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ORIGINAL ARTICLE

Unveiling differentially expressed genes upon regulation of transcription factors in sepsis

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Abstract In this study, we integrated the gene expression data of sepsis to reveal more precise genome-wide expression signature to shed light on the pathological mechanism of sepsis. Differentially expressed genes via integrating five microarray datasets from the Gene Expression Omnibus database were obtained. The gene function and involved pathways of differentially expressed genes (DEGs) were detected by GeneCodis3. Transcription factors (TFs) targeting top 20 dysregulated DEGs (including up- and downregulated genes) were found based on the TRANSFAC. A total of 1339 DEGs were detected including 788 upregulated and 551 downregulated genes. These genes were mostly involved in DNA-dependent transcription regulation, blood coagulation, and innate immune response, pathogenic escherichia coli infection, epithelial cell signaling in helicobacter pylori infection, and chemokine signaling pathway. TFs bioinformatic analysis of 20 DEGs generated 374 pairs of TF-target gene involving 47 TFs. At last, we found that five top ten upregulated DEGs (S100A8, S100A9, S100A12, PGLYRP1 and MMP9) and three downregulated DEGs (ZNF84, CYB561A3 and BST1) were under the regulation of three hub TFs of Pax-4, POU2F1, and Nkx2–5. The identified eight DEGs may be regarded as the diagnosis marker and drug target for sepsis.

Keywords Sepsis · Differentially expressed gene · Transcription factor · Pathological mechanism

Introduction

Sepsis is a complex clinical syndrome induced by the interaction between the host and pathogens products, such as endotoxin and the host immune system (Brunkhorst and Reinhart 2009). Sepsis leads to various organ dysfunctions including acute renal, liver injury, and acute respiratory distress syndrome which is the main cause of increased mortality in patients (de Montmollin and Annane 2011). Although great process is performed in various researches, the pathological mechanism of sepsis remains unclear. Additionally, the incidence and mortality of sepsis are still high (Angus et al. 2001; Annane et al. 2003). Thus, discovery of important mediators involved in the process of sepsis is urgently needed.

Microarray strategies (Calvano et al. 2005) seem to be a powerful option for finding crucial mediators involving in disease of humans. Based on the superiority of large sample and reliable result, integration analysis of multiple microarrays may be useful to provide evidence for understanding the mechanism of sepsis. Additionally, the TFs and its target genes have been the study focus of system biology. The regulatory network between TFs and target genes is valuable in the field of biomedicine. Several TFs such as NF-κB, AP1, p53, PPAR, CREB, STAT, and E2F were closely related to some important diseases

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(inflammation and cancer) (Hoesel and Schmid 2013; Kesh et al. 2015; Lopez-Bergami et al. 2010; Mullen and Gonzalez-Perez 2016; Pal et al. 2014; Ramana et al. 2010; Wang and DuBois 2010). This may provide the drug target for different diseases.

In this study, we conducted an integrated analysis of sepsis microarray data, and identified differentially expressed genes (DEGs) between sepsis and normal control samples. Moreover, we also obtained significantly enriched functions of these DEGs to reveal the biological processes and signaling pathways associated with sepsis. Finally, some transcription factors (TFs) that targeted top 20 DEGs were found. We hope that this integrated analysis may provide additional understanding of sepsis that was helpful to explore novel diagnostic marker of sepsis and drug targets for future therapeutic tests.

Materials and methods

Microarray data

In this study, we searched datasets from the GEO (http://www.ncbi.nlm.nih.gov/geo/) database with the keywords "sepsis" [MeSH Terms] or sepsis [All Fields] and "Homo sapiens" [porgn] AND "gse" [Filter]. The study type was described as "expression profiling by array." All selected datasets were genome-wide expression sequencing data in blood of sepsis group and/or normal group (no drug stimulation or being transfected treatment) samples. And these datasets were standardized and original, and were downloaded by R (3.2.1) GEO query. Finally, there were five datasets obtained in this study.

Detection of DEGs and meta-analysis

Limmapackage (3.2.1) (Diboun et al. 2006) and Meta-MA package were used to identify the DEGs between sepsis and normal group. Limma is used to calculate the *P* value and FDR value of one gene in one dataset. The metaMA is applied to combine the *P* values of one gene in different datasets by inverse normal method. The gene with FDR < 0.05 was deemed to indicate a DEG.

Functional and biological pathway analysis of DEGs

In order to investigate the functional changes of DEGs, the gene function annotation analysis tool GeneCodis3 (http://genecodis.cnb.csic.es/analysis/) (Tabas-Madrid et al. 2012) was used to find the biological meaning of groups of genes, including gene ontology (GO) categories (Young et al. 2010) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation (Kanehisa and Goto 2000).

Analysis of potential TFs to target DEGs

TFs play an important role in regulating gene expression. We downloaded the TFs in the human genome and the motifs of genomic binding sites from the TRANSFAC (Wingender 2008). Moreover, the 2 KB sequence in the upstream promoter region of DEGs was downloaded from UCSC (http://www.genome.ucsc.edu/cgi-bin/hgTables). Target TFs were subsequently obtained by the method of minimize false-positive matches. Finally, the transcriptional regulatory network was visualized by cytoscape software (Smoot et al. 2011).

Results

Identification of DEGs in sepsis

We downloaded five gene expression datasets of sepsis from microarray experiments. GEO IDs were GSE69528, GSE67652, GSE57065, GSE26378, and GSE26440. In summary, there were 293 sepsis samples and 118 normal samples, respectively. The characteristics of these five datasets are provided in Table 1. Based on the integrated analysis of five microarray datasets, 8332 genes were identified. A total of 1339 DEGs were screened under the statistical significance threshold of FDR < 0.05. Among which, there were 788 upregulated and 551 downregulated DEGs. The heat map of top 100 DEGs is shown in Fig. 1. And the heat map of sample clustering is shown in supplementary Fig. 1. The top ten upregulated or downregulated DEGs between sepsis and normal sample are shown in Table 2.

GO enrichment and KEGG signaling pathway analysis of DEGs

Among 1339 DEGs, a total of 1243 DEGs were recognized in GO and KEGG signaling pathway enrichment analysis. GO enrichment analysis showed that these DEGs were significantly enriched in the apoptotic process (GO: 0006915, FDR = 4.78E−14), mitotic cell cycle (GO: 0000278, FDR = 4.44E−09), regulation of transcription depending on DNA (GO: 0006355, FDR = 4.51E−09), blood coagulation (GO: 0007596, FDR = 3.80E−07), innate immune response (GO: 0045087, FDR = 6.18E−07) and so on under the biological process category. The top fifteen significantly enriched GO functions of DEGs are listed in Table 3. Furthermore, KEGG pathway enrichment analysis indicated that these DEGs were significantly involved in huntington's disease (FDR = 9.50E−09), alzheimer's disease (FDR = 1.01E−08), pathogenic escherichia coli infection (FDR = 1.61E−07), phagosome

Table 1 Characteristics of the five microarray datasets for integrated analysis

GEO ID	Platform	Gene number	Sample count (N:P)	Notes
GSE69528	GPL10558Illumina humanht-12 V4.0 expression beadchip	18939	101 (28:73)	Cazalis et al. (2014)
GSE67652	GPL16699Agilent-039494 sureprint G3 human GE v2 8 × 60 K microarray 039381 (feature number version)	62976	24 (12:12)	Pellegrina et al. (2015)
GSE57065	GPL570[HG-U133_Plus_2] affymetrix human genome U133 plus 2.0 array	54675	53 (25:28)	Speake et al. (2015)
GSE26378	GPL570[HG-U133_Plus_2] affymetrix human genome U133 plus 2.0 array	54675	103 (21:82)	Standage and Wong (2011)
GSE26440	GPL570[HG-U133_Plus_2] affymetrix human genome U133 plus 2.0 array	54675	130 (32:98)	Standage and Wong (2011)

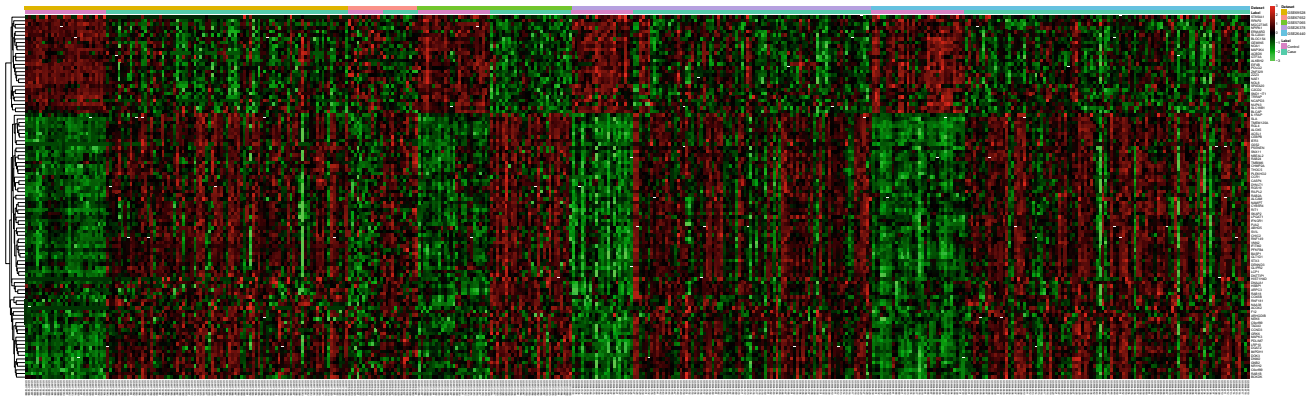

Fig. 1 Heat map of top 100 DEGs that were significantly upregulated or downregulated (P value < 0.05) in sepsis compared to relatively healthy controls

Table 2 Top 20 upregulated or downregulated DEGs between sepsis and normal controls

ID	Symbol	Combined.ES	P value	FDR	Regulation
6283	S100A12	3.77042	0.00000	0.00000	Up
6280	S100A9	3.02895	0.00000	0.00000	Up
8291	DYSF	2.66283	0.00000	0.00000	Up
6279	S100A8	2.62050	0.00000	0.00000	Up
266747	RGL4	2.52765	0.00000	0.00000	Up
683	BST1	2.52574	0.00000	0.00000	Up
8993	PGLYRP1	2.50512	0.00000	0.00000	Up
4318	MMP9	2.49083	0.00000	0.00000	Up
7295	TXN	2.35942	0.00000	0.00000	Up
116844	LRG1	2.28872	0.00000	0.00000	Up
221061	FAM171A1	−2.00105	0.00000	0.00000	Down
25875	LETMD1	−1.90124	0.00000	0.00000	Down
79673	ZNF329	−1.86837	0.00000	0.00000	Down
7637	ZNF84	−1.81614	0.00000	0.00000	Down
10194	TSHZ1	−1.77981	0.00000	0.00000	Down
220002	CYB561A3	−1.77349	0.00000	0.00000	Down
56916	SMARCAD1	−1.73668	0.00000	0.00000	Down
4216	MAP3K4	−1.70413	0.00000	0.00000	Down
25894	PLEKHG4	−1.66204	0.00000	0.00000	Down
55114	ARHGAP17	−1.63496	0.00000	0.00000	Down

Table 3 Enriched top 15 GO terms of DEGs between sepsis and normal samples

GO ID	GO term	No. of genes	FDR
Biological process			
GO:0006915	Apoptotic process	69	4.78E−14
GO:0042981	Regulation of apoptotic process	33	8.32E−10
GO:0015031	Protein transport	47	4.41E−09
GO:0000278	Mitotic cell cycle	39	4.44E−09
GO:0006355	Regulation of transcription, DNA-dependent	114	4.51E−09
GO:0016192	Vesicle-mediated transport	30	6.59E−09
GO:0007049	Cell cycle	47	1.16E−08
GO:0000084	S phase of mitotic cell cycle	21	1.71E−07
GO:0022904	Respiratory electron transport chain	18	3.59E−07
GO:0006281	DNA repair	34	3.59E−07
GO:0007596	Blood coagulation	45	3.80E−07
GO:0045087	Innate immune response	35	6.18E−07
GO:0006916	Anti-apoptosis	27	8.42E−07
GO:0051301	Cell division	33	9.31E−07
GO:0000075	Cell cycle checkpoint	21	1.73E−06
Molecular function			
GO:0005515	Protein binding	432	3.42E−86
GO:0000166	Nucleotide binding	176	1.69E−22
GO:0046872	Metal ion binding	207	2.45E−19
GO:0005524	ATP binding	123	3.84E−15
GO:0008270	Zinc ion binding	141	5.10E−13
GO:0003677	DNA binding	128	2.45E−11
GO:0016740	Transferase activity	62	8.39E−11
GO:0016787	Hydrolase activity	77	1.87E−08
GO:0003676	Nucleic acid binding	62	3.63E−06
GO:0004672	Protein kinase activity	30	1.18E−05
GO:0047485	Protein N-terminus binding	15	1.57E−05
GO:0003723	RNA binding	50	1.58E−05
GO:0042802	Identical protein binding	30	4.38E−05
GO:0004197	Cysteine-type endopeptidase activity	12	5.98E−05
GO:0016301	Kinase activity	25	6.31E−05
Cellular component			
GO:0005634	Nucleus	460	2.15E−73
GO:0005737	Cytoplasm	450	3.48E−72
GO:0005829	Cytosol	231	1.19E−49
GO:0005739	Mitochondrion	141	2.64E−26
GO:0016020	Membrane	278	2.14E−24
GO:0005730	Nucleolus	139	1.82E−23
GO:0005654	Nucleoplasm	102	6.78E−23
GO:0005783	Endoplasmic reticulum	85	2.65E−11
GO:0005886	Plasma membrane	209	1.03E−10
GO:0005794	Golgi apparatus	81	1.12E−10
GO:0005743	Mitochondrial inner membrane	37	9.65E−09
GO:0048471	Perinuclear region of cytoplasm	44	1.28E−08
GO:0005625	Soluble fraction	42	1.59E−08
GO:0005694	Chromosome	33	2.80E−08
GO:0005856	Cytoskeleton	66	1.99E−07

(FDR = 1.74E−07), epithelial cell signaling in helicobacter pylori infection (FDR = 3.57E−07), parkinson's disease (FDR = 9.47E−07), and chemokine signaling pathway (FDR = 1.75E−05). The top fifteen remarkably enriched KEGG signaling pathways of DEGs are presented in Table 4.

Establishment of TF-target genes regulatory network for sepsis

In order to disclose the TF-target genes′ regulatory network for sepsis, we utilized TRANSFAC to obtain TFs regulating top 20 upregulated or downregulated DEGs. Finally, we obtained transcriptional regulatory networks consisting of 374 pairs of TFs genes involving 47 TFs. In the network, the three most downstream genes covered by TFs were ZNF84, CYB561A3, and BST1. The three hub TFs were Pax-4 (degree = 13), POU2F1 (degree = 12), and Nkx2–5 (degree = 11) (Table 5). Among the top 20 upregulated or downregulated DEGs, five upregulated genes (S100A8, S100A9, S100A12, PGLYRP1, and MMP9) and three downregulated genes (ZNF84, CYB561A3, and BST1) were co-regulated by Pax-4, POU2F1, and Nkx2–5.

Discussion

Sepsis is associated with substantial morbidity and is a rapidly growing public health concern in older people. The understanding of molecular mechanisms underlying sepsis will lead to new therapies that improve survival. TF-target genes′ regulatory network may be available to investigate the underlying mechanisms and provide additional evidence for the therapeutic method of sepsis. In our study, based on the integrated analysis of five microarray datasets for sepsis, we identified 1339 DEGs including 788 upregulated and 551 downregulated DEGs. It is well known that inflammation is a fundamental component of sepsis pathogenesis and severe sepsis is associated with blood coagulation and immune system dysfunctions. In this

Table 4 Enriched top 15 KEGG pathways of DEGs between sepsis and normal samples

KEGG ID	KEGG term	Count	FDR	Genes
hsa00190	Oxidative phosphorylation	27	3.52E−11	ATP5J, NDUFA2, COX17, COX6A1, ATP6V1D, COX5A, ATP6V0A1, COX6B1, COX5B, NDUFB11, ATP5J2, ATP6V0E1, ATP6V1E1, SDHB, TCIRG1, NDUFA4, COX8A, NDUFA13, COX7A2, COX7B, NDUFA1, ATP6V1E2, ATP6V0B, UQCR11, UQCRQ, ATP6V0D1, ATP5B
hsa00240	Pyrimidine metabolism	20	8.20E−09	POLR2J, POLR2H, POLR1C, POLD2, POLR2L, NME4, AK3, TYMP, POLA1, NME7, NT5C2, POLD1, NME6, PRIM1, POLR3A, NME1, NT5E, CDA, NT5M, POLR3F
hsa04380	Osteoclast differentiation	23	8.54E−09	TYROBP, MAPK3, MAPK13, IKBKG, SIRPA, NFKBIA, TNFRSF1A, SIRPB1, LILRB3, SYK, CYBA, FCGR2A, IFNGR1, LILRA2, SPI1, NCF4, LILRB2, NCF2, IFNAR2, JUNB, PIK3CG, LILRA6, PPARG
hsa05016	Huntington's disease	28	9.50E−09	POLR2J, ATP5J, POLR2H, NDUFA2, AP2S1, COX6A1, POLR2L, COX5A, COX6B1, COX5B, NDUFB11, CASP9, SDHB, NDUFA4, COX8A, CLTCL1, SOD2, NDUFA13, COX7A2, HIP1, COX7B, NDUFA1, DNAL4, UQCR11, PPARG, UQCRQ, TBPL1, ATP5B
hsa05010	Alzheimer's disease	26	1.01E−08	ATP5J, MAPK3, NDUFA2, COX6A1, TNFRSF1A, FAS, COX5A, COX6B1, COX5B, PSENEN, NDUFB11, CASP9, PPP3R1, NAE1, SDHB, NDUFA4, COX8A, GRIN2A, NDUFA13, COX7A2, COX7B, NDUFA1, UQCR11, UQCRQ, ATP5B, PSEN1
hsa05130	Pathogenic Escherichia coli infection	14	1.61E−07	CDC42, ARPC2, ARPC4, ABL1, YWHAZ, YWHAQ, RHOA, LY96, TUBA1B, CD14, ARPC3, TUBA1C, TUBA1A, TUBA4A
hsa04145	Phagosome	22	1.74E−07	CTSS, TLR2, ATP6V1D, ATP6V0A1, PIK3C3, ATP6V0E1, ATP6V1E1, CYBA, FCGR2A, TCIRG1, TUBA1B, CD14, RAB5A, NCF4, NCF2, ATP6V1E2, ATP6V0B, VAMP3, ATP6V0D1, TUBA1C, TUBA1A, TUBA4A
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	15	3.57E−07	CDC42, MAPK13, IKBKG, NFKBIA, ATP6V1D, ATP6V0A1, CXCL1, ATP6V0E1, ATP6V1E1, CXCR1, LYN, TCIRG1, ATP6V1E2, ATP6V0B, ATP6V0D1
hsa04666	Fc gamma R-mediated phagocytosis	17	7.49E−07	CDC42, ARPC2, VAV1, MAPK3, ARPC4, PRKCD, RAC2, DNM2, SYK, GSN, FCGR2A, LYN, PTPRC, ARPC3, PIK3CG, HCK, LIMK2
hsa05012	Parkinson's disease	20	9.47E−07	ATP5J, NDUFA2, COX6A1, COX5A, COX6B1, COX5B, NDUFB11, CASP9, SDHB, NDUFA4, COX8A, NDUFA13, COX7A2, COX7B, NDUFA1, HTRA2, UQCR11, PINK1, UQCRQ, ATP5B
hsa05152	Tuberculosis	23	1.48E−06	MAPK3, CTSS, MAPK13, ITGAX, TLR2, NFYA, IL10RB, TNFRSF1A, ATP6V0A1, RHOA, SYK, PIK3C3, CASP9, RFXANK, PPP3R1, FCGR2A, TCIRG1, IFNGR1, CD14, RAB5A, ATP6V0B, CEBPB, ATP6V0D1
hsa00230	Purine metabolism	21	5.46E−06	POLR2J, POLR2H, POLR1C, POLD2, AK1, POLR2L, NME4, IMPDH1, POLA1, NME7, NT5C2, POLD1, NME6, PFAS, PRIM1, POLR3A, AMPD3, NME1, NT5E, NT5M, POLR3F
hsa04110	Cell cycle	18	8.22E−06	MDM2, ABL1, YWHAZ, FZR1, PTTG1, CDC7, YWHAQ, ANAPC4, ORC2, SKP1, CDC16, CDKN2D, ANAPC11, ZBTB17, RBL1, CCND3, MAD1L1, E2F4
hsa04621	NOD-like receptor signaling pathway	12	1.16E−05	TAB3, MAPK3, CASP5, MAPK13, IKBKG, BIRC2, CASP1, NFKBIA, CXCL1, BIRC3, PYCARD, PSTPIP1
hsa04062	Chemokine signaling pathway	22	1.75E−05	CDC42, VAV1, MAPK3, IKBKG, PTK2B, PRKCD, GRK6, RAC2, NFKBIA, GNB4, CXCL1, RHOA, ARRB2, GNG10, CXCR1, LYN, CCR1, GNB2, PIK3CG, HCK, FGR, CCR6

study, these DEGs were significantly enriched in the GO term for biological processes especially in regulation of blood coagulation and innate immune response. Furthermore, the KEGG pathway of pathogenic escherichia coli infection was also significantly enriched. At last, we found that five top ten upregulated DEGs (S100A8, S100A9, S100A12, PGLYRP1, and MMP9) and three downregulated DEGs (ZNF84, CYB561A3, and BST1) were under the regulation of the three hub TFs of Pax-4, POU2F1, and Nkx2–5. These eight DEGs played a significant role in sepsis.

As the family members of S100 proteins, S100A8, S100A9, and S100A12 have relationship with inflammatory diseases and aggravate inflammatory response (Roth

Table 5 Top eight TFs targeting more than five DEGs

Transcription factor	Count	Genes
Pax-4	13	ZNF84, ZNF329, SMARCAD1, S100A9, PLEKHG4, PGLYRP1, MAP3K4, LRG1, LETMD1, FAM171A1, CYB561A3, BST1, ARHGAP17
POU2F1	12	ZNF84, ZNF329, TXN, SMARCAD1, S100A8, S100A12, RGL4, PGLYRP1, DYSF, CYB561A3, BST1, ARHGAP17
Nkx2–5	11	ZNF84, ZNF329, SMARCAD1, RGL4, PGLYRP1, MMP9, MAP3K4, LETMD1, CYB561A3, BST1, ARHGAP17
AP-1	7	ZNF84, TXN, SMARCAD1, S100A8, RGL4, PLEKHG4, LRG1
HNF-1	7	ZNF329, SMARCAD1, S100A8, S100A12, PGLYRP1, LRG1, CYB561A3
COMP1	6	TSHZ1, PGLYRP1, DYSF, CYB561A3, BST1, ARHGAP17
HNF-4	6	ZNF84, S100A9, S100A8, S100A12, PLEKHG4, MMP9
Elk-1	5	ZNF84, SMARCAD1, RGL4, PLEKHG4, CYB561A3

et al. 2003). The heterodimer S100A8/A9, also known as calprotectin, is elevated in the circulation and has been severed as a potential diagnostic marker of sepsis (Terrin et al. 2011). S100A12 released from granulocytosis is overexpressed and can activate human monocytes via toll-like receptor 4 during clinical and experimental sepsis (Foell et al. 2013). In this study, S100A8, S100A9, and S100A12 were upregulated in sepsis, which were in accordance with the previous reports.

PGLYRP1 (also called PGRP-S) is said to be participated in neutrophil production of reactive oxygen species, as well as regulation of immune responses in vivo (Dziarski et al. 2003; Park et al. 2013). It is strongly expressed in bone marrow and polymorphonuclear leukocytes and has direct antibacterial effect in vitro (Kang et al. 1998; Liu et al. 2000, 2001; Tydell et al. 2002). In our study, we found PGLYRP1 was upregulated, which may result in dysfunction of immune response in sepsis.

MMP9 is a multi-domain zinc metalloproteinase released by inflammatory cells. MMP9 regulates the activity of numerous cytokines that are critical to inflammation (Galliera et al. 2015; Vandooren et al. 2013). It is noted that MMP9 levels in plasma are elevated in patients with septic shock and severe sepsis, and it may cause severe sepsis (Nakamura et al. 1998). In this study, we found that MMP9 was upregulated in sepsis that was consistent with previous reports.

Zincfinger (ZNF) genes are the largest family of TFs in mammalian genomes. It is suggested that ZNF84 is upregulated in mature MII oocytes and human ES cells compared the gene expression profile of somatic tissues (Assou et al. 2009). However, very few researches about ZNF84 existed in sepsis. In this study, the expression of ZNF84 decreased, which may serve as a novel insight into the relationship between ZNF84 and sepsis.

In mammals, lysosome cytochrome b561 (CYB561A3) is expressed at the plasma membrane and intracellular sites (McKie et al. 2001). Lysosome iron pools play an important part in oxidative stress (Kurz et al. 2006), which involves CYB561A3-Fe^{3+}-reductase activity. It is pointed out that the expression of CYB561A3 is found in chronic lymphocytic leukemia (Yepes et al. 2015). In this study, we found that CYB561A3 was downregulated and may have a role of oxidative stress in sepsis.

Bone marrow stromal cell antigen-1 (BST1, also called CD157) is highly conserved and has been found in organisms of mammals. BST1 plays numerous roles in humoral immune response, neutrophil transmigration, and hematopoietic stem cell support (Ishihara and Hirano 2000). It is reported that BST1 is involved in inflammatory pathways of alzheimer's disease (Chang et al. 2015). Also, BST1 is expressed in epithelial ovarian carcinoma and its high expression is associated with variations in tumor cell morphology, decreased cell–cell interactions, motility, and mesothelial invasion (Morone et al. 2012). Herein, we found that the expression of BST1 was reduced and may be involved in sepsis via mediating immune response.

Depending on the results of TF-target genes regulation network, we identified 47 TFs in sepsis. In the network, top three TFs regulating the most downstream target genes were Pax-4, POU2F1, and Nkx2–5. Pax-4 belongs to the PAX family and contains the paired domain and homeodomain (Inoue et al. 1998; Walther et al. 1991), which are potential DNA-binding domains. POU family is a class of DNA-binding transcription factors that function in cell specification and developmental regulation (Phillips and Luisi 2000; Ryan and Rosenfeld 1997). POU2F1 is a member of the POU family that has been reported as being both a positive and negative regulator of transcription and can regulate transcription by interacting with other transcription factors (Mordvinov et al. 1999). The homeobox transcription factor Nkx2–5 is a critical regulator of cardiac gene expression and heart development (Komuro and

Izumo 1993; Lints et al. 1993). The regulation of these three TFs for above eight DEGs also played a part in the process of sepsis.

In a word, our integrated analysis found a number of DEGs in sepsis. Furthermore, the results of GO enrichment analysis and KEGG signal pathway analysis revealed that some biological functions or pathways may be closely linked to the development of sepsis. The constructed transcriptional regulatory network uncovered top three TFs (Pax-4, POU2F1, and Nkx2–5) regulating most downstream target genes including S100A8, S100A9, S100A12, PGLYRP1, MMP9 ZNF84, CYB561A3, and BST1. All these genes appeared to play vital roles in the development of disease and may therefore be potential diagnostic marker of sepsis and drug targets for the treatment of sepsis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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