Identification of key genes in Gram-positive and Gram-negative sepsis using stochastic perturbation

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Abstract. Sepsis is an inflammatory response to pathogens (such as Gram-positive and Gram-negative bacteria), which has high morbidity and mortality in critically ill patients. The present study aimed to identify the key genes in Gram-positive and Gram-negative sepsis. GSE6535 was downloaded from Gene Expression Omnibus, containing 17 control samples, 18 Gram-positive samples and 25 Gram-negative samples. Subsequently, the limma package in R was used to screen the differentially expressed genes (DEGs). Hierarchical clustering was conducted for the specific DEGs in Gram-negative and Gram-negative samples using cluster software and the TreeView software. To analyze the correlation of samples at the gene level, a similarity network was constructed using Cytoscape software. Functional and pathway enrichment analyses were conducted for the DEGs using DAVID. Finally, stochastic perturbation was used to determine the significantly differential functions between Gram-positive and Gram-negative samples. A total of 340 and 485 DEGs were obtained in Gram-positive and Gram-negative samples, respectively. Hierarchical clustering revealed that there were significant differences between control and sepsis samples. In Gram-positive and Gram-negative samples, myeloid cell leukemia sequence 1 was associated with apoptosis and programmed cell death. Additionally, NADH:ubiquinone oxidoreductase subunit S4 was associated with mitochondrial respiratory chain complex I assembly. Stochastic perturbation analysis revealed that NADH:ubiquinone oxidoreductase subunit B2 (*NDUFB2*), *NDUFB8* and ubiquinol-cytochrome c reductase hinge protein (*UQCRH*) were associated with cellular respiration in Gram-negative samples, whereas large tumor suppressor kinase 2 (*LATS2*) was associated with G1/S transition of the mitotic cell cycle in Gram-positive samples. *NDUFB2*, *NDUFB8* and *UQCRH* may be biomarkers for Gram-negative sepsis, whereas *LATS2* may be a biomarker for Gram-positive sepsis. These findings may promote the therapies of sepsis caused by Gram-positive and Gram-negative bacteria.

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Abbreviations: DEGs, differentially expressed genes; FDR, false discovery rate; FC, fold-change; ICU, intensive care unit; PCC, Pearson's correlation coefficient; KEGG, Kyoto Encyclopedia of Genes and Genomes

Key words: Gram-negative sepsis, Gram-positive sepsis, similarity network, functional enrichment, stochastic perturbation

Introduction

Sepsis is a systemic and deleterious inflammatory response to noxious infection (1,2). Sepsis causes ~18 million new cases and millions of deaths worldwide annually; therefore, it is a major cause of morbidity and mortality globally in critically ill patients (3,4). The excessive activation of inflammation, complement and coagulation systems may damage the host's own tissues and organs, leading to multiple organ failure and death (5). In a group of patients diagnosed with sepsis, the most common causative agents are Gram-positive and Gram-negative bacteria (6,7).

Tang *et al* (8) used the microarray expression profile of GSE6535 to identify the differentially expressed genes (DEGs) between patients with Gram-positive and Gram-negative sepsis with univariate F test according to the cut-off criteria of false discovery rate (FDR) <0.05 and |log fold-change (FC)|>1.5 and determined that Gram-positive sepsis and Gram-negative sepsis had a common host response at the transcriptome level in critically ill patients (8). However, a previous study illustrated the different mechanisms of sepsis caused by Gram-positive bacteria and Gram-negative bacteria. Hypoxia-inducible factor 1α and Kruppel-like factor 2 have been identified to be involved in Gram-positive endotoxin-mediated sepsis by regulating cellular motility and proinflammatory gene expression in myeloid cells (9). In Gram-negative bacteria-induced sepsis, it has been determined that the inhibition of caspase-1 and defective interleukin 1β production are important immunological features (10). Additionally, α2-antiplasmin has been identified to be a protective mediator during Gram-negative sepsis by inhibiting bacterial growth, inflammation, tissue injury and coagulation (11). Furthermore, thrombomodulin-mediated protein C activation may contribute to protective immunity

in severe Gram-negative sepsis by regulating inflammatory and procoagulant response (12). Despite the clinical importance of the disease and extensive research, no specific treatment is available for sepsis caused by Gram-positive and Gram-negative bacteria. Therefore, it is necessary to screen the biomarkers for sepsis.

The present study aimed to use the microarray data of Tang *et al* (8) to screen the DEGs in Gram-positive and Gram-negative samples compared with control samples using the limma package based on a wide range of thresholds ($P<0.05$ and $|\log_2 FC|>0.8$). In addition, specific genes were collected as biomarkers for sepsis caused by Gram-positive and Gram-negative bacteria. A previous study has proposed that analyses based on differential statistical tests may lead to different outcomes (13). Therefore, the findings of the present study may differ to those of Tang *et al* (8).

Materials and methods

Microarray data. The microarray dataset of GSE6535 (8) was downloaded from the database of gene expression omnibus (www.ncbi.nlm.nih.gov/geo), which was sequenced on the platform GPL4274 NHICU Human 19K version 1.0. Probe annotation information for mapping the probes into gene symbols was also downloaded. From GSE6535 dataset, 17 neutrophil samples from patients without sepsis, 18 neutrophil samples from patients with Gram-positive sepsis, and 25 neutrophil samples from patients with Gram-negative sepsis were selected. Tang *et al* (8) obtained whole blood samples from critically ill patients on admission to the intensive care unit of Nepean Hospital (Sydney, Australia). Using Ficoll-Paque density gradient separation, neutrophils were isolated from the whole blood. The patients with sepsis were diagnosed retrospectively according to their medical record. According to the criteria established by Calandra and Cohen (14), the patients with sepsis were divided into Gram-positive and Gram-negative sepsis groups through assessing various clinical features, including physical examination and history and microbiological cultures, such as bronchoalveolar washings, urine, blood and cerebrospinal fluid. GSE6535 was deposited by Tang *et al* (8). The study of Tang *et al* was approved by the Ethics Committee of Nepean Hospital and written informed consent was provided by the patients or their families (8).

Data preprocessing and differential expression analysis. Based on the probe annotation information, probe IDs were converted into their corresponding gene symbols. The average value of multiple probes (that were corresponding to the same gene) was used as the gene expression value. To eliminate inherent expression differences between genes, the gene expression values were performed with Z-score normalization as previously described (15). Subsequently, the limma package version 3.32.2 in R (16) was used to screen the DEGs in the Gram-positive and Gram-negative samples compared with the control samples. The $P<0.05$ and $|\log_2 FC|>0.8$ were used as the cut-off criteria for screening DEGs. Using the VennDiagram in R (17), the common DEGs between Gram-positive and Gram-negative samples, as well as the specific DEGs in Gram-positive samples or Gram-negative samples were identified. Gene Ontology (GO; www.geneontology.org) is a bioinformatics resource that may be used to classify gene product function using controlled, structured vocabularies (18). Using the Database for Annotation, Visualization and Integrated Discovery (DAVID) (19), GO functional enrichment analysis was performed on the common DEGs. The hierarchical cluster analysis of the specific DEGs in Gram-positive or Gram-negative samples was conducted using cluster version 3.0 software (20) and then visualized using TreeView tool version 3 (21).

Similarity network construction. Pearson's correlation coefficient (PCC) (22), which determines the correlation between two variables, was used to identify the positive or negative correlations among different samples, with the threshold of $|PCC|>0.5$. Using Cytoscape version 2.8 software (23), a similarity network was constructed for the Gram-positive, Gram-negative and control samples.

Functional and pathway enrichment analyses. Kyoto Encyclopedia of Genes and Genomes (KEGG; www.genome.jp/kegg/), which integrates genomic, chemical and systemic functional information, is a useful resource for pathway mapping (24). Using the online tool DAVID (19), GO functional and KEGG pathway enrichment analyses were conducted for the DEGs. $P<0.05$ was used as the threshold.

Identification of significantly differential functions using stochastic perturbations. The average expression value in Gram-positive or Gram-negative samples was calculated for each gene enriched in the same term (GO functions or KEGG pathways). Euclidean distance (25) was used to calculate the difference between the levels of all the terms between Gram-positive and Gram-negative samples, according to the following equation:

$$\text{distance} = \sqrt{\sum_{i=1}^{T}(\bar{X}_{Pi} - \bar{X}_{Ni})^2}$$

Where distance represents the Euclidean distance between Gram-positive samples and Gram-negative samples; $\overline{X}_{pi}$ stands for the average expression value of gene i in Gram-positive samples; $\overline{X}_{pi}$ represents the average expression value of gene i in Gram-negative samples; and T indicates the gene number in each term.

Subsequently, stochastic perturbations were used (26) to determine the significance findings. The 18 Gram-positive and 25 Gram-negative samples were randomly sorted. Subsequently, 18 samples were randomly selected and defined as Gram-positive samples and the remaining 25 samples were defined as Gram-negative samples. The Euclidean distance between the newly defined Gram-positive samples and Gram-negative samples was recalculated. This was repeated for 10,000 times and the Euclidean distance for 10,000 perturbations were sorted from small to large and used as the background distribution. The ranking order of the initial Euclidean distance in the background distribution was calculated and converted to a P-value. The terms with $P<0.05$ were considered significantly differential functions between Gram-positive and Gram-negative samples.

Table I. Top 10 upregulated and downregulated genes in patients with Gram-negative and Gram-positive sepsis.

A, Gram-negative

DEGs	-$\log_2$ (P-value)	logFC
Upregulated genes		
RPL27	3.735442	1.654937
TM4SF1	2.691156	1.541493
SEC11A	2.258718	1.518767
PLOD2	2.255042	1.494549
UQCRH	2.154078	1.446315
AFP	1.889918	1.429409
CDK5RAP2	3.965291	1.413672
EPB41L4A-AS1	4.122053	1.411759
SOD1	2.91784	1.40033
CANX	4.013587	1.392226
Downregulated genes		
EVI2B	4.312471	-2.08489
MME	5.521434	-1.73605
ZBP1	5.974694	-1.56361
LITAF	3.113137	-1.54349
CYTH4	2.874971	-1.53818
FBXL5	2.808339	-1.53
CHI3L1	4.498941	-1.45407
QPCT	4.411504	-1.45154
TREM1	4.12983	-1.43918
MXD1	3.392031	-1.41323

B, Gram-positive

DEGs	-$\log_2$ (P-value)	logFC
Upregulated genes		
SSBP1	1.896196279	1.5341469
LAIR1	3.8569852	1.4491332
MRPS18A	2.377785977	1.4338711
NDUFC2	3.935542011	1.4093212
CTSC	3.982966661	1.3851966
MT1L	2.991399828	1.3843636
TM4SF1	2.249491605	1.3772427
FCHSD2	1.694648631	1.301164
CYP1B1	2.460923901	1.297874
NDUFA4	1.876148359	1.267824
Downregulated genes		
CHI3L1	6.359519	-1.92246
EVI2B	3.271646	-1.71993
MME	4.36251	-1.68036
KCNB1	2.300162	-1.56111
LITAF	2.415669	-1.44533
FUS	2.767004	-1.42285
QPCT	3.090444	-1.38819
CKAP4	4.251812	-1.35146
MCL1	4.221126	-1.34034
EFHC2	3.458421	-1.32892

DEGS, differentially expressed genes; FC, fold-change.

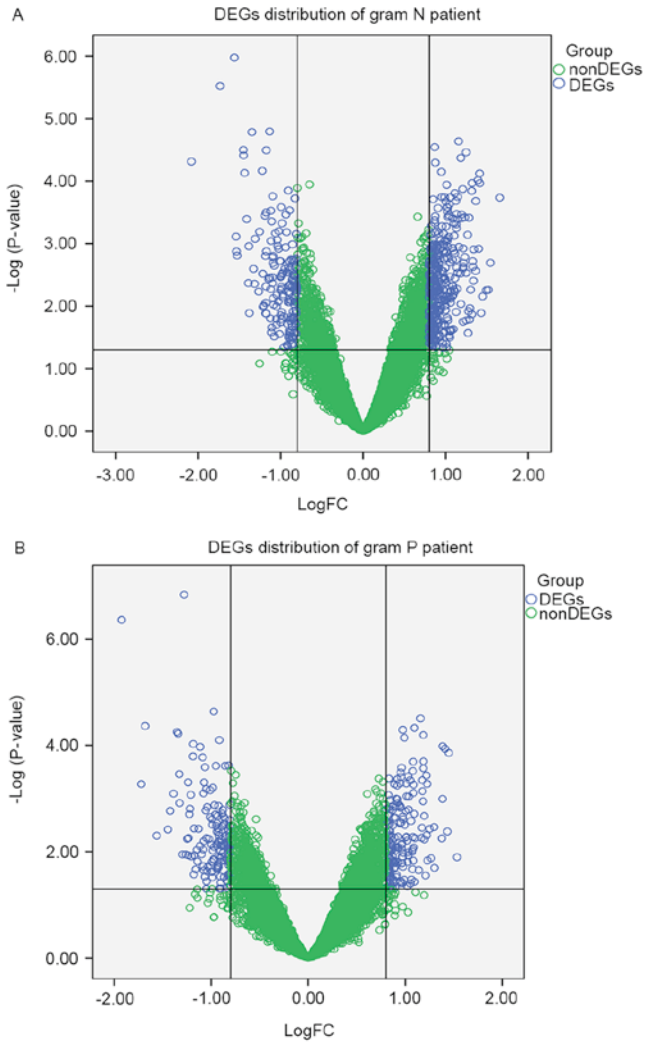

Figure 1. Volcano plots indicate the gene distribution of (A) Gram-negative samples and (B) Gram-positive samples. DEGs, differentially expressed genes; FC, fold-change.

Results

DEGs analysis. The gene distribution of Gram-negative (Fig. 1A) and Gram-positive samples (Fig. 1B) are presented using a volcano plot. Using the $P<0.05$ and $|\log_2 FC|>0.8$ as thresholds, a total of 340 DEGs, including 181 upregulated genes, including large tumor suppressor kinase 2 (*LATS2*), NADH:ubiquinone oxidoreductase subunit S4 (*NDUFS4*) and 159 downregulated genes, including myeloid cell leukemia 1 (*MCL1*) and chitinase-like 1, were obtained in Gram-positive samples compared with control samples. A total of 485 DEGs were identified, 324 upregulated genes, including *NDUFS4* and NADH:ubiquinone oxidoreductase subunit B2 (*NDUFB2*) and 161 downregulated genes, including *MCL1* and ecotropic viral integration site 2B, were identified in Gram-negative samples compared with the control samples. The top 10 significantly upregulated genes and downregulated genes in the Gram-negative and Gram-positive samples are presented in Table I.

A total of 188 common DEGs, including 120 upregulated and 68 downregulated were identified between Gram-positive and Gram-negative samples. Additionally, 152 specific DEGs,

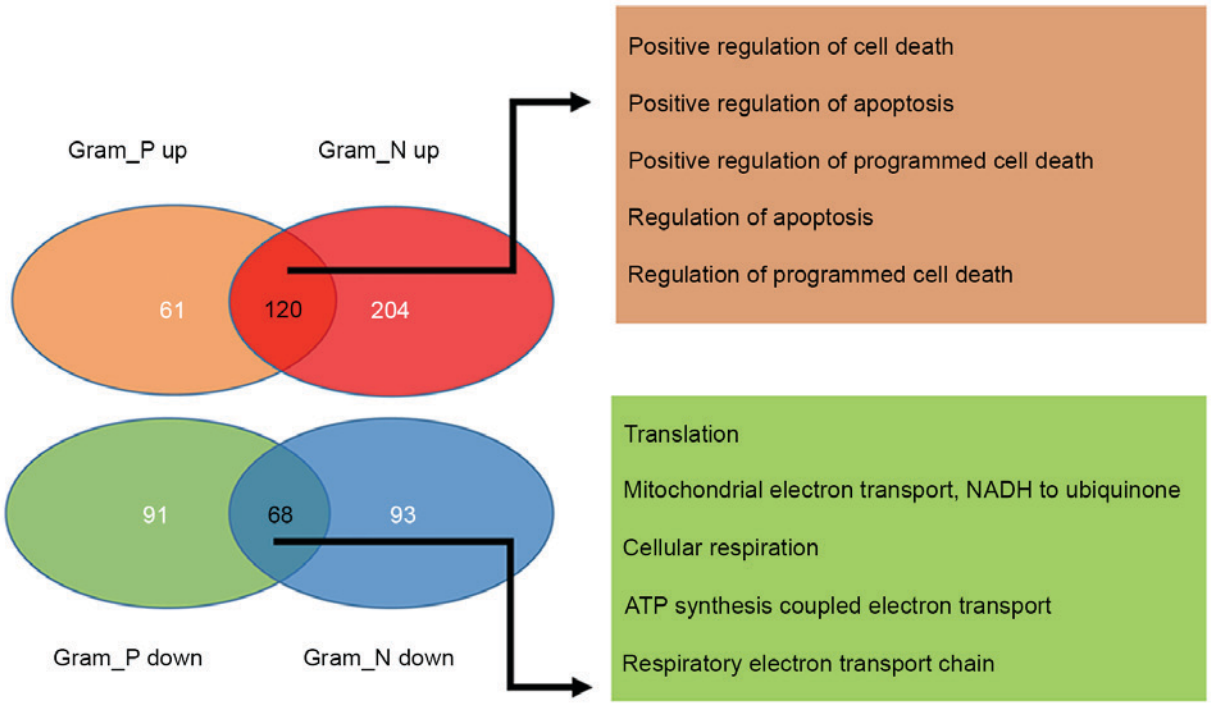

Figure 2. Summary of the common differentially expressed genes between Gram-negative and Gram-positive samples, and their respective enriched functions.

including 61 upregulated and 91 downregulated genes in the Gram-positive samples and 297 specific DEGs, including 204 upregulated and 93 downregulated genes in Gram-negative samples were also screened (Fig. 2). GO functional enrichment analysis was performed on the common DEGs, consisted of 120 upregulated and 68 downregulated genes in the Gram-positive and Gram-negative samples and the top 5 terms for each sample type were presented in Fig. 2. The findings revealed that the common upregulated genes were primarily associated with the regulation of apoptosis and cell death, whereas the common downregulated genes were primarily associated with cellular respiration (Fig. 2). Hierarchical cluster analysis of the specific DEGs revealed that there were significant differences between control and sepsis samples. However, no significant difference was identified between the Gram-positive and Gram-negative samples (Fig. 3).

Similarity network analysis. In the similarity network, positive associations were identified between the majority of the control and sepsis samples. However, negative associations were also identified between the control and sepsis samples (Fig. 4).

Functional and pathway enrichment analyses. Functional enrichment analysis was performed on the upregulated and downregulated genes in the Gram-positive or Gram-negative samples separately. For the downregulated genes in the Gram-positive samples and Gram-negative samples, *MCL1* was significantly associated with the functions of apoptosis and programmed cell death regulation. For the upregulated genes in the Gram-positive and Gram-negative samples, *NDUFS4* was significantly associated with mitochondrial respiratory chain complex I assembly. Additionally, *NDUFB2*, *NDUFB8* and ubiquinol-cytochrome *c* reductase hinge protein (*UQCRH*) were significantly enriched in the functions of cellular respiration, ATP synthesis coupled electron transport and respiratory electron transport chain in Gram-negative samples. *LATS2* was significantly associated with the G1/S transition of the mitotic cell cycle in Gram-positive samples (Tables II and III). KEGG pathway enrichment analysis was also conducted for up and downregulated genes in Gram-positive and Gram-negative samples (Tables IV and V). *NDUFS4* was significantly enriched in the pathway of oxidative phosphorylation.

Significantly differential functions screening. Based on the Euclidean distance of the biological functions, as well as the P-values of the 10,000 stochastic perturbations between Gram-positive samples and Gram-negative samples, a total of 10 significantly differential functions were obtained, including cellular respiration ($P<1.00x10^{-8}$, Euclidean distance=1.156277), ATP synthesis coupled electron transport ($P<1.00x10^{-8}$, Euclidean distance=1.156277) and G1/S transition of mitotic cell cycle (P=0.015, Euclidean distance = 0.554799; Table VI).

Discussion

In line with the results of Tang *et al* (8), the present study determined that there was no significant difference in the expression profile between Gram-positive and gram-negative samples from hierarchical clustering analysis. In the Gram-positive and Gram-negative samples, the GO functional enrichment analysis revealed that *MCL1* was significantly associated with the regulation of apoptosis and programmed cell death. A previous study has determined that the apoptosis of T-cells may induce the breakdown of defense mechanisms resulting in sepsis (27). Additionally,

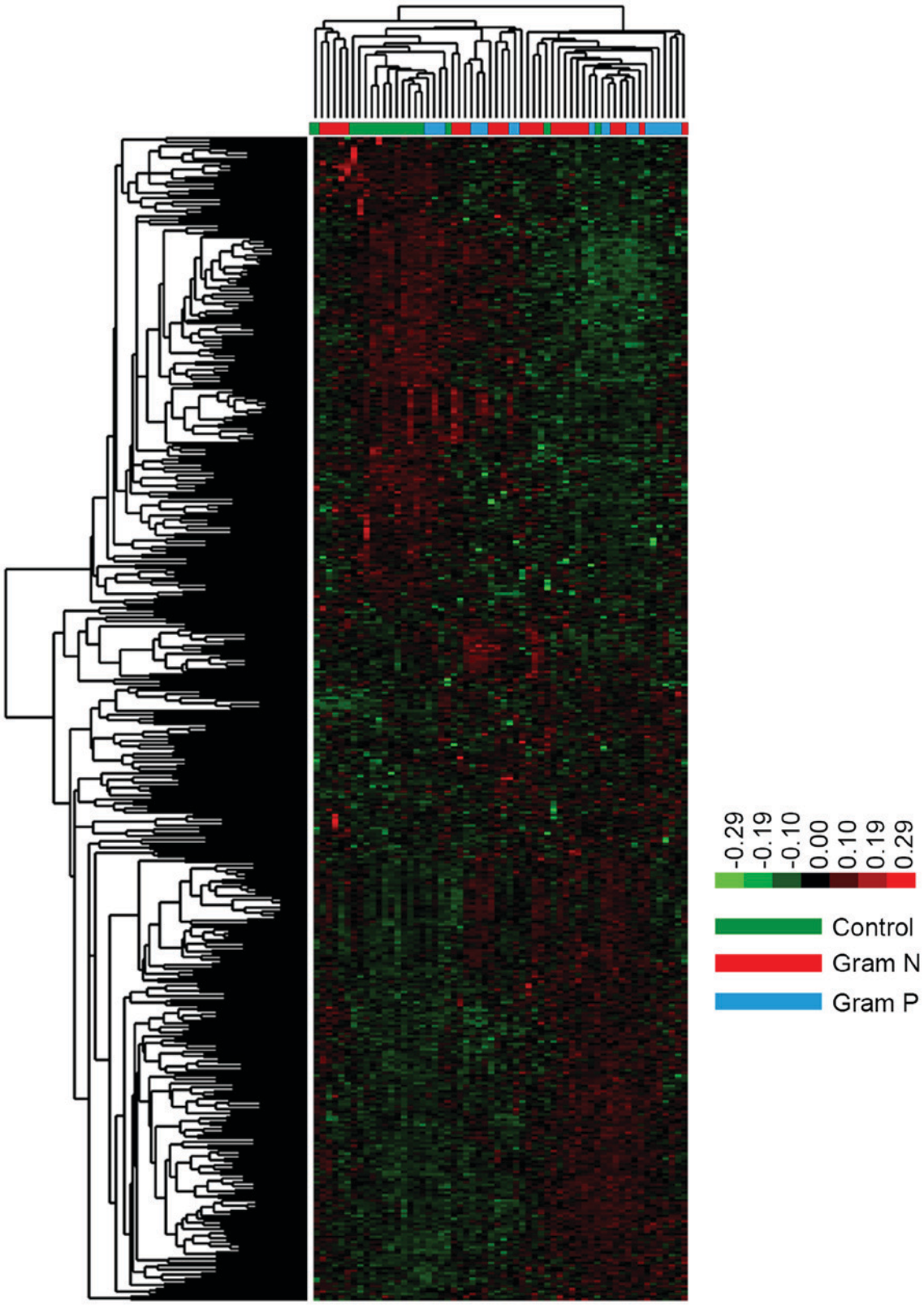

Figure 3. Hierarchical clustering of specific DEGs in Gram-P, Gram-N and control samples. Gram N, Gram-negative samples; Gram P, Gram-positive samples.

the inhibition of programmed cell death may reverse T-cell exhaustion and thus eradicate the invading pathogens which cause sepsis (28). Additionally, *MCL1* may also be associated with the reduction of apoptosis of neutrophils in patients with sepsis (29). Therefore, it is possible for *MCL1* to be involved in sepsis via the regulation of T-cell apoptosis and programmed T-cell death in both Gram-positive and Gram-negative sepsis.

Additionally, the present study also determined that *NDUFS4* was significantly associated with mitochondrial respiratory chain complex I assembly. Mitochondrial dysfunction may lead to oxidative stress and failure of

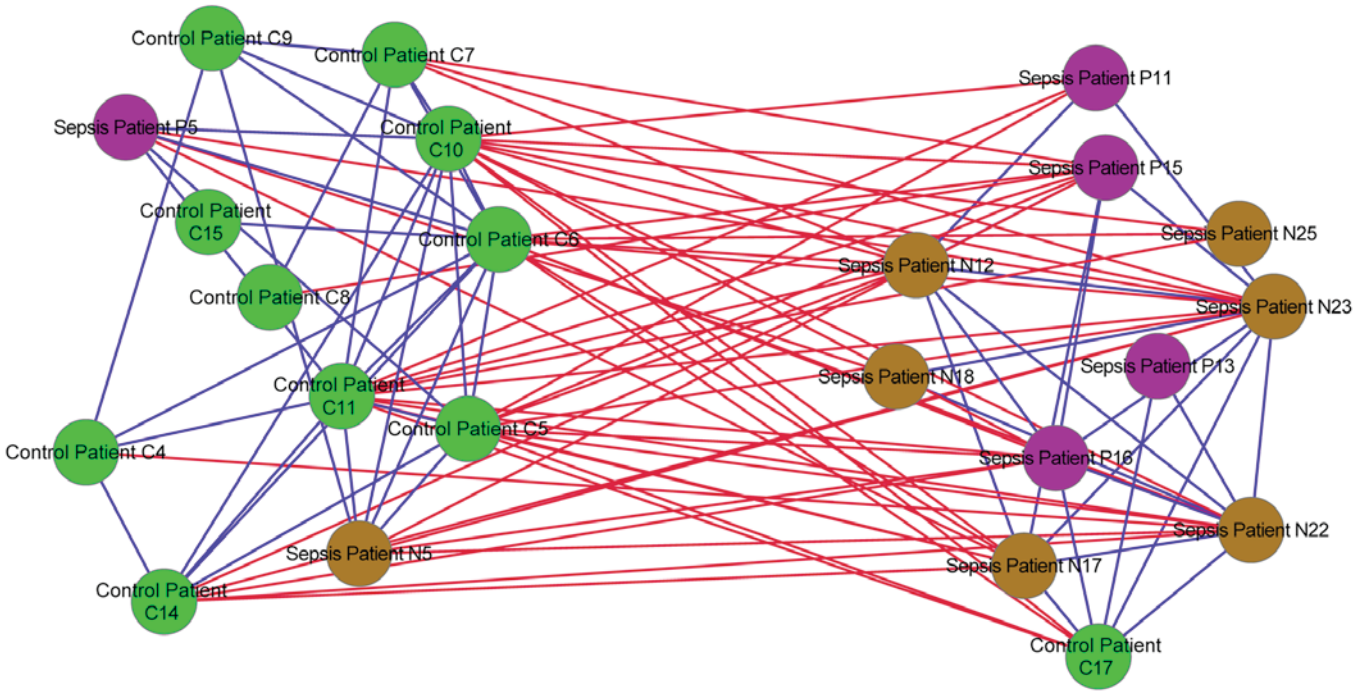

Figure 4. Correlation network of the Gram-positive, Gram-negative and control samples. Green circles indicate control samples, brown circles indicate Gram-negative samples and purple circles indicate Gram-positive samples. The red lines indicate a positive correlation between the two samples and blue lines indicate a negative correlation between the two samples.

energy production, which may result in organ dysfunction in sepsis (30). The KEGG pathway enrichment analysis revealed that *NDUFS4* was significantly enriched in oxidative phosphorylation. Lee and Hüttemann (31) have determined that the inhibition of oxidative phosphorylation may lead to a reduction of the mitochondrial membrane potential, resulting in a lack of energy, which may cause organ failure and death in septic patients (31). *NDUFS4* has been previously reported to be an important subunit of complex I which has a key role in oxidative phosphorylation (32). Additionally, *NDUFS4* may participate in the regulation of sepsis induced by Gram-negative and Gram-positive bacteria through regulation of oxidative phosphorylation.

However, the present study identified specific DEGs in Gram-positive and Gram-negative samples compared with normal samples. According to the Euclidean distance and the stochastic perturbations performed between Gram-positive and Gram-negative samples, *NDUFB2*, *NDUFB8* and *UQCRH* were significantly upregulated in the Gram-negative samples, whereas they were not upregulated in the Gram-positive samples. In addition, functional annotation revealed that they were significantly associated with cellular respiration, ATP synthesis coupled electron transport and mitochondrial electron transport, ubiquinol to cytochrome *c*. *NDUFB2* and *NDUFB8* are parts of the multisubunit mitochondrial NADH ubiquinone oxidoreductase (complex I) which has an important role in mitochondrial functioning (33,34). A previous study determined that a dysfunction of respiratory chain complex I may be associated with reactive oxygen species (ROS) production (35). Additionally, previous studies reported that ROS are toxic oxygen-containing molecules that may damage the cells and the antioxidant defense system, which is the pathogenesis of sepsis (36,37). *UQCRH*, which encodes the cytochrome b-c1 complex subunit 6 of complexes III (cytochrome *c*-oxidoreductase), is involved in the mitochondrial oxidative phosphorylation and the dysfunction of *UQCRH* may lead to breast and ovarian cancer by altering the function of the mitochondria (38,39). To the best of our knowledge, this is the first study investigating the functions of *NDUFB2, NDUFB8* and *UQCRH* in Gram-negative bacteria-induced sepsis. The present study concluded that *NDUFB2, NDUFB8* and *UQCRH* may be involved in the Gram-negative bacteria-induced sepsis by altering mitochondrial oxidative phosphorylation and may also be potential targets for the treatment of Gram-negative bacterial sepsis.

In addition, the function of the G1/S transition of the mitotic cell cycle was also determined to be significantly different between the Gram-positive and Gram-negative samples. *LATS2* was enriched in this function and was significantly upregulated in patients with Gram-positive sepsis, whereas it was not significantly expressed in Gram-negative patients. *LATS2*, encoding serine/threonine-protein kinase, has been identified to inhibit the G1/S transition in the cell cycle of tumor cells (40). Additionally, G1 cell cycle arrest may be important for the initiation of kidney injury in sepsis (41). Therefore, *LATS2* may be associated with Gram-negative bacterial sepsis by the modulation of G1/S transition in cell cycle.

In conclusion, *MCL1*, *NDUFS5* and *NDUFS4* may be potential target genes for the treatment of Gram-positive and Gram-negative bacterial sepsis. Additionally, *NDUFB2, NDUFB8* and *UQCRH* may also be associated with Gram-negative bacterial sepsis. *LATS2* may contribute to the progression of Gram-negative bacterial sepsis. However, further studies are still required in order to elucidate their action mechanisms in sepsis.

Table II. Top 10 enriched GO terms for the upregulated and the downregulated genes in Gram-positive samples.

A, Upregulated genes

Term	Function	Count	P-value	Gene symbol
GO:0006412	Translation	22	3.52×10^{-11}	*AIMP1, EEF1A2, GARS, MRPS10, RPS27L, MRPS18C, MRPL15, MRPS18A, RPL22, MRPL27, EEF1E1, NARS2, EIF2S2, HARS, MRPL19, MRPL36, RPL10, RPL11, RSL24D1, MRPL32, EEFSEC, MRPL33*
GO:0006120	Mitochondrial electron transport, NADH to ubiquinone	7	4.78×10^{-6}	*NDUFA4, NDUFS6, NDUFS5, NDUFS4, NDUFA8, NDUFA9, NDUFC2*
GO:0042773	ATP synthesis coupled electron transport	7	2.62×10^{-5}	*NDUFA4, NDUFS6, NDUFS5, NDUFS4, NDUFA8, NDUFA9, NDUFC2*
GO:0022904	Respiratory electron transport chain	7	5.65×10^{-5}	*NDUFA4, NDUFS6, NDUFS5, NDUFS4, NDUFA8, NDUFA9, NDUFC2*
GO:0045333	Cellular respiration	8	7.34×10^{-5}	*NDUFA4, NDUFS6, NDUFS5, NDUFS4, NDUFA8, NDUFA9, NDUFC2, MDH1*
GO:0044267	Cellular protein metabolic process	44	1.09×10^{-4}	*FASTK, FKBP3, PRDX4, MRPS10, RPS27L, CANX, LATS2, VRK1, PSMB7, PSMB6, MRPL15, PLOD2, NARS2, MRPL36, B3GNT1, MRPL19, RPL10, RPL11, RSL24D1, MRPL32, LOXL1, FGF2, MRPL33, HSP90AA1, AIMP1, EEF1A2, GARS, SOD1, LRPAP1, IKBKE, MAST4, HSP90B1, PPIH, MRPS18C, PSMA5, MRPL27, RPL22, MRPS18A, EEF1E1, EIF2S2, HARS, DSP, EEFSEC, FKBP2*
GO:0016310	Phosphorylation	19	1.87×10^{-3}	*NDUFA4, NDUFA8, MVD, NDUFA9, FASTK, HK2, NDUFC2, PRDX4, SOD1, LATS2, NDUFS6, IKBKE, MAST4, VRK1, NDUFS5, NDUFS4, ATP5C1, ATP5A1, FGF2*
GO:0000079	Regulation of cyclin-dependent protein kinase activity	5	2.51×10^{-3}	*GTPBP4, CDKN2C, CKS2, CDKN3, LATS2*
GO:0033365	Protein localization in organelle	7	4.53×10^{-3}	*PPIH, MTX2, NDUFA13, FGF2, TIMM44, SEC61G, NR5A1*
GO:0010257	NADH dehydrogenase complex assembly	3	4.73×10^{-3}	*NDUFAF4, NDUFS5, NDUFS4*

B, Downregulated genes

Term	Function	Count	P-value	Gene symbol
GO:0010942	Positive regulation of cell death	17	1.51×10^{-6}	*PTGS2, PREX1, STK17B, RRAGA, PRKDC, NLRP3, NLRP1, SERINC3, NOTCH1, EI24, SSTR3, CASP4, DUSP1, CASP8, BNIP3L, FGD3, KALRN*
GO:0043065	Positive regulation of apoptosis	16	6.31×10^{-6}	*PTGS2, PREX1, STK17B, PRKDC, NLRP3, NLRP1, SERINC3, NOTCH1, EI24, SSTR3, CASP4, DUSP1, CASP8, BNIP3L, FGD3, KALRN*

Table II. Continued.

B, Downregulated genes

Term	Function	Count	P-value	Gene symbol
GO:0043068	Positive regulation of programmed cell death	16	6.86×10^{-6}	*PTGS2, PREX1, STK17B, PRKDC, NLRP3, NLRP1, SERINC3, NOTCH1, EI24, SSTR3, CASP4, DUSP1, CASP8, BNIP3L, FGD3, KALRN*
GO:0042981	Regulation of apoptosis	20	8.53×10^{-5}	*PTGS2, MCL1, PREX1, STK17B, PRKDC, PIM2, NLRP3, NLRP1, SERINC3, NOTCH1, EI24, SSTR3, CASP4, DUSP1, IGF2R, BNIP3L, CASP8, DLG5, FGD3, KALRN*
GO:0043067	Regulation of programmed cell death	20	9.73×10^{-5}	*PTGS2, MCL1, PREX1, STK17B, PRKDC, PIM2, NLRP3, NLRP1, SERINC3, NOTCH1, EI24, SSTR3, CASP4, DUSP1, IGF2R, BNIP3L, CASP8, DLG5, FGD3, KALRN*
GO:0012502	Induction of programmed cell death	12	1.38×10^{-4}	*SERINC3, EI24, CASP4, SSTR3, PREX1, BNIP3L, CASP8, STK17B, NLRP3, NLRP1, FGD3, KALRN*
GO:0009966	Regulation of signal transduction	20	2.68×10^{-4}	*LITAF, PREX1, KLK5, CYTH4, RABGAP1L, PIM2, TBC1D22A, OSM, ECE1, CXCR4, SOSTDC1, CASP8, GPSM1, RAMP1, RAPGEF1, RUNX2, ARAP1, FGD3, GNG7, KALRN*
GO:0008277	Regulation of G-protein coupled receptor protein signaling pathway	5	1.10×10^{-3}	*ECE1, KLK5, GPSM1, RAMP1, GNG7*
GO:0051056	Regulation of small GTPase mediated signal transduction	8	7.45×10^{-3}	*PREX1, CYTH4, RABGAP1L, RAPGEF1, FGD3, ARAP1, TBC1D22A, KALRN*
GO:0010647	Positive regulation of cell communication	8	2.82×10^{-2}	*OSM, LAMA2, ECE1, PTGS2, LITAF, KLK5, CASP8, PIM2*

GO, gene ontology.

Table III. Top 10 enriched GO terms for the upregulated and the downregulated genes in Gram-negative samples.

A, Upregulated genes

Term	Function	Count	P-value	Gene symbol
GO:0045333	Cellular respiration	15	8.97×10^{-9}	*UQCRC2, NDUFA8, NDUFB8, NDUFA6, NDUFA7, CYCS, NDUFC2, NDUFB2, NDUFS6, UQCR10, NDUFS5, NDUFS4, UQCRH, UQCRB, MDH1*
GO:0042773	ATP synthesis coupled electron transport	12	1.31×10^{-8}	*NDUFS6, NDUFS5, UQCR10, NDUFS4, NDUFA8, UQCRH, NDUFB8, NDUFA6, NDUFA7, NDUFC2, UQCRB, NDUFB2*
GO:0022904	Respiratory electron transport chain	12	5.68×10^{-8}	*NDUFS6, NDUFS5, UQCR10, NDUFS4, NDUFA8, UQCRH, NDUFB8, NDUFA6, NDUFA7, NDUFC2, UQCRB, NDUFB2*
GO:0006412	Translation	24	2.78×10^{-7}	*MRPL3, RPL19, EEF1B2, EEF1A2, HBS1L, RPL15, MRPS10, RPL27, RPS27L, RPL22L1, IARS2, RPS7, MRPS18C, MRPL15, MRPS18A, RPL22, MRPL27, EEF1E1, MRPL19, RPL11, RSL24D1, MRPL32, MRPL33, RPS23*
GO:0006457	Protein folding	17	6.33×10^{-7}	*HSP90AA1, FKBP5, FKBP4, FKBP3, TTC9, PDIA5, CCT3, LMAN1, CANX, LRPAP1, CCT7, PPIH, HSP90B1, SIL1, RUVBL2, HSPD1, FKBP2*
GO:0006120	Mitochondrial electron transport, NADH to ubiquinone	9	1.70×10^{-6}	*NDUFS6, NDUFS5, NDUFS4, NDUFA8, NDUFB8, NDUFA6, NDUFA7, NDUFC2, NDUFB2*
GO:0051437	Positive regulation of ubiquitin-protein ligase activity during mitotic cell cycle	9	6.75×10^{-5}	*CDK1, PSMB7, PSMD14, PSMB6, PSMA6, PSMA5, PSMC2, PSMA4, PSMD1*
GO:0051351	Positive regulation of ligase activity	9	1.12×10^{-4}	*CDK1, PSMB7, PSMD14, PSMB6, PSMA6, PSMA5, PSMC2, PSMA4, PSMD1*
GO:0051438	Regulation of ubiquitin-protein ligase activity	9	1.80×10^{-4}	*CDK1, PSMB7, PSMD14, PSMB6, PSMA6, PSMA5, PSMC2, PSMA4, PSMD1*
GO:0051436	Negative regulation of ubiquitin-protein ligase activity during mitotic cell cycle	8	3.37×10^{-4}	*PSMB7, PSMD14, PSMB6, PSMA6, PSMA5, PSMC2, PSMA4, PSMD1*

B, Downregulated genes

Term	Function	Count	P-value	Gene symbol
GO:0043067	Regulation of programmed cell death	22	3.47×10^{-6}	*IFIH1, PTGS2, MCL1, PREX1, TGFBR1, BCL2A1, STK17B, IFI16, NLRP3, NLRP1, TNFRSF9, CASP4, DUSP1, BTG2, IGF2R, BNIP3L, CHST11, CASP8, LRRK2, MX1, IFI6, KALRN*

Table III. Continued.

B, Downregulated genes

Term	Function	Count	P-value	Gene symbol
GO:0010942	Positive regulation of cell death	16	3.57×10^{-6}	*PTGS2, PREX1, TGFBR1, STK17B, RRAGA, IFI16, NLRP3, NLRP1, TNFRSF9, CASP4, DUSP1, CASP8, BNIP3L, MX1, LRRK2, KALRN*
GO:0042981	Regulation of apoptosis	21	1.10×10^{-5}	*IFIH1, PTGS2, MCL1, PREX1, TGFBR1, BCL2A1, STK17B, IFI16, NLRP3, NLRP1, TNFRSF9, CASP4, DUSP1, BTG2, IGF2R, BNIP3L, CHST11, CASP8, MX1, IFI6, KALRN*
GO:0043068	Positive regulation of programmed cell death	15	1.61×10^{-5}	*PTGS2, PREX1, TGFBR1, STK17B, IFI16, NLRP3, NLRP1, TNFRSF9, CASP4, DUSP1, CASP8, BNIP3L, MX1, LRRK2, KALRN*
GO:0043065	Positive regulation of apoptosis	14	6.62×10^{-5}	*PTGS2, TGFBR1, PREX1, STK17B, IFI16, NLRP3, NLRP1, TNFRSF9, CASP4, DUSP1, CASP8, BNIP3L, MX1, KALRN*
GO:0012502	Induction of programmed cell death	12	8.32×10^{-5}	*TNFRSF9, CASP4, PREX1, TGFBR1, BNIP3L, CASP8, STK17B, IFI16, MX1, NLRP3, NLRP1, KALRN*
GO:0031401	Positive regulation of protein modification process	7	5.07×10^{-3}	*OSM, CCND3, TGFBR1, CD4, RICTOR, UBE2D1, LRRK2*
GO:0010562	Positive regulation of phosphorus metabolic process	5	1.02×10^{-2}	*OSM, CCND3, TGFBR1, CD4, RICTOR*
GO:0045937	Positive regulation of phosphate metabolic process	5	1.02×10^{-2}	*OSM, CCND3, TGFBR1, CD4, RICTOR*
GO:0019048	Virus-host interaction	3	1.22×10^{-2}	*IRF7, RRAGA, CD4*

Table IV. Enriched pathways for the upregulated and the downregulated genes in Gram-negative samples.

A, Upregulated genes

Term	Function	Count	P-value	Gene symbol
hsa05012	Parkinson's disease	19	9.00×10^{-9}	*UQCRC2, NDUFA8, SLC25A5, NDUFA4L2, NDUFB8, SLC25A6, NDUFA6, COX7B, NDUFA7, CYCS, NDUFC2, NDUFB2, NDUFS6, UQCR10, NDUFS5, NDUFS4, UQCRH, ATP5A1, UQCRB*
hsa05016	Huntington's disease	21	7.73×10^{-8}	*UQCRC2, NDUFA8, SLC25A5, NDUFA4L2, NDUFB8, POLR2K, SLC25A6, NDUFA6, CYCS, COX7B, NDUFA7, NDUFC2, SOD1, NDUFB2, NDUFS6, UQCR10, NDUFS5, NDUFS4, UQCRH, ATP5A1, UQCRB*
hsa00190	Oxidative phosphorylation	17	4.25×10^{-7}	*UQCRC2, NDUFA8, NDUFA4L2, NDUFB8, NDUFA6, COX7B, NDUFA7, NDUFC2, NDUFB2, NDUFS6, UQCR10, NDUFS5, NDUFS4, UQCRH, ATP5A1, ATP5I, UQCRB*
hsa05010	Alzheimer's disease	18	1.96×10^{-6}	*UQCRC2, NDUFA8, NDUFA4L2, NDUFB8, NDUFA6, COX7B, NDUFA7, CYCS, NDUFC2, NAE1, NDUFB2, NDUFS6, UQCR10, NDUFS5, NDUFS4, UQCRH, ATP5A1, UQCRB*
hsa03050	Proteasome	9	3.61×10^{-5}	*PSMB7, PSMD14, PSMB6, PSMA6, PSMA5, PSMC2, PSMA4, SHFM1, PSMD1*
hsa03010	Ribosome	10	6.12×10^{-4}	*RPL19, RPL22, RPL15, RPL27, RPS27L, RPL11, RSL24D1, RPL22L1, RPS23, RPS7*
hsa00620	Pyruvate metabolism	6	4.60×10^{-3}	*LDHA, ACYP1, GLO1, ACAT2, PCK1, MDH1*
hsa04260	Cardiac muscle contraction	7	2.05×10^{-2}	*UQCRC2, UQCR10, UQCRH, COX7B, ATP1A2, TNNI3, UQCRB*
hsa04110	Cell cycle	9	2.21×10^{-2}	*CDK1, YWHAG, CDKN2C, YWHAQ, TFDP2, PCNA, CDK6, GADD45A, SMC3*
hsa04115	p53 signaling pathway	6	3.94×10^{-2}	*CDK1, CYCS, CDK6, PERP, IGFBP3, GADD45A*

B, Downregulated genes

Term	Function	Count	P-value	Gene symbol
hsa04622	RIG-I-like receptor signaling pathway	5	5.32×10^{-3}	*IFIH1, ISG15, IRF7, CASP8, IFNA8*
hsa04612	Antigen processing and presentation	5	9.21×10^{-3}	HSPA6, CD4, IFNA8, CTSS, HLA-F
hsa04620	Toll-like receptor signaling pathway	4	1.99×10^{-2}	*IRF7, CASP8, IFNA8, CD14*
hsa04660	T cell receptor signaling pathway	4	2.33×10^{-2}	*PTPN6, RAF1, CD4, MAP3K14*

Table V. Enriched pathways for the upregulated and the downregulated genes in Gram-positive samples.

A, Upregulated genes

Term	Function	Count	P-value	Gene symbol
hsa05012	Parkinson's disease	10	3.37×10^{-5}	*NDUFA4*, *NDUFS6*, *NDUFS5*, *NDUFS4*, *NDUFA8*, *SLC25A5*, *NDUFA9*, *NDUFC2*, *ATP5C1*, *ATP5A1*
hsa05016	Huntington's disease	11	9.07×10^{-5}	*NDUFA4*, *NDUFS6*, *NDUFS5*, *NDUFS4*, *NDUFA8*, *SLC25A5*, *NDUFA9*, *NDUFC2*, *ATP5C1*, *ATP5A1*, *SOD1*
hsa00190	Oxidative phosphorylation	9	2.43×10^{-4}	*NDUFA4*, *NDUFS6*, *NDUFS5*, *NDUFS4*, *NDUFA8*, *NDUFA9*, *NDUFC2*, *ATP5C1*, *ATP5A1*
hsa05010	Alzheimer's disease	9	1.11×10^{-3}	*NDUFA4*, *NDUFS6*, *NDUFS5*, *NDUFS4*, *NDUFA8*, *NDUFA9*, *NDUFC2*, *ATP5C1*, *ATP5A1*
hsa03010	Ribosome	5	2.58×10^{-2}	*RPL22*, *RPL10*, *RPS27L*, *RPL11*, *RSL24D1*
hsa04612	Antigen processing and presentation	4	9.23×10^{-2}	*HSP90AA1*, *IFI30*, *HSPA4*, *CANX*
hsa00970:	Aminoacyl-tRNA biosynthesis	3	9.85×10^{-2}	NARS2, HARS, GARS

B, Downregulated genes

Term	Function	Count	P-value	Gene symbol
hsa04650	Natural killer cell mediated cytotoxicity	6	9.37×10^{-3}	*PTPN6*, *ICAM2*, *RAF1*, *IFNA8*, *NFATC2*, *KLRD1*
hsa04621	NOD-like receptor signaling pathway	4	2.25×10^{-2}	*IL8*, *CASP8*, *NLRP3*, *NLRP1*
hsa04660	T cell receptor signaling pathway	4	2.91×10^{-2}	*PTPN6*, *RAF1*, *NFATC2*, *MAP3K14*

Table VI. Top 10 significant differential functions between Gram-negative samples and Gram-positive samples.

GO ID	Term	Euclidean distance	P-value	Gene symbols
GO:0006120	Mitochondrial electron transport, NADH to ubiquinone	1.156277	$<1.00\times10^{-8}$	*NDUFB8, NDUFB2, NDUFA6, NDUFA7, NDUFA9, NDUFA4*
GO:0042773	ATP synthesis coupled electron transport	1.156277	$<1.00\times10^{-8}$	*UQCRH, NDUFB8, NDUFB2, UQCRB, NDUFA6, NDUFA7, UQCR10, NDUFA9, NDUFA4*
GO:0022904	Respiratory electron transport chain	1.156277	$<1.00\times10^{-8}$	*UQCRH, NDUFB8, NDUFB2, UQCRB, NDUFA6, NDUFA7, UQCR10, NDUFA9, NDUFA4*
GO:0045333	Cellular respiration	1.156277	$<1.00\times10^{-8}$	*UQCRH, NDUFB8, NDUFB2, UQCRC2, UQCRB, NDUFA6, NDUFA7, UQCR10, CYCS, NDUFA9, NDUFA4*
GO:0016310	Phosphorylation	1.413364	1.00×10^{-3}	*UQCRH, PAK4, FGFR1, NDUFB8, NDUFB2, CDK1, CDK6, UQCRC2, GHR, IGFBP3, UQCRB, NDUFA6, NDUFA7, UQCR10, MET, ATP5I, MVD, NDUFA9, LATS2, MAST4, NDUFA4, IKBKE, ATP5C1*
GO:0042981	Regulation of apoptosis	1.508092	2.70×10^{-3}	*IFI16, TNFRSF9, IFIH1, MX1, BTG2, CHST11, TGFBR1, BCL2A1, IFI6, LGALS1, PRDX1, PHLDA1, HSPD1, SORT1, MAL, DHCR24, GLO1, ITGB3BP, CDK1, GHR, SERPINB2, NQO1, ANXA1, IGFBP3, SMO, CADM1, CD44, KRT18, CYCS, NAE1, PERP, DLG5, EI24, PRKDC, NOTCH1, SERINC3, FGD3, PIM2, SSTR3*
GO:0043067	Regulation of programmed cell death	1.517301	3.60×10^{-3}	*IFI16, TNFRSF9, IFIH1, MX1, BTG2, CHST11, LRRK2, TGFBR1, BCL2A1, IFI6, LGALS1, PRDX1, PHLDA1, HSPD1, SORT1, MAL, DHCR24, GLO1, ITGB3BP, CDK1, GHR, SERPINB2, NQO1, ANXA1, IGFBP3, SMO, CADM1, CD44, KRT18, CYCS, NAE1, PERP, DLG5, EI24, PRKDC, NOTCH1, SERINC3, FGD3, PIM2, SSTR3*
GO:0000082	G1/S transition of mitotic cell cycle	0.554799	1.50×10^{-2}	*LATS2*
GO:0044267	Cellular protein metabolic process	2.267426	2.37×10^{-2}	*RPS23, IARS2, HSPD1, PAK4, FGFR1, SEC11A, HEXB, FKBP5, PSMA4, MRPL3, RPL27, PSMC2, SIL1, SUPT3H, RPL27, RPS7, RPL19, FKBP4, LMAN1, PTPN1, CDK1, CDK6, GHR, RPL22L1, PDIA5, CCT7, FBXO7, ANXA1, IGFBP3, PSMA6, PSMD1, CCT3, HERC3, TTC9, MET, NAE1, PSMD14, HBS1L, RABGGTB, EEF1B2, RPL15, RUVBL2, AIMP1, LATS2, MAST4, EEFSEC, LOXL1, NARS2, HARS, B3GNT1, MRPL36, IKBKE, EIF2S2, DSP, RPL10, GARS*
GO:0007517	Muscle organ development	1.050407	4.15×10^{-2}	*FAM65B, LAMA2, ANKRD2, FOXP1, CACNB4*

GO, gene ontology.

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