Pathway analysis of sepsis-induced changes gene expression

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Abstract

Background: Sepsis reaction is a response to an infection composed of genetic elements. This research aims to better understand how sepsis affects the molecular pathways in whole blood samples.

Methods: Whole blood samples from healthy controls ($n = 18$), sepsis nonsurvivors ($n = 9$), and sepsis survivors ($n = 26$) were retrieved from the gene expression omnibus (GEO) collection of the national center for biotechnology information (NCBI) (accession number GSE54514). The NCBI's GEO2R program was used to determine differential expression, and the ingenuity pathway analysis (IPA) software was utilized to do a pathway analysis.

Results: In sepsis patients, 2672 genes were substantially differently expressed (*p* value 0.05). One thousand three hundred four genes were overexpressed, and one thousand three hundred sixty-eight were under-expressed. The inhibition of ARE-mediated mRNA degradation pathway and the PI3K/AKT signaling spliceosomal cycle were the most significant canonical pathways identified by ingenuity pathway analysis (IPA). The IPA upstream analysis predicted the ESR1, SIRT1, and PTPRR proteins, and the drugs filgrastim and fluticasone were top transcriptional regulators.

Conclusions: The inhibition of ARE-mediated mRNA degradation pathway and the PI3K/AKT signaling spliceosomal cycle were highlighted as essential pathways of inflammation by IPA, indicating widespread cancer owing to sepsis. Our data imply that sepsis considerably influences gene pathways in whole blood samples, pointing to possible targets for sepsis treatment.

Keywords: Gene expression, Sepsis, Ingenuity pathway analysis, Whole blood samples

Background

A dysregulated host response to infection causes sepsis, a life-threatening organ failure that affects over 19 million individuals yearly, killing ~ 11 million persons [1–4]. General management measures such as supportive care, source control, and antibiotics are still used to treat sepsis. Despite numerous clinical trials, there is no sepsis-specific drug beneficial in clinical practice [5]. A complete list of gene names and their abbreviations are delivered in the Additional file 1.

According to two consensus publications, the lack of tools to reliably diagnose sepsis at the molecular level and significant human heterogeneity in the sepsis syndrome are the main reasons for the persistent failure of proposed sepsis therapeutics [5, 6]. Clinical severity ratings are used to classify the risk of sepsis blood lactate levels, such as Acute Physiology, Age and Chronic Health Evaluation (APACHE) or Sequential Organ Failure Assessment (SOFA). These ratings estimate the overall severity of the illness, and they are incapable of quantifying the patient's response severity [7].

There are various advantages to having a molecular definition of the seriousness of the sepsis host response. The clinical outcomes can be improved by improving sepsis diagnosis accuracy by better matching resources with patients; more accurate diagnosis predictions

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would allow for more information about the efficiency of interventions and patient preferences. Clinical trials can be boosted by better molecular phenotyping of sepsis patients through enhancing medication, intervention, patient selection, and calculating observed-to-expected mortality ratios [5, 6, 8]. Since molecular biomarkers are a lineal quantitative indicator of the host response dysregulations, they may be used to help construct a quantitative diagnosis of sepsis versus non-septic critical illness [9, 10]. Overall, a quantitative sepsis test might be valuable for doctors if used as a fast assay.

This research aimed to figure out which molecular pathways are changed in sepsis. IPA (Ingenuity Pathway Analysis) is a web-based software program that identifies new targets within biological systems and is used to examine gene expression data from whole blood of sepsis patients versus healthy controls.

Methods
Data collection
In the present work, the investigated microarray dataset was obtained from (NCBI) the National Center for Biotechnology Information's (GEO) Gene expression Omnibus repository (accession number GSE54514). The dataset included gene expression data of whole blood samples collected for five days for healthy controls ($n = 18$), sepsis nonsurvivors ($n = 9$), and sepsis survivors ($n = 26$) [11]. Sepsis was described as the occurrence of at least two of four clinical criteria in addition to a proven bacterial infection. These clinical criteria are the change in white blood cell count, abnormally rapid breathing or if mechanical ventilation is required, abnormal rapid heart rate, and the presence of hypothermia or fever [11]. Whole blood samples collected from patients were preserved in PAXgene tubes, then RNA extraction was carried out in batches. Illumina Sentrix was used to profile gene expression for the extracted RNA.

The discovery of genes that are differently expressed
The NCBI's GEO2R software generated a list of 14,703 genes that were expressed differently between sepsis and non-sepsis blood samples. Microsoft Excel was used to sort and process the 14,703 genes. After applying stringent cutoff criteria, the list of differentially expressed genes was limited down to 2672 genes after applying stringent cutoff criteria (p value 0.05 and absolute fold change between -0.1 and 0.1).

Pathway analysis using IPA
The differentially expressed gene list was entered into IPA software (QIAGEN, Hilden, Germany), which employed the program's 'core analysis' feature to analyze the data regards upstream regulators and canonical pathways.

Results
DE genes (differently expressed genes) and upstream regulators by IPA
Figure 1 (A) Graphical summary and (B) Different shapes represent the molecular class of the protein. Inhibition and activation are shown by blue and orange, respectively. A solid line denotes a direct relationship, a dashed line denotes an indirect interaction, and a dotted line denotes machine-based learning inferred association. Multiple gene IDs in the dataset are represented by a single gene or molecule in the Global Molecular Network, indicated by an asterisk.

Figure 2 Upstream regulators: filgrastim and the estrogen receptor 1 (ESR1). (A) Chemical drug filgrastim is predicted to be activated in sepsis with p value $= 1.36 \times 10^{-7}$ and Z-score $= 4.170$. (ESR1 is predicted to be activated in sepsis with p value $= 1.55 \times 10^{-8}$ and Z-score $= 4.064$). Different forms represent the molecular class of the protein. Red and green show upregulation and down-regulation, respectively. Inhibition and activation are indicated by blue and orange, respectively, in predicted relationships. A solid line denotes a direct relationship, a dashed line denotes an indirect interaction, and a dotted line denotes machine-based learning inferred association.

Figure 3 Regulatory effect genes PTPRR and EPO are predicted during sepsis. Different forms represent the molecular class of the protein. Up-regulation and down-regulation are shown in red and green, respectively. Inhibition and activation are indicated by blue and orange, respectively. A solid line denotes a direct relationship, a dashed line denotes an indirect interaction, and a dotted line denotes machine-based learning inferred association.

Figure 4 Regulatory effect genes EIF4G2 and NFKB2 are predicted during sepsis. Different forms represent the molecular class of the protein. Up-regulation and down-regulation are shown in red and green, respectively. Inhibition and activation are indicated by blue and orange, respectively. A solid line denotes a direct relationship, a dashed line denotes an indirect interaction, and a dotted line denotes machine-based learning inferred association.

Upstream regulators
Results showed that (ESR1, SIRT1, and PTPRR) proteins, filgrastim and fluticasone drugs were among the top 20 regulators predicted by IPA (Table 1). Figure 2 depicts the data in Table 1 and emphasizes the major upstream regulators' anticipated activation state as reported by IPA. The ESR1 protein and medication filgrastim are the most active upstream regulator in sepsis. As shown in Fig. 2, *ESR1* is among the essential proteins in IPA's graphical summary results.
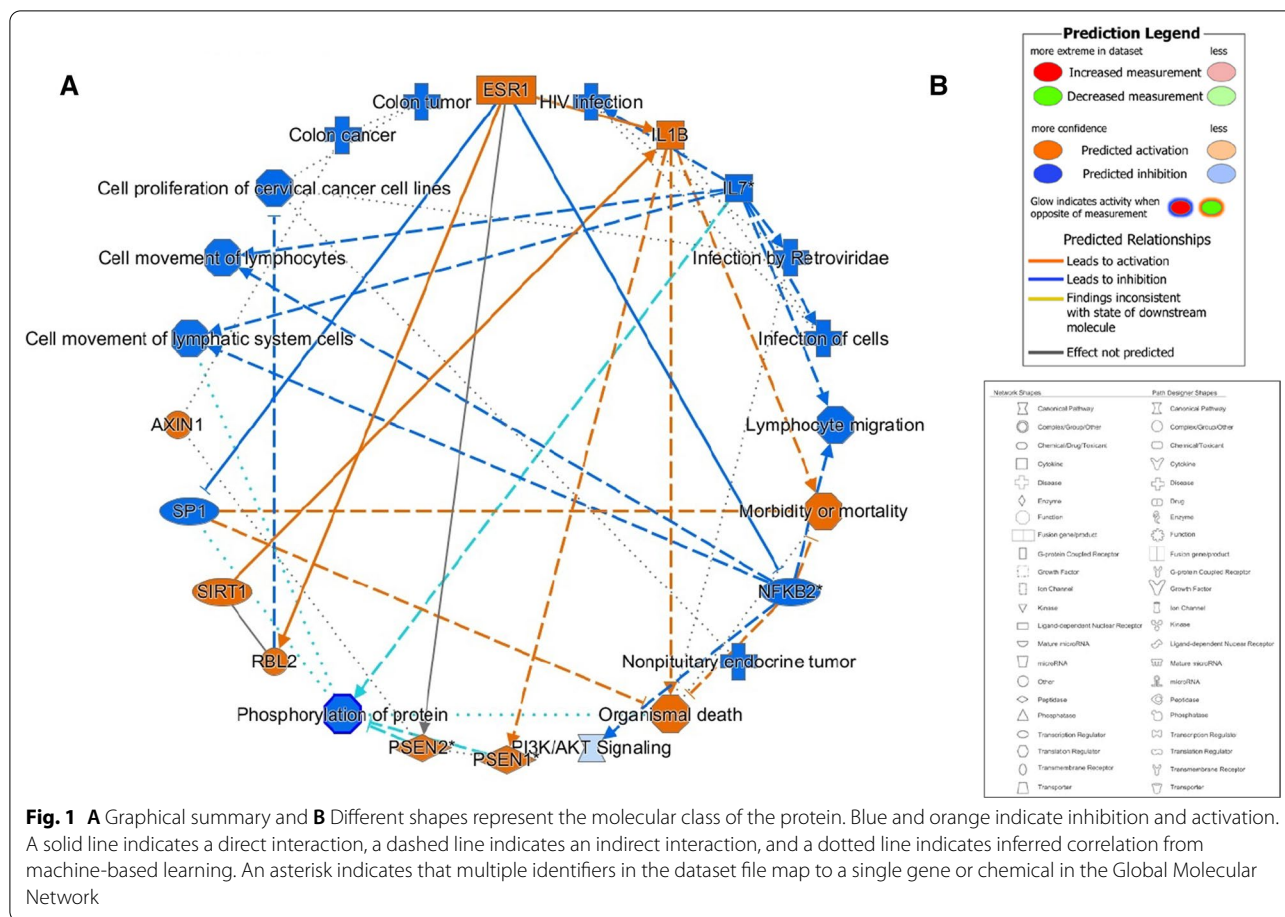
Fig. 1 **A** Graphical summary and **B** Different shapes represent the molecular class of the protein. Blue and orange indicate inhibition and activation. A solid line indicates a direct interaction, a dashed line indicates an indirect interaction, and a dotted line indicates inferred correlation from machine-based learning. An asterisk indicates that multiple identifiers in the dataset file map to a single gene or chemical in the Global Molecular Network

The most significant regulatory effects are networks *EIF4G2* and *NFKB2*. They are important regulatory underlying factors in sepsis pathogenesis identified by IPA. Figures 3, 4, and Table 4 show that the most significantly differentially expressed protein-coding genes during sepsis exposure were the *CLEC1B, PPBP, HBE1, SNX10*, and *H3P6* genes.

Biological pathways that have been enriched by IPA
The inhibition of ARE-Mediated mRNA Degradation Pathway and the Pl3K/AKT Signaling Spliceosomal Cycle were essential canonical pathways (Table 2).

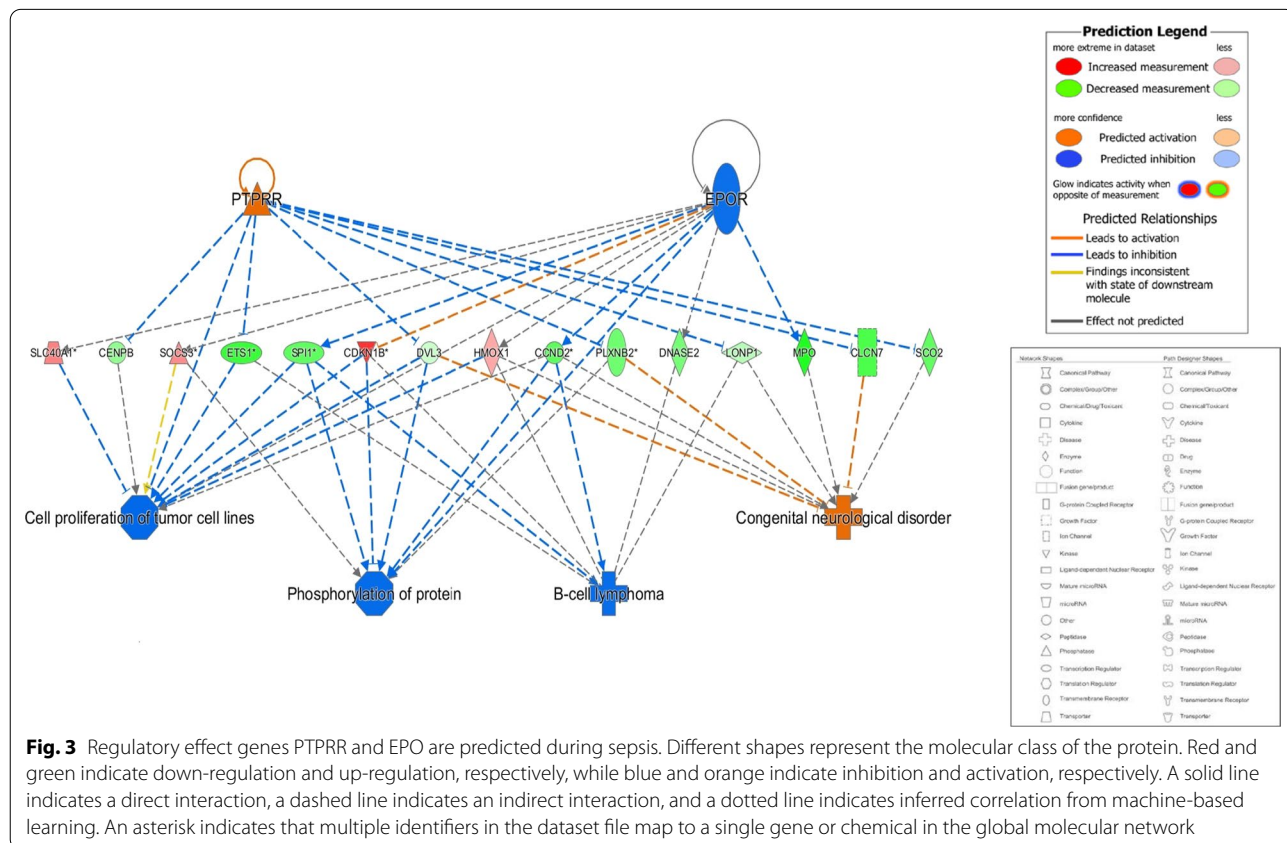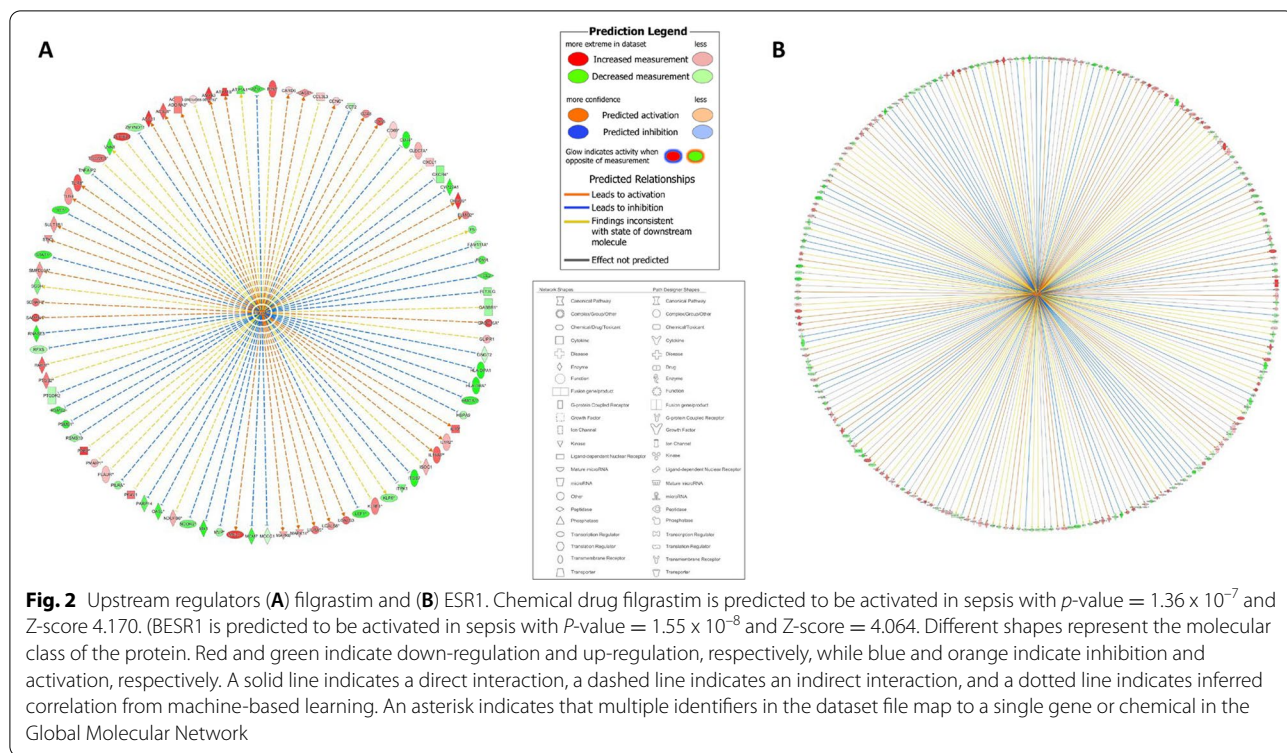### The relationship between sepsis and other illnesses
The differently expressed genes in sepsis are linked to cancer and organ harm, among other illnesses (Table 3).

Discussion
We applied the IPA tool to find important molecular pathways and regulatory networks in the context of septic disease. Consequently, we carried out upstream regulators analysis, revealing that estrogen receptor 1 (ESR1) and filgrastim drug are the most significant DE regulators during sepsis. *ESR1* gene was not revealed to be associated with sepsis before. Recent studies showed that the *ESR1* gene was associated with other diseases such as osteoporosis [12], coronary artery disease [13], Parkinson's disease [14], ovarian cancer [15], multiple myeloma [16], and finally, Alzheimer's disease [17].

Consequently, we carried out upstream regulators analysis that revealed the estrogen receptor 1 (*ESR1*) and filgrastim drug. Filgrastim (NEUPOGEN®) is a humanized granulocyte colony-stimulating factor used to treat and prevent neutropenia [18]. Filgrastim is the best agent for patients with severe sepsis/septic shock [19]. A recent report showed that Filgrastim is useful in postoperative patients at risk of sepsis. It results in improved production and function of neutrophils. It also appeared to counter the regulatory process of hyperactivation of pro-inflammatory processes [20]. Such inflammatory processes might agree with our results that filgrastim modulating many inflammatory genes, such as IL-10, is a crucial anti-inflammatory cytokine that was overexpressed during sepsis and was targeted by filgrastim as his upstream regulator discovered by IPA.
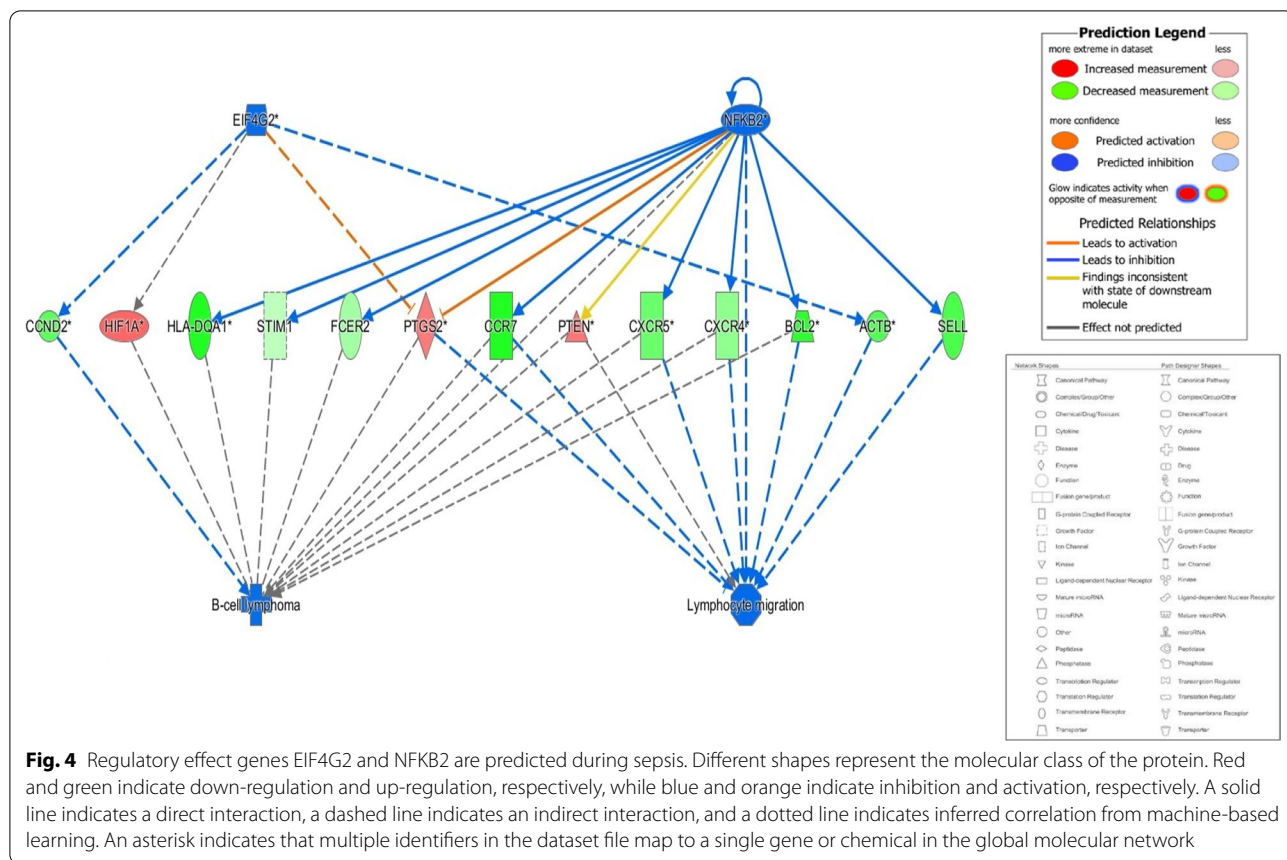
Fig. 2 Upstream regulators (**A**) filgrastim and (**B**) ESR1. Chemical drug filgrastim is predicted to be activated in sepsis with *p*-value $= 1.36 \times 10^{-7}$ and Z-score 4.170. (BESR1 is predicted to be activated in sepsis with *P*-value $= 1.55 \times 10^{-8}$ and Z-score $= 4.064$. Different shapes represent the molecular class of the protein. Red and green indicate down-regulation and up-regulation, respectively, while blue and orange indicate inhibition and activation, respectively. A solid line indicates a direct interaction, a dashed line indicates an indirect interaction, and a dotted line indicates inferred correlation from machine-based learning. An asterisk indicates that multiple identifiers in the dataset file map to a single gene or chemical in the Global Molecular Network

Fig. 3 Regulatory effect genes PTPRR and EPO are predicted during sepsis. Different shapes represent the molecular class of the protein. Red and green indicate down-regulation and up-regulation, respectively, while blue and orange indicate inhibition and activation, respectively. A solid line indicates a direct interaction, a dashed line indicates an indirect interaction, and a dotted line indicates inferred correlation from machine-based learning. An asterisk indicates that multiple identifiers in the dataset file map to a single gene or chemical in the global molecular network

Fig. 4 Regulatory effect genes EIF4G2 and NFKB2 are predicted during sepsis. Different shapes represent the molecular class of the protein. Red and green indicate down-regulation and up-regulation, respectively, while blue and orange indicate inhibition and activation, respectively. A solid line indicates a direct interaction, a dashed line indicates an indirect interaction, and a dotted line indicates inferred correlation from machine-based learning. An asterisk indicates that multiple identifiers in the dataset file map to a single gene or chemical in the global molecular network

Table 1 Ingenuity pathway analysis uncovered the top 20 upstream regulators

Upstream regulator	Molecule type	Log$_2$ ratio	*p*-value	Z score
Filgrastim	Biologic drug		1.36×10^{-7}	4.170
ESR1	Ligand-dependent nuclear receptor		1.55×10^{-8}	4.064
Fluticasone propionate	Chemical drug		2.65×10^{-4}	3.768
SIRT1	Transcription regulator	0.121	2.22×10^{-3}	3.666
PTPRR	Phosphatase	0.034	7.07×10^{-3}	3.561
Dexamethasone	Chemical drug		4.60×10^{-9}	3.SOl
5-fluorouracil	Chemical drug		3.13×10^{-9}	3.481
IL1B	Cytokine	0.237	1.77×10^{-2}	3.211
Fulvestrant	Chemical drug		3.47×10^{-4}	3.141
Levodopa	Chemical endogenous neurotransmitter		9.64×10^{-4}	3.030
JUNB	Transcription regulator	− 0.066	5.20×10^{-3}	3.023
Cdk	Group		3.50×10^{-5}	2.994
Phenylephrine	Chemical drug		1.00×10^{0}	2.804
CXCL12	Cytokine	0.000	4.02×10^{-2}	2.732
Cisplatin	Chemical drug		2.14×10^{-5}	2.686
NOS2	Enzyme		1.39×10^{-1}	2.661
EFNA2	Kinase	0.013	4.82×10^{-1}	2.646
TFE3	Transcription regulator	− 0.059	1.12×10^{-1}	2.621
Cerivastatin	Chemical drug		2.63×10^{-1}	2.620
TRAP1	Enzyme	− 0.101	6.68×10^{-4}	2.618

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Table 2 Ingenuity Pathway Analysis uncovered the top five canonical pathways

Pathway	*p* value
Inhibition of ARE-mediated mRNA degradation pathway	2.54×10^{-10}
PI3K/AKT signaling spliceosomal cycle	6.65×10^{-9}
TCA cycle 11 (Eukaryotic) B cell receptor signaling	1.40×10^{-8}
Inhibition of ARE-mediated mRNA degradation pathway	2.69×10^{-8}
PI3K/AKT signaling spliceosomal cycle	5.99×10^{-8}

Table 3 Ingenuity pathway analysis found the top five illnesses

Disease	Number of molecules	*p* value
Cancer	2479	9.13×10^{-8}–2.62×10^{-126}
Organismal injury and abnormalities	2504	9.13×10^{-8}–2.62×10^{-126}
Endocrine system disorders	1997	1.04×10^{-65}–$4.2\,1 \times 10^{-67}$
Gastrointestinal disease	2191	4.81×10^{-8}–1.61×10^{-65}
Infectious diseases	557	1.07×10^{-8}–4.05×10^{-45}

Table 4 The most differentially expressed protein-coding genes (most overexpressed)

Pathway	Expression-value
CLEC1B	0.814
PPBP	0.802
HBE1	0.799
SNX10	0.759
H3P6	0.750

IL-1RA increased in 10 patients in the previous study [20], was increased in our dataset, and targeted by filgrastim. Interestingly, some cytokines were associated with sepsis; IL-8, IL-6, and IL-10 are practical sepsis biomarkers. The same report showed that Filgrastim increased the expression of these markers, and authors observed deficiency in the IL-23-IL-17 dual genes associated with sepsis [21].

The most significant regulatory effects are networks *EIF4G2* and *NFKB2*. They are important regulatory underlying factors in sepsis pathogenesis identified by IPA as shown in Fig. 4.

Firstly, Eukaryotic Translation Initiation Factor 4 Gamma 2 (*EIF4G2*) was found to be associated with sepsis previously when sepsis changed the distribution of eukaryotic initiation factor 4E (eIF4E) [22]. Another report showed that Eukaryotic Translation Initiation Factor 4 Gamma 1 (EIF4G1) is a potential target for cancer treatment [23]. The same report showed that

this gene, EIF4G1, was dominant in multiple cancers, for instance, cervical cancer, prostate cancer, Head and Neck Cancer, and ovarian cancer [23].

Secondly, Nuclear Factor Kappa B Subunit 2 (*NFKB2*), Nuclear factor-kappa B (NF-κB), is a master regulator of the inflammatory response and represents a key regulatory node in the complex inflammatory signaling network [24].

We highlighted that this gene is an essential regulator of sepsis-induced genetic expressions. Recent reports showed that sepsis provoked cardiac malfunction by NF-κB Pathway in animal models [25]. Another report signifies the role of this gene in sepsis; toll-like receptors activation provoked the nuclear factor-κB pathway, which led to the downregulation of specific sodium transporter expression during sepsis [26]. This vital gene is involved in acute inflammation [24], respiratory diseases [27], and joint diseases such as osteoarthritis [28].

We also discovered that the most significantly differentially expressed protein-coding genes during sepsis exposure were the *CLEC1B, PPBP, HBE1, SNX10,* and *H3P6* genes, as shown in Table 4. The *CLEC1B* gene, CLEC1B lower expression was a prognostic factor indicating the poor outcome for hepatic cancer [29]. Another report showed that this gene was among the hub genes associated with hepatocellular carcinoma [30]. Overexpression of *CLEC1B* gene inhibited hepatocellular carcinoma cells' proliferation and migration [31]. *PPBP* gene translated to pro-platelet basic protein was associated with the diagnosis and prognosis of sepsis in an animal model; rats [32], and other diseases such as chronic, allergic aspergillosis [33] and tongue cancer [34]. *PPBP* gene is a biomarker in acute ischemic stroke in Type 2 Diabetes [35].

The current report has limitations. The sample size was small, and the patients were not equally distributed, which could confound the interpretation of the genetic variation. Additionally, several genes in sepsis were uncharacterized or unmapped to pathways, meaning their effects are not considered in the current analysis.

Conclusion

The current findings signify the importance of inflammation as a significant component of sepsis-induced tissue injury. Most significantly, EIF4G2 and NFKB2 are the regulatory effects networks underlying genetic and molecular pathway changes coupled with exposure to sepsis. Future lines of research should focus on validating the results of the current study in a larger population to ascertain potential therapeutic targets in the context of sepsis-induced damage.

Abbreviations
IPA: Ingenuity pathway analysis; DE: Differentially expressed; GEO: Gene expression omnibus; NCBI: National centre for biotechnology information.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s43042-022-00352-3.

> **Additional file 1** RAW DATA GSE54514.top.table supplementary file 1.

Availability of data and materials
The current report utilized a previously published dataset for the analysis. The dataset used in this work was acquired from The National Center for Biotechnology Information's (NCBI) Gene Expression Omnibus (GEO) depository (accession number GSE54514).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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

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