor 5 (ATF5) and specificity protein (SP) 1:SP3 were identified to be critical TFs in this disease. The present study suggested that the olfactory transduction subpathway, mitochondria and oxidative phosphorylation pathways were involved in AAA, and TFs, such as EGR-1, Myc, ATF5 and SP1:SP3, may be potential candidate molecular targets for this disease.

Introduction

Abdominal aortic aneurysm (AAA), the most common form of aortic aneurysm, refers to a localized dilatation of the abdominal aorta exceeding the normal aortic diameter by >50% (1). The most severe complication of AAA is AAA rupture, which is the tenth primary cause of mortality for American Caucasian males between 65-74 years old (2). As AAA rupture is fatal within minutes, in the majority of cases, the patients do not reach hospital in time to receive treatment. Therefore, the mortality rate of AAA rupture is ~90% (3).

Thus, there is an urgent requirement for the development of effective therapies for AAA, and elucidating the etiology of AAA is important in this development. Chronic tobacco smoking has been identified as the most important risk factor for AAA (4,5). In addition to smoking, inherited susceptibility to AAA has also been identified as a critical causative factor accounting for this disease (6). The molecular mechanism of AAA has been widely investigated. In particular, protease inhibitors, such as metalloproteinase inhibitor-2 and plasminogen activator inhibitor-1 have been reported to be involved in the development of AAA from original atherosclerotic plaques (7). β-arrestin-2, a scaffolding protein, has been suggested to promote AAA formation induced by angiotensin II in mice in a previous study (8). Additional studies suggested that Sortilin-1 and microRNA-29b were also involved in the pathogenesis of AAA (9,10).

Thus, previous studies have made progress in understanding the pathogenesis of AAA; however, the underlying mechanisms of AAA remain to be fully elucidated. The current study aimed to clarify the molecular mechanism of AAA using bioinformatics techniques. Differentially expressed genes (DEGs) were identified through analyzing the whole genome gene expression profiles of 14 AAA samples. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were conducted for DEGs, and a protein-protein interaction (PPI) network was constructed followed by analysis of clusters from the PPI network. Additionally, important transcription factors (TFs) that regulated DEGs were investigated. The observations of the current study may provide novel insights into the pathogenesis of this disease and aid in the development of future therapeutic approaches to treat AAA.

Materials and methods

Microarray data. In order to investigate the molecular mechanism of AAA, the gene expression profile of GSE47472 was obtained from the National Center of Biotechnology

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Information (NCBI) Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/). This was used with the Illumina HumanHT-12 V4.0 Expression BeadChip kit (Illumina, Inc., San Diego, CA, USA), which had a total of 22 gene chips, consisting of 14 AAA samples and 8 control aortic samples.

Data preprocessing and DEG analysis. The probe-level data in CEL files was converted into expression measures using the Log2 transformation following data preprocessing with the median method using the preprocessCore package (11). In total, there were 39,426 probes for 17,393 genes. When there were multiple probes corresponding to one given gene, expression values of these probes were averaged.

DEGs between AAA specimens and controls were identified using the multiple linear regression package limma (12) in Bioconductor (13), followed by multiple testing correction using the Bayesian inference method. $|\log FC| > 1$ and false discovery rate (FDR)<0.05 were set as the strict cutoffs.

GO and KEGG enrichment analysis for DEGs. For functional annotation of DEGs, the Database for Annotation, Visualization and Integrated Discovery (DAVID) (14) was utilized to perform GO (15) and KEGG (16) analyses for the identified DEGs. P<0.05 was set as the strict threshold.

PPI network construction. In order to investigate the interactions among proteins encoded by DEGs and their associations with diseases, the Search Tool for the Retrieval of Interacting Genes online tool (17) was applied to construct a PPI network, which was visualized using Cytoscape 3.0.0 software (http://www.cytoscape.org/) (18). Hub proteins were identified by analyzing the node degree. The proteins in the network were defined as the 'nodes' and a pair of interacted proteins were linked by an edge. The 'degree' of a node represents the number of interactions that node has. The nodes with high degrees were considered as hub nodes.

Analysis of network clustering. Network clustering was performed using ClusterONE (19) in Cytoscape software with P<0.01 as a cutoff. The DAVID online tool was applied to perform GO and KEGG pathway analysis for network clusters with P<0.05 set as the threshold.

Detection of upstream regulatory elements. To investigate TFs that modulated the up- and downregulated DEGs, the upstream regulatory elements for TFs, which were also termed transcription factor binding sites (TFBS) were identified using the Whole-Genome rVISTA online tool (http://genome.lbl.gov/cgi-bin/WGRVistaInputCommon.pl). The length parameter for the gene promoter region was set at 1,000 base pairs upstream of the transcriptional start site with P<0.0001 as the strict cutoff.

Results

DEG screening. In total, 346 DEGs were selected between 14 AAA and 8 control samples. Among these DEGs, 61% (212) were upregulated, while 39% (134) were downregulated.

GO and KEGG enrichment analysis. GO functional analysis was performed for up- and downregulated DEGs. As presented in Table I, up- and downregulated DEGs were enriched in 6 and 4 GO function terms, respectively. Cellular sodium ion homeostasis and regulation of RNA metabolic process were identified to be the most significant GO function terms for the up- and downregulated DEGs, respectively. Using P<0.05 as the threshold for significance, no DEG was observed to be significantly enriched in any sub-pathway of KEGG.

PPI network construction. As demonstrated in Fig 1, 88 interactions were identified among proteins in the PPI network. Proteins with a degree >4 consisted of tyrosine-protein kinase (HCK), ribosomal protein L5 (RPL5), olfactory receptor 52E4 (OR52E4), TYRO protein tyrosine kinase-binding protein (TYROBP) and nuclear receptor co-repressor 1 (NCOR1).

Network cluster analysis. Four network clusters were identified from the PPI network (Fig. 2). Among the four clusters, cluster 1 included OR52E4, and cluster 3 included HCK and TYROBP. The results of the GO enrichment analysis for the 4 clusters are presented in Table II. Cluster 1 was identified to be most significantly enriched in the plasma membrane and sensory perception of smell. A number of olfactory receptor genes were included in cluster 1. The most significant GO terms for cluster 2 and 3 were response to virus and defense response, respectively. Interferon-induced GTP-binding protein (MX1), interferon-α/β receptor (IFNAR) and interferon-stimulated gene 20 kDa protein (ISG20) were enriched in cluster 2. In addition, cluster 4 was enriched in mitochondria-associated functions. As presented in Table III, for cluster 1, the olfactory transduction subpathway was the most significantly enriched KEGG subpathway. DEGs including NADH dehydrogenase (ubiquinone) iron-sulfur protein 8 (NDUFS8) and cytochrome c1 (CYC1) in cluster 4 were observed to be enriched in the oxidative phosphorylation subpathway.

Identification of TFBS and TFs. For the upregulated DEGs, the important TFs identified included early growth response protein 1 (EGR-1) and Myc. In the downregulated DEGs however, activating transcription factor 5 (ATF5), specificity protein (SP)1:SP3, E2F transcription factor 4 (E2F4) and TFII-I were the critical TFs identified.

Discussion

In the current study, a total of 212 upregulated DEGs and 134 downregulated DEGs were identified between AAA samples and control samples. HCK, OR52E4 and TYROBP were identified as hub nodes in the PPI network. Four clusters from the PPI network were validated in terms of GO functions and KEGG pathways individually. In addition, important TFs were identified for up- and downregulated DEGs.

Of the four clusters from the PPI network, cluster 1 was identified to be enriched in sensory perception of smell and the olfactory transduction subpathway. Consistently, OR52E4, which was part of cluster 1, is a member of the family of olfactory receptor proteins (20). It has been reported that tobacco exposure is able to impair olfactory function in a dose-dependent manner (21), thus given that tobacco smoking is an important

Table I. GO enrichment analysis of DEGs.

A, Upregulated genes

ID	Name	Gene symbol	P-value	FDR
GO:0006883	Cellular sodium ion homeostasis	C7, NEDD4L	0.046429183	52.31338009
GO:0003924	GTPase activity	SEPT5, GBP5, RAB11B, ERAS, MX1, GNG5	0.044676591	45.15145139
GO:0005886	Plasma membrane	TGOLN2, SEPT5, OR2J2, PCDHGA5, LGR5, TAAR9, OR9A4, S1PR1, DYNLL1, RAET1G, CEACAM6, SV2B, ERAS, GNG4, SV2C, GNG5, HTR1F, GJD4, ZP1, GBP5, PCDHB5, CACNG8, PIK3C2A, SLC34A1, MPP5, MRGPRF, IFNAR1, SLC26A3, GRASP, TM4SF5, C7, GPRC5D, OR1L8, OR2T3, ABI1, CDH8, GORASP1, RAB11B, KCNE1, SERPINC1, PCSK9, OR2T8, SPRN, IL2RB, DLGAP2, TMEM47, OR51A2, OR8B12, EMR3	0.007482427	9.0256518
GO:0016023	Cytoplasmic membrane bounded vesicle	SEPT5, TGOLN2, ANGPTL6, CACNG8, PIK3C2A, DLD, RAB11B, SV2B, VGF, SV2C, ARHGDIB	0.032382066	33.93883034
GO:0030136	Clathrin-coated vesicle	SEPT5, TGOLN2, PIK3C2A, SV2B, SV2C	0.034758195	35.95313043
GO:0031988	Membrane bounded vesicle	SEPT5, TGOLN2, ANGPTL6, CACNG8, PIK3C2A, DLD, RAB11B, SV2B, VGF, SV2C, ARHGDIB	0.039021284	39.42595138

B, Downregulated genes

ID	Name	Gene symbol	P-value	FDR
GO:0051252	Regulation of RNA metabolic process	ZFP36, ZNF584, HSFX2, ETV7, HOXA13, RFX7, SIX3, ZNF230, PA2G4, FOXF1, NR2F6, HOXA10, ZNF462, PER3, CARM1, TCF3, NCOR1, ZNF257	0.046908154	52.01470738
GO:0006350	Transcription	ZNF584, HSFX2, ETV7, SNAPC2, HOXA13, ZNF507, PPP1R10, ZNF230, PA2G4, NCOA5, FOXF1, NR2F6, HOXA10, ZNF462, PER3, CARM1, TCF3, ZNF575, NCOR1, ZNF257	0.049224445	53.76642617
GO:0043565	Sequence-specific DNA binding	HSFX2, ETV7, HOXA13, FOXF1, SIX3, HOXA10, NR2F6, TCF3, NCOR1	0.035160922	37.25923349
GO:0003677	DNA binding	H1F0, ZFP36, ZNF584, HSFX2, ETV7, SNAPC2, HOXA13, ZNF507, RFX7,	0.046429791	46.16041287

Table I. Continued.

ID	Name	Gene symbol	P-value	FDR
		SIX3, PPP1R10, ZNF230, XPA, PA2G4, FOXF1, NR2F6, HOXA10, ZNF462, TCF3, ZNF575, NCOR1, ZNF257		

GO, Gene ontology; DEG, differentially expressed genes; FDR, false discovery rate.

Table II. GO enrichment analysis for four clusters.

A, Cluster 1

ID	Name	Gene symbol	P-value	FDR
GO:0005886	Plasma membrane	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$2.91x10^{-2}$	10.65718378
GO:0007608	Sensory perception of smell	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$4.95x10^{-6}$	0.00285105
GO:0007606	Sensory perception of chemical stimulus	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$7.48x10^{-6}$	0.004306871
GO:0007600	Sensory perception	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$6.08x10^{-5}$	0.034971424
GO:0050890	Cognition	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$9.59x10^{-5}$	0.055165167
GO:0007186	G-protein coupled receptor protein signaling pathway	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$2.21x10^{-4}$	0.126911001
GO:0050877	Neurological system process	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$2.96x10^{-4}$	0.170141842
GO:0007166	Cell surface receptor linked signal transduction	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	0.001573052	0.901913236
GO:0004984	Olfactory receptor activity	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	$1.20x10^{-6}$	$1.20x10^{-4}$

B, Cluster 2

ID	Name	Gene symbol	P-value	FDR
GO:0009615	Response to virus	MX1, IFNAR1, ISG20	$3.82x10^{-4}$	0.354852933

C, Cluster 3

ID	Name	Gene symbol	P-value	FDR
GO:0006952	Defense response	S100A8, NCF1, HCK, TYROBP	$8.73x10^{-4}$	0.795749167
GO:0006968	Cellular defense response	NCF1, TYROBP	$2.23x10^{-2}$	18.6793053
GO:0005739	Mitochondrion	MRPS34, TIMM17A, NDUFS8, CYC1, TIMM50	$5.20x10^{-5}$	0.044320277
GO:0005743	Mitochondrial inner membrane	TIMM17A, NDUFS8, CYC1, TIMM50	$5.34x10^{-5}$	0.045471679

Table II. Continued.

ID	Name	Gene symbol	P-value	FDR
GO:0019866	Organelle inner membrane	TIMM17A, NDUFS8, CYC1, TIMM50	$6.63x10^{-5}$	0.056473574

D, Cluster 4

ID	Name	Gene symbol	P-value	FDR
GO:0031966	Mitochondrial membrane	TIMM17A, NDUFS8, CYC1, TIMM50	$1.14x10^{-4}$	0.096745997
GO:0005740	Mitochondrial envelope	TIMM17A, NDUFS8, CYC1, TIMM50	$1.37x10^{-4}$	0.116223644
GO:0044429	Mitochondrial part	TIMM17A, NDUFS8, CYC1, TIMM50	$3.88x10^{-4}$	0.329680741
GO:0031967	Organelle envelope	TIMM17A, NDUFS8, CYC1, TIMM50	$4.38x10^{-4}$	0.372446101
GO:0031975	Envelope	TIMM17A, NDUFS8, CYC1, TIMM50	$4.42x10^{-4}$	0.376016181
GO:0044455	Mitochondrial membrane part	TIMM17A, NDUFS8, TIMM50	$5.62x10^{-4}$	0.47771995
GO:0031090	Organelle membrane	TIMM17A, NDUFS8, CYC1, TIMM50	$2.4x10^{-3}$	1.987624717
GO:0005744	Mitochondrial inner membrane presequence translocase complex	TIMM17A, TIMM50	$3.7x10^{-3}$	3.15011107
GO:0070469	Respiratory chain	NDUFS8, CYC1	$2.3x10^{-2}$	18.17151041
GO:0007005	Mitochondrion organization	TIMM17A, NDUFS8, TIMM50	$3.08x10^{-4}$	0.286135591
GO:0022900	Electron transport chain	NDUFS8, CYC1	$2.5x10^{-2}$	21.04388668

GO, Gene ontology; FDR, false discovery rate.

risk factor for AAA, it is not surprising that olfactory receptor genes, including OR52E4, were enriched in cluster 1.

According to the result of GO function analysis cluster 2 was enriched in response to viruses and MX1, IFNAR and ISG20 were all included in cluster 2. Among these three DEGs, MX1 and IFNAR were observed to be upregulated, while ISG20 was downregulated. Previous studies have demonstrated that MX1, IFNAR and ISG20 are associated with the immune response to viruses (22-24). Accordingly, immune and inflammatory responses have been identified to be critical in AAA formation (25). These previous studies further confirm the role of the immune response in the pathogenesis of AAA.

HCK is an enzyme encoded by the HCK gene and is a member of the Src family of tyrosine kinases. HCK has been demonstrated to be involved in the migration and degranulation of neutrophils (26). TYROBP is an adaptor protein encoded by the TYROBP gene, which has been previously observed to be abnormally expressed in AAA (27). In agreement with this, the current study demonstrated that TYROBP and HCK were enriched in cluster 3.

Various studies have established that oxidative stress may promote inflammation in the pathogenesis of AAA (28-30). In addition, mitochondrial-dependent apoptosis is reported to promote AAA formation in rodent experimental models (31). In accordance with this, the present study demonstrated that cluster 4 was enriched in mitochondria-associated functions and the oxidative phosphorylation subpathway. A variety of genes were enriched in cluster 4, including NDUFS8 and CYC1. NDUFS8 is encoded by the NDUFS8 gene and is a subunit of mitochondrial NADH (32). Consistently, NDUFS8 has been previously observed to be involved in oxidative phosphorylation (33). CYC1 is a heme protein encoded by the CYC1 gene, and cytochrome *c* is a critical component of the electron transport chain in mitochondria (34). These studies are in agreement with the results of the current study, further suggesting the importance of mitochondria and oxidative phosphorylation in AAA.

Table III. KEGG subpathway enrichment analysis for 4 clusters.

A, Cluster 1

ID	Name	Gene symbol	P-value	FDR
hsa04740	Olfactory transduction	OR9A4, OR1L8, OR8B12, OR52E4, OR4C46	3.04×10^{-5}	0.003040948

B, Cluster 4

ID	Name	Gene symbol	P-value	FDR
hsa05012	Parkinson's disease	NDUFS8, CYC1	0.025172075	10.49506004
hsa00190	Oxidative phosphorylation	NDUFS8, CYC1	0.025565388	10.6520097
hsa05010	Alzheimer's disease	NDUFS8, CYC1	0.032055064	13.21121831
hsa05016	Huntington's disease	NDUFS8, CYC1	0.03539823	14.50736559

KEGG, Kyoto Encyclopedia of Genes and Genomes; FDR, false discovery rate.

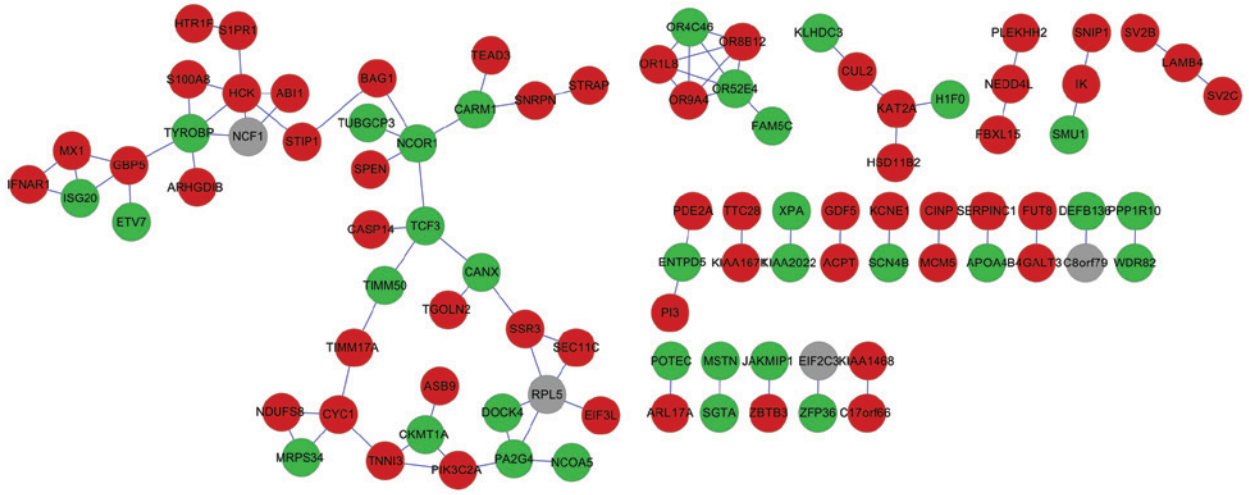

Figure 1. Protein-protein interaction network. Nodes, proteins; edges, interactions; red nodes, upregulated genes; green nodes, downregulated genes; gray nodes, genes whose expression remained unchanged between the abdominal aortic aneurysm samples and controls.

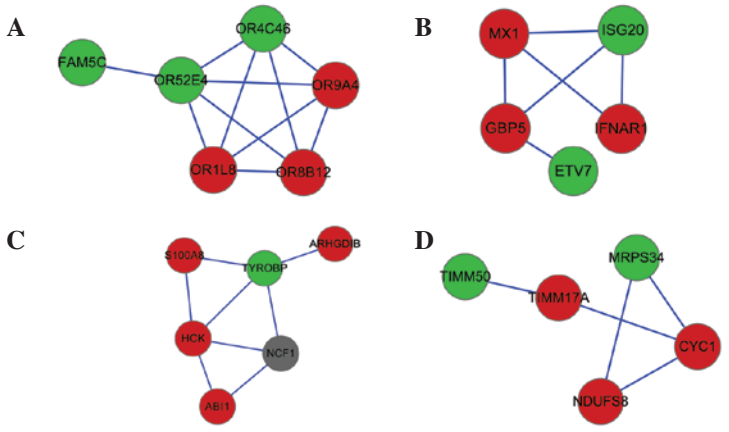

Figure 2. Four clusters from the protein-protein interaction network. Clusters (A) 1, (B) 2, (C) 3 and (D) 4. Nodes, proteins; edges, interactions; red nodes, upregulated genes; green nodes, downregulated genes; gray nodes, genes whose expression remained unchanged between the abdominal aortic aneurysm samples and controls.

The current study demonstrated that EGR-1 and Myc were important TFs modulating upregulated DEGs, while ATF5 and SP1:SP3 were critical TFs for downregulated DEGs. EGR-1 has been identified to be an important TF and a tumor suppressor gene in addition (35). EGR-1 has been observed to be involved in thrombus formation and the inflammatory pathogenesis of AAA (36). The Myc protein is a member of the Myc family of transcription factors and has been demonstrated to be involved in regulating cell apoptosis and proliferation (37). The current study hypothesized that Myc may promote cell proliferation in AAA. In addition, SP1 is a protein encoded by the SP1 gene and belongs to the SP/Krüppel-like factor family of transcription factors (38). SP1 has been observed to modulate inflammation associated with AAA by increasing the expression levels of cyclooxygenase-2 (39). ATF5, encoded by ATF5 gene, belongs to the ATF/cyclic adenosine monophosphate response-element binding (CREB) protein family (40). CREB has been reported to serve a role in modulating the apoptosis and proliferation of vascular smooth muscle cells (41,42).

In conclusion, the current study indicated critical roles of the olfactory transduction, mitochondria and oxidative phosphorylation subpathways, and suggested the importance of the immune response in the pathogenesis of AAA. In addition, crucial TFs, including EGR-1, Myc, ATF5 and SP1:SP3, were identified and were suggested as potential treatment targets for this disease. Thus the present study aided in the further investigation of the pathogenesis of AAA. Further experimental studies are required in order to validate the results of the current study.

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