Identification of Potential core genes in Sevoflurane induced Myocardial Energy Metabolism in Patients Undergoing Off-pump Coronary Artery Bypass Graft Surgery using Bioinformatics analysis

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Abstract

Background: Myocardial ischemia-reperfusion injury always happened after Off-pump coronary artery bypass graft (OPCABG), and this can not be avoided altogether. In this study, we tried to detect potential genes of sevoflurane-induced myocardial energy metabolism in patients undergoing OPCABG using bioinformatics analysis.

Methods: We download and analyze the gene expression profile data from the Gene Expression Omnibus (GEO) database using bioinformatics methods. We downloaded the gene expression data from the Gene Expression Omnibus (GEO) database using bioinformatics methods. Gene Ontology (GO) functional annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were used to analyse the screened differentially expressed genes (DEGs). Then, we established a protein–protein interaction (PPI) network to find hub genes associated with myocardial energy metabolism.

Results: Through PPI network, we find ten hub genes, including JUN, EGR1, ATF3, FOSB, JUNB, DUSP1, EGR2, NR4A1, BTG2, NR4A2.

Conclusions: In conclusion, the proteins encoded by EGR1·ATF3·c-Fos·Btg2·JunB·DUSP1·NR4A1·BTG2 and NR4A2 were related to cardiac function. ATF3, FOSB, JUNB, DUSP1, NR4A1, NR4A2 are related to apoptosis of cardiomyocytes. The protein encoded by BTG2 is related to hypertrophy. Sevoflurane regulates cell transcription, inflammatory and apoptosis through those hub genes to protect myocardial.

Background
Off-pump coronary artery bypass graft (OPCABG) surgery is an effective way to avoid the side effect of extracorporeal circulation, like the whole-body inflammatory syndrome, Postoperative cognitive dysfunction, coagulation disorders, and multiple organ dysfunction syndromes. At present, gas anaesthesia, sevoflurane has been widely used during the CABG. Coronary artery bypass grafting (CABG) is an effective way to treat left primary coronary disease or three-vessel disease. Lousy lifestyle and habits cause the happening of coronary artery disease (CAD) in China increased gradually. Patients with clinical symptoms and multiple CAD need surgery. Off-pump coronary artery bypass graft (OPCABG) is a right choice of surgical procedure. Even so, after OPCABG, myocardial ischemia-reperfusion injury can also not be avoided entirely and happened high probability. In this study, we tried to detect potential genes of sevoflurane-induced myocardial energy metabolism in patients undergoing OPCABG. To find the differentially expressed genes (DEGs) between before inhalation (baseline sevoflurane) and after inhalation (sevoflurane), we download and analyze the gene expression profile data from the Gene Expression Omnibus (GEO) database using bioinformatics methods. Gene Ontology (GO) functional annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed for the screened DEGs. Then, we established a protein–protein interaction (PPI) network to find hub genes related to myocardial energy metabolism. Functional analysis of DEGs was selected using Gene Ontology (GO) database and signal pathway of DEGs was carried out using the Kyoto Encyclopedia of Genes and Genomes (KEGG). Then, through the search tools, protein–protein interaction (PPI) network and hub genes related to myocardial energy metabolism were selected.
Methods

Materials and methods

We download a database from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) to obtain the gene expression datasets. One series (GDS2772) was selected out from the database about sevoflurane affect human myocardial energy metabolism. GDS2772 was based on the Agilent GPL570: [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. This data was available online searched by “sevoflurane” and "myocardial energy metabolism". This study has not been reported by any experiment on humans and declared by any other authors.

Data processing of DEGs

R: The R Project for Statistical Computing (https://www.r-project.org/) was used to detect the DEGs between before inhalation (baseline sevoflurane) and after inhalation (sevoflurane) samples, and the adjusted P-value and |logFC| were calculated. We selected the DEGs by adjusting P≤0.01 and |logFC|≥2.0.

GO and KEGG pathway analysis of DEGs

GO analysis is a widely used method for functional enrichment studied. Also, gene functions were composed of biological process (BP), molecular function (MF), and cellular component (CC) three parts. KEGG is a large-scale used database, including vast amounts of genomes, biological pathways, diseases, chemicals, and drugs. We use the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tools (https://david.ncifcrf.gov/) to analysis the DEGs through GO annotation analysis and KEGG pathway enrichment analysis. Once P≤0.01 and gene counts≥10, the genes were considered statistically significant.¹

PPI network construction and hub gene
Identification

In this study, we use the Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/) and GeneMANIA online database (https://genemania.org/) to analyze the PPI information and evaluate the potential PPI relationship. They were also used to identify the DEGs to analyze the PPI information. A combined score was set to 0.4, and then the PPI network was visualized by Cytoscape software (www.cytoscape.org/). The stability of the entire system was guaranteed by a higher degree node of connectivity. We calculated the degree of each protein node by using CytoHubba, a plugin in Cytoscape. Through those steps, we can select ten hub genes.¹

Results

Identification of DEGs

Gene expression profile (GDS2772) was selected in this study using the following keywords: “sevoflurane,” and “myocardial energy metabolism.” GDS2772 contained 10 baseline sevoflurane samples, 10 sevoflurane samples. Based on the criteria of P0.01 and |logFC|≥2, a total of 726 DEGs were identified from baseline sevoflurane samples compared with sevoflurane samples, including 297 upregulated genes and 429 downregulated genes(Table 1).

| Number | Differentially expressed genes |
|--------|--------------------------------|
| up-regulated | B3GNT5 UGCGBT G2 OTUD1 UTP20 PANX1 SOX7 IER2 SLC7A6 CCDC55 RBM15 LOC101928762 AW963634 TICAM1 UTP4 FGFR1 C18965 IRF1 NR4A2 DNAJb1 AI939580 CHD1 MAPKAPK2 CHSY1 SLC39A14 ABL2 RETL MOB3C PPP1R5B INT56 FOXK2 NFATC1. HES1 PRDM2 ATF3 H15073 MIR8085 XIRP1 ARL5B SRSF6 HBEFG FOXC1 OTUD4 TIPARP AI540253 MAFK DUSP5 DUSP2 GPCPD1 SLC25A44 LRRCA8 RASIP1 RASSF5 ATAD3B LOC100507258 FLNC ARID5B NFI L3 SLC1A5 STK40 NOP58 EGR1 RIPK2 SELE ARID5A COQ10B RARA AS1 TRAPPC2B PIM1 ZBTB43 VAPA KLF6 THBD KLF4 RBBP6 AA828232 CDC42 IER3 HIST2H2AA4 AKIRIN1 CEBDP JUNDF ZFP36 AI189587 STC1 EGR2 TCP111L EFNA1 LDLR KLHL21 DUSP14 SGK1 WARS CSF3 LDHA EIF2S1 NFKB1 NFKB2 RAB20 SERTAD1 PHC2 MSANTD3 DUSP1 SPIR RCAR1 PGRCSA SOX17 AI218358 MIL FAM53C CD83 BAG3 HTRA3 PLEKHO2 IRS2 ZNF134 ISG20L2 PIM3 RND3 PNR PDE4D TRIB1 RALGDS CENPN BCL6 VEGFA CSRNP1 TINF2 MYC NR4A3 PNPLA1 SOCS3 H2AFX LARP1 ATG101 SRSF3 TNFRSF12A EGR3 VPS37B ATF4 TNAIP3 MCL1 CCL2 LOC101927933 NXT1 PSME4 CREM GMEB2 RPF2 GADD45B ADGR KIAA0040 NF1AIP1 KCTD20 PPARD RGS2 SLC25A25 LINC00921 FOSL2 PPF1R DYRK3 NUP98 LATS2 AW057518 TUBB2A NIFK ZPR1 NAMPT NC51 FOXC2 CC3 DUSP6 GRASP BRPF1 MAPK6 PXDC1 GPR183 GADD45A C17orf96 TEMEM70 [M] ADAMTS1 SLC7A5 PIGA KLHL15 CXCL2 GPR4 PAPD7 TWISTNB NXXS 1 NR4A1 |
Table 1 Differentially expressed genes

| Gene ID | Gene Name |
|---------|-----------|
| TSC22D2 | SERPINB1 | DDX3Y | TDG |
| HSPA14 | TFB7B1 | APOL1 | METRNL |
| EHD4 | DNAJC2 | MTRF1L | DNAJC27 |
| HSPH1 | FAM47E | STBD1 | THBS1 |
| ABL1 | DNAJC27 | CA2 | IER5 |
| TNFRSF10B | SH2B3 | ADAM1 | USP36 |
| EHD4 | DNAJC2 | MTRF1L | DNAJC27 |
| ABL1 | DNAJC27 | CA2 | IER5 |
| TNFRSF10B | SH2B3 | ADAM1 | USP36 |
| EHD4 | DNAJC2 | MTRF1L | DNAJC27 |
| ABL1 | DNAJC27 | CA2 | IER5 |
| TNFRSF10B | SH2B3 | ADAM1 | USP36 |
| EHD4 | DNAJC2 | MTRF1L | DNAJC27 |
| ABL1 | DNAJC27 | CA2 | IER5 |
| TNFRSF10B | SH2B3 | ADAM1 | USP36 |
| EHD4 | DNAJC2 | MTRF1L | DNAJC27 |
| ABL1 | DNAJC27 | CA2 | IER5 |

Table 1 Differentially expressed genes

Functional enrichment analyses of DEGs

We analysis GO function and KEGG pathway enrichment analysis for DEGs using the DAVID (Table 2). The GO database was based on CC, BP, and MF ontologies. The results of the GO analysis indicated that DEGs were mainly involved in BPs and MFs.

BPs, including positive regulation of endothelial cell migration, positive regulation of transcription from RNA polymerase II promoter, and transcription, DNA-templated.

MFs, including transcription factor activity, sequence-specific DNA binding, protein
binding, sequence-specific DNA binding, and DNA binding. CC, including the nucleus. Besides, significantly enriched KEGG pathway of DEGs included PI3K-Akt signaling pathway, MAPK signaling pathway, Rap1 signaling pathway, TNF signaling pathway, and Neurotrophin signaling pathway and so on (Table 3).

| Category               | Term                                      | Count | PValue     |
|------------------------|-------------------------------------------|-------|------------|
| GOTERM_BP_DIRECT       | GO:0010595–positive regulation of endothelial cell migration | 11    | 4.51E-06   |
| GOTERM_BP_DIRECT       | GO:0045944–positive regulation of transcription from RNA polymerase II promoter | 64    | 6.63E-06   |
| GOTERM_BP_DIRECT       | GO:0006351–transcription, DNA-templated   | 108   | 6.86E-06   |
| GOTERM_CC_DIRECT       | GO:0005634–nucleus                        | 241   | 2.78E-06   |
| GOTERM_MF_DIRECT       | GO:0003700–transcription factor activity, sequence-specific DNA binding | 70    | 3.22E-08   |
| GOTERM_MF_DIRECT       | GO:0005515–protein binding                | 381   | 9.94E-08   |
| GOTERM_MF_DIRECT       | GO:0005515–protein binding                | 42    | 2.17E-06   |
| GOTERM_MF_DIRECT       | GO:0003677–DNA binding                    | 93    | 2.48E-05   |

Table 2 GO function enrichment analysis of DEG

| Term                                      | Count | PValue     |
|-------------------------------------------|-------|------------|
| hsa05161:Hepatitis B                      | 16    | 3.85E-04   |
| hsa05200:Pathways in cancer               | 27    | 0.003972827|
| hsa05219:Bladder cancer                   | 7     | 0.00422136f|
| hsa05164:Influenza A                      | 15    | 0.006402674|
| hsa04668:TNF signaling pathway            | 11    | 0.00735675f|
| hsa04010:MAPK signaling pathway           | 19    | 0.007532121|
| hsa04115:p53 signaling pathway            | 8     | 0.01327929f|
| hsa04015:Rap1 signaling pathway           | 16    | 0.013754862|
| hsa04012:ErbB signaling pathway           | 9     | 0.017306612|
| hsa04110:Cell cycle                       | 11    | 0.01949773 |
| hsa04151:PI3K-Akt signaling pathway       | 22    | 0.02202650f|
| hsa05168:Herpes simplex infection         | 14    | 0.02213092f|
| hsa05133:Pertussis                        | 8     | 0.02348344 |
| hsa05203:Viral carcinogenesis             | 15    | 0.02407624 |
| hsa05160:Hepatitis C                      | 11    | 0.03000838f|
| hsa05166:HTLV-I infection                 | 17    | 0.03228334f|
| hsa04722:Neurotrophin signaling pathway   | 10    | 0.03897174f|
| hsa05205:Proteoglycans in cancer          | 14    | 0.04127373f|
| hsa05169:Epstein-Barr virus infection     | 10    | 0.04260830f|
| hsa05215:Prostate cancer                  | 8     | 0.04977789f|

Table 3 KEGG pathway enrichment analysis of DEG

PPI network construction and hub gene identification
PPI network analysis among the DEGs was predicted with STRING tools and GeneMANIA online database. The STRING online database and GeneMANIA online database were performed to analyse the protein-protein interaction networks of the differentially expressed genes and modular, as presented in Figure 1. Those 10 genes showed by connectivity degree in the PPI network were identified (Figure 2). The results showed that Jun proto-oncogene, AP-1 transcription factor subunit (JUN) was the most outstanding gene with connectivity degree=93, followed by baculoviral early growth response 1 (EGR1; degree=55), activating transcription factor 3 (ATF3; degree=48), FosB proto-oncogene, AP-1 transcription factor subunit (FOSB; degree=34), JunB proto-oncogene, AP-1 transcription factor subunit (JUNB; degree=28), dual specificity phosphatase 1 (DUSP1; degree=39), early growth response 2 (EGR2; degree=26), nuclear receptor subfamily 4 group A member 1 (NR4A1; degree=32), BTG anti-proliferation factor 2 (BTG2; degree=26), nuclear receptor subfamily 4 group A member 2 (NR4A2; degree=25). All of these hub genes were upregulated after sevoflurane inhalation.

Discussion

We have already known sevoflurane has myocardial protective effects. DEGs between before inhalation (baseline sevoflurane) and after inhalation (sevoflurane) samples based on gene expression profiling data were screened out from the GEO database. Finally, we identified 297 upregulated DEGs and 429 downregulated DEGs. The GO annotation analysis of those selected DEGs shows that BP terms including positive regulation of endothelial cell migration, positive regulation of transcription from RNA polymerase II promoter and transcription, DNA-templated, MFs terms including transcription factor activity, sequence-specific DNA binding, protein binding, sequence-specific DNA binding and DNA binding and CCs including the nucleus. KEGG pathway analysis showed that DEGs were mainly enriched in pathways in the PI3K-Akt signaling pathway, MAPK signaling pathway, Rap1 signaling pathway, TNF signaling pathway, and Neurotrophin signaling pathway, and
A PPI network was constructed to investigate the interrelationship of the DEGs, and ten hub genes were identified, including *JUN, EGR1, ATF3, FOSB, JUNB, DUSP1, EGR2, NR4A1, BTG2, NR4A2*.

EGR1 encodes the protein which belongs to the EGR family of C2H2-type zinc-finger proteins. The protein is a nuclear protein that performs transcription. The products of target genes are necessary for differentiation and mitogenesis.9 Xiang Y, et al. find that after undergoing Percutaneous Transluminal Coronary Intervention (PCI) in CHD patients, once EGR1 level significantly decreased once in the early postoperative period, the patient’s coronary may be suspected not having reflow and should be examined timely to improve the effectiveness of therapeutic. 10 EGR1 has been named for the widespread presence and expressing rapidly in human cells. Shajahan-Haq AN, et al. showing that EGR1 has a complex signal pathway, playing a significant role in cell growth and affecting differentiation, proliferation, and inflammatory response.11 Another article, once in the plasma of patients with coronary heart disease, the expression level of EGR1 decreased, it suggests the aggravating of the disease of patients. The level of EGR1 can be used to assess the patient’s current status and the progression of disease.12

*ATF3* is a gene encoding transcription factors of the mammalian activation transcription factor/cAMP responsive element-binding (CREB) protein family. This gene is induced by a variety of signals, which is related to the happening of the cancer cells and the complex process of the cellular responding to stress. This gene has multiple transcript variants encoding different isoforms. Alternative splicing of this gene may play an important physiological role in regulating target genes. Li YU, et al. shows that upregulation of *ATF3* can reduce the heart damage and heart failure induced by hypertension and inhibit cardiac fibroblast cells.13
FOS encodes proteins having been implicated significant relationship with cell proliferation, differentiation, and transformation. The Fos gene family consists of 4 members, including FOS, FOSB, FOSL1, and FOSL2. Dunand-Sauthier I, et al find that c-Fos participates in proliferation, differentiation and apoptosis various cellular processes. Several studies have shown that c-Fos decreases proinflammatory cytokine production, and decrease cardiomyocytes death under conditions of hypoxia.

The protein encoded by BTG2 is a member of the BTG/Tob family which has structurally related proteins have antiproliferative function and is involved in the regulations of the G1/S transition during the cell cycle. BTG2 only affect cytosolic, but not nuclear, RNA levels. Masumura Y, et al shows that under adrenergic stimulation, BTG2 knockdown further enhances cytosolic RNA accumulation in cardiomyocytes. It indicates that BTG2 decrease RNA accumulation to protect cardiomyocytes from hypertrophy.

The protein encoded by JUNB is a member of the activator protein–1 (AP–1) transcription factor family including Jun (c-Jun, JunB and JunD) and Fos (c-Fos, FosB, Fra–1 and Fra–2). JunB combines with the cognitive binding sequence localized in the cis-regulatory region of target genes and participates in cell cycle, proliferation, and apoptosis biological processes. Szremska AP, et al. and Gurzov EN, et al. find that overexpressing JunB can inhibit the proliferation of malignant keratinocytes in mouse, and inhibit cell apoptosis in pancreatic beta cells. Also, Chen J, et al. find that JunB can protect heart failure from inflammatory cardiomyopathy, while in zebrafish decreased JunB leads to HF.

The protein encoded by DUSP1 is an anti-apoptotic phosphatase, and exited in a
wide variety of organizations, especially having a high level in the heart.\textsuperscript{21} One study finds that once I/R injuries happening, decreased DUSP1 can lead to scar expansion, cardiac dysfunction, and cellular death. The absence of DUSP1 triggered fatal mitochondrial fission leading to extensive cell death through increased JNK phosphorylation and the expression of Mff.\textsuperscript{22}

NR4A1 encodes a member of the steroid-thyroid hormone-retinoid receptor superfamily. The encoded protein acts as a nuclear transcription factor. When the protein encoded by NR4A1 transferred from nucleus to the mitochondria leads to apoptosis. It has different subtypes of several transcriptional variants which have an efficient function of cardiac repair.\textsuperscript{23}

The protein encoded by BTG2 is affiliated to the BTG/Tob family. This family related proteins have antiproliferative properties. The protein encoded by BTG2 plays an important role in regulating the G1/S transition of the cell cycle. BTG2 can impact the accumulation of cytosolic, but not nuclear, RNA levels. Masumura Y, et al. suggest that though down-regulating the cardiomyocytes accumulation of RNA, BTG2 can attenuate reactive hypertrophy.\textsuperscript{5}

NR4A2, nuclear receptor subfamily 4, group A, member 2, with NR4A1 and NR4A3 composed NR4A orphan nuclear receptor family.\textsuperscript{24} The NR4A family is the immediate early response transcription factors, which has great relationship with ischemic stroke.\textsuperscript{25} NR4A2 participates the apoptosis of various cancer cells under stress through different functions.\textsuperscript{26} In the MI injury mouse, NR4A2 is upregulated. Furthermore, NR4A2 can protect heart from apoptosis and hypertrophy, and also alleviate heart injury.
Conclusions

In conclusion, the proteins encoded by EGR1\textsuperscript{a}\textsuperscript{-}\textbf{ATF3}\textsuperscript{c}\textsuperscript{-c-Fos}\textsuperscript{t}\textsuperscript{Btg2}\textsuperscript{t}\textsuperscript{JunB}\textsuperscript{t}\textsuperscript{-}\textbf{DUSP1} and NR4A1\textsuperscript{\textemdash}\textbf{BTG2} and NR4A2 were related to cardiac function. \textbf{ATF3}, FOSB, JUNB, DUSP1, NR4A1, NR4A2 are related to apoptosis of cardiomyocytes. The protein encoded by B\textsuperscript{\textemdash}TG2 is related to hypertrophy. Sevoflurane regulates cell transcription, inflammatory and apoptosis through those hub genes to protect myocardial.

Abbreviations

OPCABG: Off-pump coronary artery bypass graft; GEO: Gene Expression Omnibus; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; DEGs: Differentially expressed genes; PPI: Protein–protein interaction; CAD: Coronary artery disease; PCI: Percutaneous Transluminal Coronary Intervention; CREB: CAMP responsive element-binding; AP–1: Activator protein–1; ER: Endoplasmic reticulum; HF: Heart failure; CMT1D: Charcot-Marie-Tooth disease type 1D; CMT4E: Charcot-Marie-Tooth disease type 4E; DSS: Dejerine-Sottas syndrome.

Declarations

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

**Competing interests**
The authors declare that they have no competing interests.

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**Authors’ contributions**

Hua Lin analyzed and interpreted the data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1
Genemania network
Figure 2

Ten hub genes