

# Roles of NK cells in sepsis

Ayriana Safari Baesmat, Lokman Hekim University, Ankara, Turkey

## Abstract

**Purpose** The body's severe reaction to an infection is known as sepsis. It's a medical emergency that might put your life in jeopardy. Sepsis occurs when an existing infection sets off a chain reaction throughout your body. Sepsis is caused by infections that begin in the lungs, urinary tract, skin, or gastrointestinal system. During prolonged sepsis, apoptosis and diminished immunological activities of natural killer (NK) cells contribute to patients' vulnerability to secondary/nosocomial infections and viral reactivation, resulting in worse life quality and long-term death.

**Methods:** The gene expression data were retrieved from Gene Expression Omnibus (GEO) (GSE60424). Fold change and p value analysis, hierarchical clustering, and pathway analysis were performed.

**Results:** In this study, we identified altered genes involved in sepsis in NK cells. Ten genes corresponding 11 probe sets were differentially expressed following the sepsis. We identified a network between these genes and pathways they belong to. Pathway analysis showed that these genes are mostly associated with autoimmune response.

**Conclusion:** DLL1, SERPINA1, IFI44L, XCL1, CD3G, IGHM, PAX8-AS1, PACSIN1, PDE4B and SCML1 genes were found to be associated with sepsis. Almost all of these genes are effective in the autoimmune response, especially during the sepsis. Therefore, it is hypothesized that downregulation or upregulation of these genes may affect immune response. And it is predicted that NK cells may be an important factor for autoimmune disease.

**Keywords:** Sepsis, NK cells, Autoimmune response.

## Introduction

Sepsis is a perilous disease that happens when the body's insusceptible framework goes after its own tissues and organs in response to contamination. The safe framework is stifled past this beginning phase. Fever, expanded pulse, expanded breathing rate, and bewilderment are largely normal signs and side effects. Side effects of a specific ailment, like a hack with pneumonia or excruciating pee with a kidney disease, may likewise be available. The incredibly youthful, the old, and those with a compromised insusceptible framework might give no indications or side effects of a disease, and their internal heat level might be low or ordinary instead of high. Extreme sepsis disables organ work as well as blood stream. Restricted pulse, high blood lactate, and low pee result can all demonstrate insufficient

of inadequate blood flow. Low blood pressure caused by sepsis that does not improve after fluid replacement is referred to as septic shock (1,2,3).

People with sepsis may have a fever, low body temperature, rapid breathing, a high heart rate, disorientation, and edema, in addition to symptoms associated to the real cause. A quick heart rate, reduced urine, and elevated blood sugar are all early indications. Confusion, metabolic acidosis (which may be accompanied by a faster breathing rate that leads to respiratory alkalosis), low blood pressure due to decreased systemic vascular resistance, higher cardiac output, and blood-clotting disorders that may lead to organ failure are all signs of established sepsis. Fever is the most prevalent sign of sepsis, however it may not be present in

certain people, such as the elderly or those with impaired immune systems (4). Sepsis is brought about by bacterial contaminations; however it can likewise be brought about by contagious, parasitic, or viral diseases. Before the revelation of anti-microbials during the 1950s, Gram-positive microorganisms were the main source of sepsis. From the 1960s through the 1980s, gram-negative microscopic organisms turned into the most well-known reason for sepsis after the approach of anti-infection agents. Gram-positive microscopic organisms, most frequently staphylococci, are viewed as liable for the greater part of all sepsis cases since the 1980s. *Streptococcus pyogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* species are among the microorganisms regularly embroiled (5). Fungal sepsis is a common hospital-acquired illness that accounts for around 5% of severe sepsis and septic shock cases. The most prevalent cause of fungal sepsis is a yeast infection caused by *Candida* species. *Plasmodium* (which causes malaria), *Schistosoma*, and *Echinococcus* are the most prevalent parasite sepsis causes. The lungs, abdomen, and urinary tract are the most prevalent sites of infection that result in severe sepsis. Approximately half of all sepsis cases begin with a lung infection. The source of infection is unknown in one-third to one-half of cases. (6). Regular executioner cells, usually known as NK cells or enormous granular lymphocytes (LGL), are a sort of cytotoxic lymphocyte essential to the natural resistant framework. They have a place with the quickly expanding natural lymphoid cell (ILC) family and record for 5-20 percent of all coursing lymphocytes in people. In the vertebrate versatile resistant reaction, NK cells play a comparable part to cytotoxic T cells. At about 3 days after disease, NK cells produce fast reactions to infection tainted cells and other intracellular microorganisms, and they answer cancer development. Invulnerable cells perceive

the significant histocompatibility complex (MHC) on tainted cell surfaces, which sets off the development of cytokines, which makes the contaminated cell bite the dust by lysis or apoptosis. (7). NK cells, on the other hand, are unusual in that they can detect and destroy stressed cells without the need of antibodies or MHC, allowing for a much speedier immune response. They were given the label "natural killers" because they destroy cells that lack MHC class 1 "self" signals without the need for activation. Because dangerous cells without MHC I signals cannot be identified and eliminated by other immune cells, such as T lymphocyte cells, this role is critical (8). NK cells are cytotoxic, with proteins like perforin and proteases known as granzymes put away in small granules in their cytoplasm. Perforin produces openings in the phone layer of the objective cell when delivered in closeness to it, giving a fluid channel through which the granzymes and related synthetic compounds can enter, setting off one or the other apoptosis or osmotic cell lysis. In immunology, the difference among apoptosis and cell lysis is critical: lysing an infection contaminated cell could deliver the virions, yet apoptosis makes the infection die inside the cell. Antimicrobial substances called - defensins are additionally delivered by NK cells and straightforwardly kill microbes by breaking their phone dividers along these lines to neutrophils.

Antibodies are used to opsonize infected cells so that immune cells can recognize them. Antibodies attach to antigens and are recognized by FcRIII (CD16) receptors on NK cells, causing NK activation, the release of cytolytic granules, and cell death. Some monoclonal antibodies, such as rituximab (Rituxan), ofatumumab (Azzera), and others, use this technique to destroy cancer cells. The contribution of antibody-dependent cell-mediated cytotoxicity to tumor cell killing can be measured using a specific test that employs

NK-92, an immortal line of NK-like cells licensed to NantKwest, Inc.: the response of NK-92 cells transfected with a high-affinity Fc receptor is compared to that of "wild type" NK-92 cells that do not express the Fc receptor. Cytokines are fundamental for NK cell enactment. These pressure atoms, which are created by cells because of viral disease, help to make the NK cell aware of the presence of viral microbes in the distressed locale. IL-12, IL-15, IL-18, IL-2, and CCL5 are cytokines engaged with NK initiation. In response to interferons or macrophage-determined cytokines, NK cells become enacted. They help to control viral contaminations while the versatile invulnerable framework produces antigen-explicit cytotoxic T cells that can assist with wiping out the disease. By emitting IFN and TNF, NK cells help to stifle viral contaminations. TNF advances direct NK growth cell passing by enacting macrophages for phagocytosis and lysis. (9).

Natural killer (NK) cells, which are the basic components of the innate immune system, play a role in the development of multiple autoimmune diseases such as systemic lupus erythematosus, type I diabetes mellitus and autoimmune liver disease, but the role of NK cells in sepsis is not very clear, in this study we researched the role of NK cells in sepsis. Complete blood purification NK cells were selected in healthy individuals and sepsis due to healthy type 1 diabetes, amyotrophic lateral sclerosis, and sepsis.

## Materials and methods

### Microarray gene expression data

The gene expression data was obtained from the Gene Expression Omnibus (GEO) database. Transcription profile data of human Natural killer cells from Sepsis patients were obtained from GEO (GSE60424).

### Processing and normalization of data

The raw data from GEO were normalized with the DESeq2 package in the R software. Normalized transcription profile data consists of 11,895 different genes/ 12,744 probe sets. The data contains 4 groups of control and 2 groups of patients with sepsis, whole genome expression data.

### Fold change and p value analysis

Among the groups, significant genes with a fold change greater than  $|3|$  were identified. In order to group the identified genes more specifically P value was calculated and genes under 0.05 were selected.

Analyses were done using GraphPad Prism 9.0.0 (Graphpad Prism 9 Software, San Diego, CA, USA). Genes with a P value less than 0.05 and fold change greater than  $|3|$  were selected.

### Hierarchical clustering

The Euclidean Gene Cluster 3.0 tool was used to hierarchically cluster genes discovered using linear regression analysis using mean standardized gene expression levels. After cluster analysis, the data was normalized, and the standardized data was examined in Treeview. Using Euclidian distance as a similarity metric and full linkage as a clustering approach, hierarchical clustering was done on both genes and arrays.

### Pathway enrichment analysis

The "Database for Annotation, Visualization, and Integrated Discovery" (DAVID) software was utilized to investigate the biological relationship underlying these genes. The pathways linked to our genes have been discovered.

GSEA was performed according to the GSEA guideline protocol (<http://software.broadinstitute.org/gsea/docGS>

EAUserGuideFrame.html). The analysis was carried out using GSE60424 data. There are 12,744 probe sets in this data collection (11,895 different genes). To further understand the trend, a comparison was made between the four control groups and the two sepsis patient groups. The major goal of this study is to figure out which genes are considerably enriched in various GSEA gene sets, as well as to figure out which gene sets are enriched in which groups.

The enhancement score (ES), the standardized advancement score (NES), the notional P esteem (NOM P esteem), the bogus revelation rate q esteem (FDR q esteem), and the familywise mistake rate P esteem are totally determined utilizing GSEA (FWER). The ES esteem addresses a quality's most noteworthy deviation in a gathering of qualities; as such, this score supports the ID of the most upregulated qualities. The distinction or connection between quality sets and quality articulation is addressed by the NES esteem. The more prominent the NES esteem, the more prospects there are.

As a result, gene sets with a higher NES value have more relevance. The NOM P value, in addition to the ES and NES values, assesses the significance of the ES computation. As a result, the NOM P value was closely tied to the ES and NES values. The importance of ES is demonstrated by the increase in NOM P value. On the other side, the FWER P value reflects the likelihood of NES false positives, and a lower FWER P value is directly and strongly connected to the accuracy of NES computation. In addition, the FDR q value is the most important parameter in this study. This number must be less than 0.25, and the enrichment of gene sets becomes more significant as this value decreases.

Volcanoplot

Volcano plot was shown with the EnhancedVolcano package in the R software. volcano plot shows the log2 of the fold change on the x-axis and minus log10 of the p-value. Genes with P value lesser than 0.05 and fold change greater than |1,5| are shown.

Changes in gene expression in a sepsis patient's NK cell line Human NK cells were evaluated using whole genome expression data to see if there were any differences in gene expression between four control groups and two sepsis patient groups. According to the findings, 10 genes belonging to 11 probe sets revealed statistically significant expression changes with a fold change larger than |3| and a P value less than 0.05. We focused our additional research on the genes that influenced expression diversity between groups. Two genes were positively connected and elevated in human NK cells from four control groups and two sepsis patient groups, whereas eight genes were negatively linked and downregulated (Supplementary Table 1).

Gene changes were discovered using hierarchical cluster analysis in two groups: four healthy people and two sepsis patients. Eight genes were found to be negatively associated, strongly expressed in the control groups, and reduced in the sepsis groups. In contrast, two genes were positively associated, with low expression in the control groups and higher expression in the sepsis groups. The image depicted 10 genes, with the remainder provided as supplemental information (Fig. 1) Sepsis causes gene changes.

Fold change analysis and p value were done on 10 genes/11 probe set expression data from 4 control groups and 2 sepsis groups to see if this expression change was caused by sepsis in patients. Thus, 11 probe sets with a fold change more than |3| and a P value less than 0.05 were determined for 10 statistically significant genes (DLL1, SERPINA1, IFI44L, XCL1, CD3G,

IGHM, PAX8-AS1, PACSIN1, PDE4B, and SCML1) (Table 1).

Eight of the ten genes were shown to be downregulated and negatively linked. Figure 2 compares the expression of these 10 genes in four groups and two sepsis groups (Fig. 2)

Gene Name	Fold change	P value
DLL1	-4.005240681	1.02E-07
SERPINA1	-3.903689361	0.023160899
IFI44L	-3.763217156	0.000325333
XCL1	-3.704187412	0.001232046
CD3G	3.586105442	1.50E-05
IGHM	3.42755781	0.004404048
PAX8-AS1	-3.389036491	0.000217374
PACSIN1	-3.345921535	0.000542793
PDE4B	-3.170424395	4.43E-05
SCML1	-3.116287166	0.005822007

Table 1 The list of 10 genes (11 probe sets) which have the most alterations in expression. These genes have fold change greater than |3| and p value less than 0.05 between 4 control groups and 2 groups from patients with sepsis. These significant values indicate that the change occurred due to sepsis.

## Functional enrichment of genes and pathway connections

DAVID software was used to do a pathway analysis of biological processes to discover the link between these 10 genes and cellular activities and pathways, as well as to better grasp their new significance. During sepsis, the four pathways are related with 10 genes: T cell signaling pathway, chemokine signaling pathway, and notch signaling cAMP

signaling pathway. The relevance of the cell cycle in stomach cancer cells, for example, demonstrates the link between these pathways

and the development of cancer and autoimmune illness (Table 2)

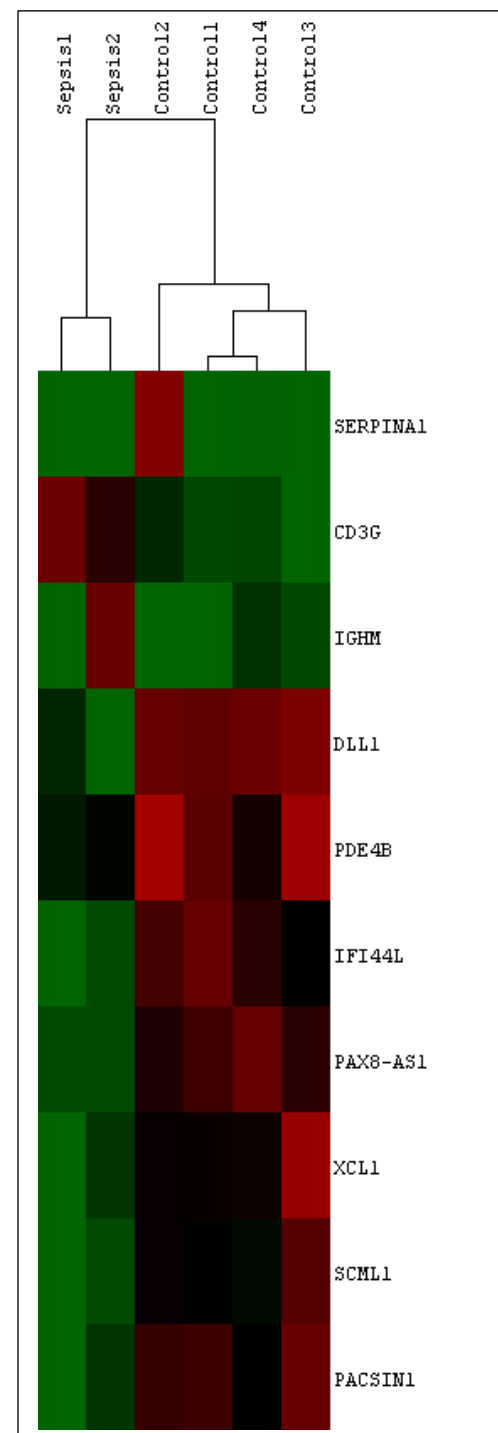


Figure 1: Hierarchical clustering of 10 statistically significant variables in the six groups. For control and sepsis, the analysis revealed sensitive low expressions (green), intermediate expressions (black), and high expressions (red) of 10 genes. The classification of designated groupings is obvious. The top ten genes were included in the graph.

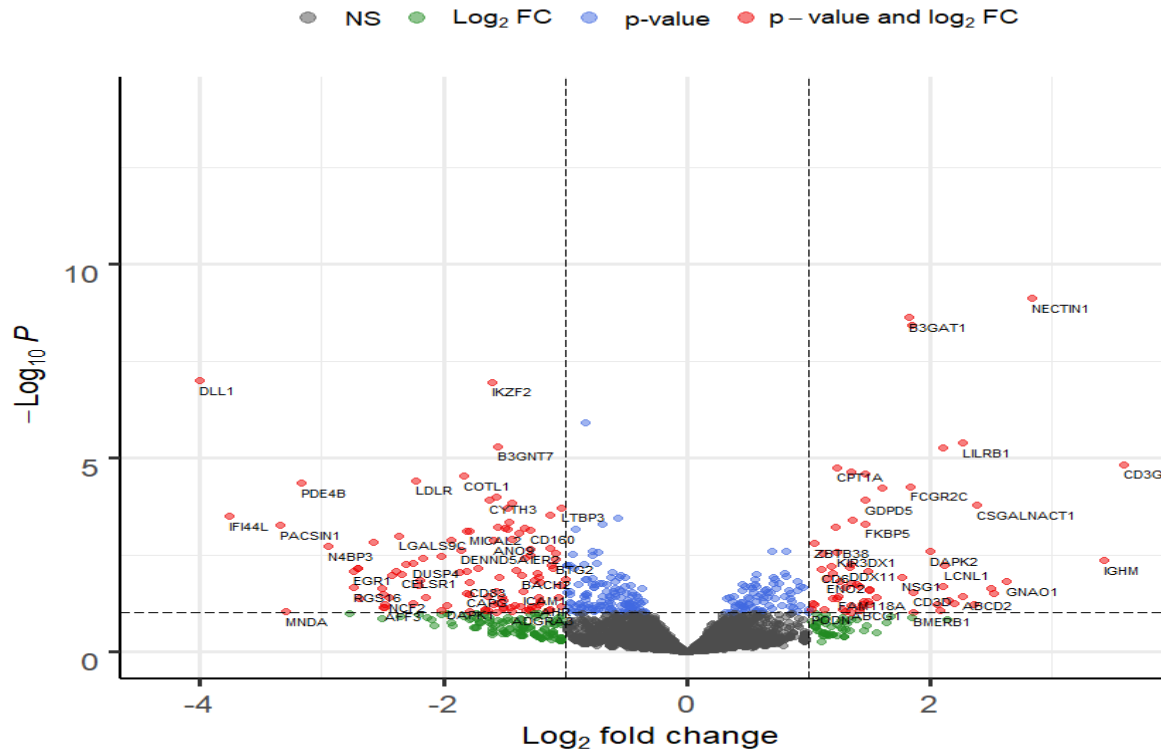


Fig 2 volcano plot shows the log2 of the fold change on the x-axis and minus log10 of the p-value. Genes with P value lesser than 0.05 and fold change greater than |1,5| are shown.

Strengthening Table 2 shows the significantly advanced quality sets, as well as their ES, NES, NOM P esteem, FWER P worth, and FDR q esteem. The negative controlled reaction to cytokine boosts and DNA blend engaged with DNA fix quality set were demonstrated to be firmly connected with the qualities contained in the information, as indicated by GSEA. Table 2 and other featured exploration observed that specific quality sets associated with pathway investigation. Strengthening Table 2 shows the significantly advanced quality sets, as well as their ES, NES, NOM P esteem, FWER P worth, and FDR q esteem. The negative controlled reaction to cytokine boosts and DNA blend engaged with DNA fix quality set were demons

rated to be firmly connected with the qualities contained in the information, as indicated by GSEA. Strengthening Table 2 shows the significantly advanced quality sets, as well as their ES, NES, NOM P esteem, FWER P worth, and FDR q esteem. The negative controlled reaction to cytokine boosts and DNA blend engaged with DNA fix quality set were demonstrated to be firmly connected with the qualities contained in the information, as indicated by GSEA. Table 2 and other featured exploration observed that specific quality sets associated with pathway investigation. Figure 4 likewise showed that the reaction to cytokine boost set plot was contrarily managed. This chart portrayed qualities that were enhanced in

four benchmark groups, a peculiarity known as emphatically connected qualities. On the other hand, the same genes were downregulated and negatively correlated in the 2 sepsis groups. The same results were obtained for the DNA synthesis involved in DNA repair genes set (Fig. 5).

Category	pathways	related disease
KEGG_PATHWAY	T cell receptor signaling	arthritis and rheumatoid
KEGG_PATHWAY	chemokines signaling	leukemia
KEGG_PATHWAY	Notch signaling	
KEGG_PATHWAY	c amp signaling	

Table 2 Pathways related to the genes are linked. It is seen that important pathways in cancer progression and autoimmune disease are related to our genes. Most of these genes are linked to T cell signaling pathway, chemokine signaling pathway and notch signaling cAMP signaling pathway from the database for annotation, visualization, and integrated discovery (DAVID)

Discussion

Sepsis is a frequent ailment that has an unacceptably high fatality rate and, for those who survive, long-term morbidity. Increased awareness of the issue as a consequence of continuous efforts, as well as evidence derived from research conducted in the last ten years, has enhanced physicians' and laypeople's comprehension of the problem, leading to better outcomes. In 2017, the World Health Assembly and the World Health Organization (WHO) declared sepsis a global health priority and approved a resolution to enhance sepsis prevention, detection, and management.

A revised definition of sepsis (Sepsis-3) was created in 2016. The term "sepsis" today refers

to an infection that causes organ malfunction. (10)

In this study, it is aimed to identify sepsis related gene expression alterations, their associated pathways using all genome expression data of NK cells from sepsis patients.

(DLL1, SERPINA1, IFI44L, XCL1, CD3G, IGHM, PAX8-AS1, PACSIN1, PDE4B and SCML1

gene expression alterations were identified in NK cells from sepsis patients. These genes were identified as differentially expressed in NK cells from sepsis patients and groups (P < 0.05 and fold change greater than |3|) were

hierarchically forming a very distinct cluster, as expected. Gene set enrichment analysis supported the results that some crucial genes function effectively in the negative regulated of response to cytokine stimulus and DNA synthesis involved in DNA repair as a result of sepsis. Most of the genes showed a statistically significant difference in negative regulated of response to cytokine stimulus and DNA synthesis involved in DNA repair gene sets.

Genes found statistically significant because of the comparison between the 4 control groups and 2 groups patients with sepsis were enriched in the specified biological gene sets. This enrichment supports that these genes have important effects on the immune system.

At the point when monocytes are animated by microorganisms, they produce Delta-like Protein 1 (DLL1), an exemplary Notch ligand. Given the job of monocytes in sepsis pathogenesis, it was anticipated that this interaction may likewise happen in the clinical setting, and DLL1 could be utilized as a biomarker for dangerous bacterial disease. DLL1 is another host-inferred biomarker for sepsis recognition that beats known biomarkers, undoubtedly because of its extraordinary strength in non-irresistible incendiary

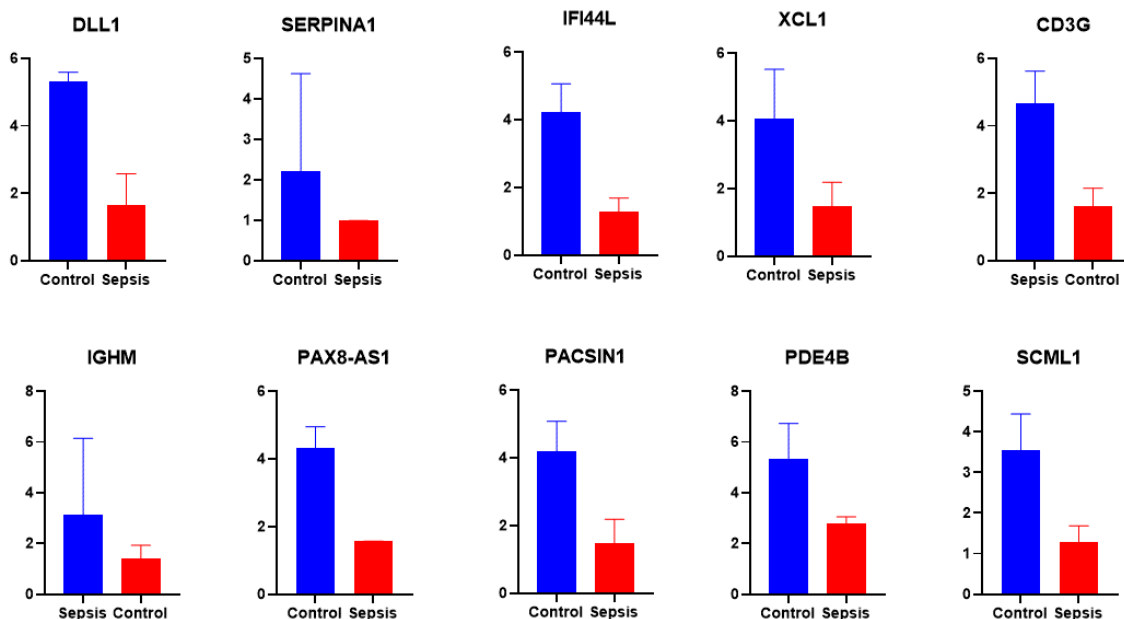


Fig 3 Ten genes that show significant differentially expressed in patients with sepsis. Statistically significant alterations were detected between 4 control groups and 2 sepsis groups.

responses. DLL1 advances disease cell duplication and angiogenesis using Notch hailing, exhibiting DLL1's part in development cell expansion and angiogenesis. These components are important for further developed improvement and versatility. In proceeding with research, DLL1 has been connected to the CSC movement of glioblastoma, renal cell dangerous turn of events, and rhabdomyosarcoma. Dll1 further develops malignant growth movement and lung metastasis in the luminal subtype of bosom sickness yet has no impact on TNBC disease movement. Indent flagging interceded by DLL1 manages cell genealogy, cell detail, cell designing, and morphogenesis through impacts on separation and expansion,

and is expected for early-stage advancement and grown-up foundational microorganism upkeep in an assortment of organs, including the safe framework. Plays a role in the immune system's development, namely in the creation of all T-cells and marginal zone (MZ) B-cells (By similarity). Blocks B-cell progenitor cell development, encouraging the creation of a population of cells with T-cell/NK-cell precursor characteristics. It also aids in the development of muscles. Restrains myoblast separation from the average dermomyotome lip during early turn of events and thusly tweaks begetter cell separation. Indent flagging straightforwardly directs cell attachment and basal lamina improvement in satellite cells. Keeps up with the pool of myogenic ancestors by restraining separation by means of MYOD1 downregulation



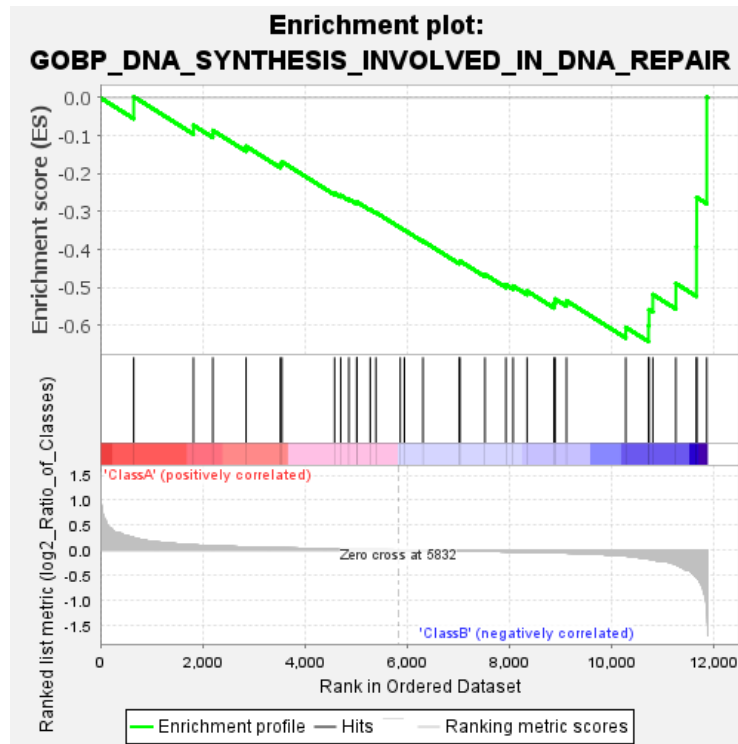


Fig. 4 The DNA synthesis involved in DNA repair plot was represented. The black straight line refers the enriched genes in the groups. Red part contains the genes that positively correlated in 4 control groups and were upregulated in control groups. On contemporarily, the blue line includes downregulated or in other words negatively regulated genes that belongs to sepsis.

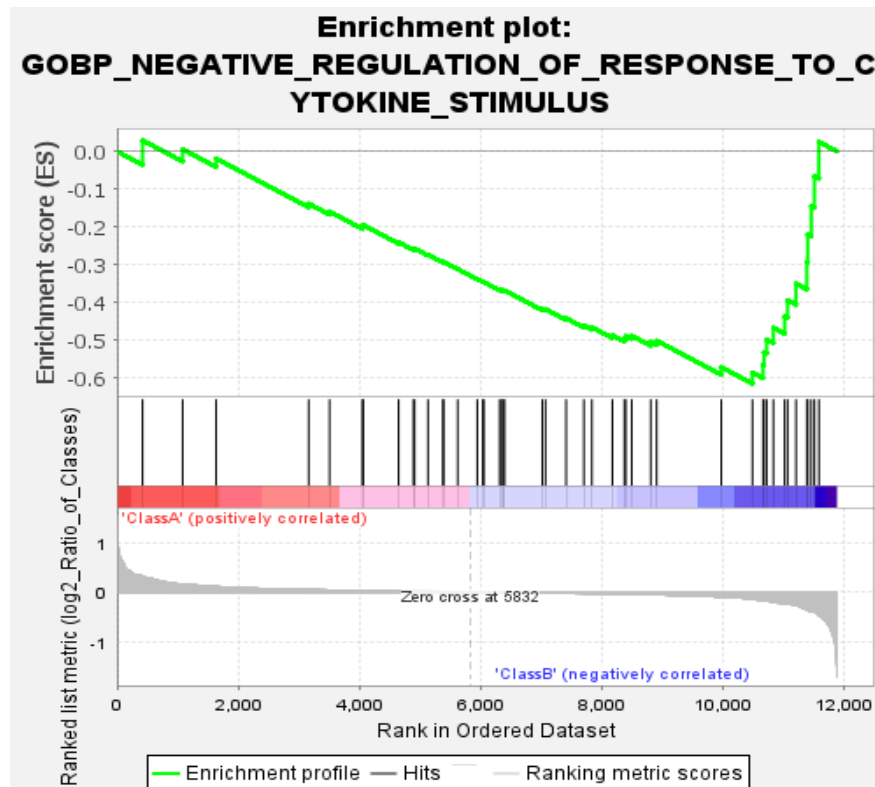


Fig. 5 The negative regulation of response to cytokine stimulus plot was represented. The black straight line refers the enriched genes in the groups. Red part contains the genes that positively correlated in 4 control groups and were upregulated in control groups. On contemporarily, the blue line includes downregulated or in other words negatively regulated genes that belong to sepsis.

and is fundamental for satellite cell homing and PAX7 articulation. Restrains myoblast separation from the average dermomyotome lip during early turn of events and thusly tweaks begetter cell separation. Indent flagging straightforwardly directs cell attachment and basal lamina improvement in satellite cells. Keeps up with the pool of myogenic ancestors by restraining separation by means of MYOD1 downregulation and is fundamental for satellite cell homing and PAX7 articulation (11,12). Because DLL1 overexpression decreased immunosuppressive invulnerable cell groups such M2-TAMs, Tregs, and PD1-positive CD4+ T cells, immunosuppression may have been reduced, and hypoxia inside the TME revived CD8+ T cell activities.

The anti-inflammatory protein alpha-1 antitrypsin (AAT) has a well-known safety profile. AAT's therapeutic potential has been investigated in a variety of autoimmune illness types. AAT gene transfer reduced the development of type 1 diabetes (T1D) in the non-obese diabetic (NOD) mouse model in the first research, which used a recombinant adeno-associated viral (rAAV) vector. Treatment with the AAT protein prevented and reversed type 1 diabetes in subsequent investigations. Other autoimmune disease models, such as rheumatoid arthritis and systemic lupus erythematosus, have shown that AAT therapy is

The anti-inflammatory protein alpha-1 antitrypsin (AAT) has a well-known safety profile. AAT's therapeutic potential has been investigated in a variety of autoimmune illness types. AAT gene transfer reduced the development of type 1 diabetes (T1D) in the non-obese diabetic (NOD) mouse model in the first research, which used a recombinant adeno-associated viral (rAAV) vector. Treatment with the AAT protein prevented and reversed type 1 diabetes in subsequent investigations. Other autoimmune disease models, such as rheumatoid arthritis and systemic lupus

erythematosus, have shown that AAT therapy is effective. (13)

Although AAT lack has been connected to the advancement of bronchial asthma and bronchiectasis, there is no convincing proof that it influences the recurrence or seriousness of these problems. Lung emphysema brought about by AAT inadequacy has a promising beginning of 35-45 years, with determined, expanding sleepiness and other vague respiratory manifestations. (14) The traditional worldview of protease/antiprotease awkwardness emerged from the disclosure that alpha-1 antitrypsin (AAT) was an effective inhibitor of neutrophil elastase, tying lung harm to the unopposed effect of proteases in people with the shortfall. Regardless of its significance as an antiprotease, alpha-1 antitrypsin has been displayed to have fundamental calming and safe administrative properties, which might assume a part in lung annihilation. (15,16) The connection among lymphotactin and XCR might direct unique lymphocyte subsets to incendiary regions. Lymphotactin can possibly control the provocative reaction. The NF-B flagging pathway might impact lymphotactin articulation, essentially to some degree.

Considering that alpha-1 antitrypsin is a potent anti-inflammatory and potential new therapeutic agent, we think that up-regulation of this gene has a negative role in the progression of sepsis due to decreased immune response.

Lymphotactin is a powerful attractant of lymphocytes, strikingly T-cells and regular executioner (NK) cells, with a ruling articulation in actuated CD8+ T cells and enacted normal executioner cells, despite the fact that it is inactive for invigorating the relocation of neutrophils and monocytes. The presence of a lymphotactin-explicit receptor, XCR, which is a particular G protein-coupled receptor communicated in circling lymphocytes and NK

cells, recommends the presence of a lymphotactin-explicit receptor, which is a particular G protein-coupled receptor communicated in flowing lymphocytes and NK cells. The lymphotactin-XCR communication has been displayed to play a part in the improvement of provocative problems like rheumatoid joint pain, foundational sclerosis, fiery entrail sickness, glomerulonephritis, and HIV disease in past clinical and creature research. (17,18,19,20) XCL1 is a C-class chemokine created by resistant cells like CD8+ T cells, CD4+ T cells, T cells, NK cells, NKT cells, and medullary thymic epithelial cells. Accordingly, this is the first in vitro and in vivo evidence that the association somewhere in the range of XCL1 and  $\alpha 9$  integrin plays a part in immune system problems, as far as anyone is concerned. XCL1 might play a part in the movement of incendiary joint inflammation. (21,22,23). Lymphotactin (Ltn) is a chemokine that recruits T and NK cells and is mainly produced by activated CD8+ T cells and activated NK cells. Considering that up-regulation of lymphotactin increases the immune system response, we think that this gene has a supportive role in the progression of ovarian expression and sepsis. mAb coordinated against the TCR/CD3 complex initiates resting T cells. TCR/CD3 motioning, then again, prompts apoptosis in youthful (CD4+CD8+) murine thymocytes and a few changed over leukemic T cell lines. Hostile to TCR and against CD3 mAb limit the advancement of cloned TCR-gamma delta + T cells within the sight of IL-2. Without exogenous IL-2, a similar enemy of TCR/CD3 mAb invigorated gamma delta (+)- clones to multiply and create IL-2. Within the sight of exogenous IL-2, against TCR/CD3 mAb prompted DNA debasement into oligosomal groups of around 200 bp length in cloned gamma delta + T cells. This pattern of DNA fragmentation is associated with apoptosis, or programmed cell death. According to these

findings, TCR/CD3 signaling can trigger cell death in cloned gamma delta + T cells. This is also the first research to show that TCR/CD3-induced death is not restricted to CD4+CD8+ immature thymocytes and converted leukemic T cell lines, but may also occur in IL-2-dependent normal (i.e. TCR-gamma delta +) T cells (24,25). Because the CD3G gene, which is a subset of TCR/CD3, boosts T cell signal, we speculate that up-regulation of this gene might result in greater immune system response.

Immunoglobulin chains with a ton of weight have a steady region. Immunoglobulins, otherwise called antibodies, are film-bound or delivered glycoproteins created by B lymphocytes. In the acknowledgment time of humoral invulnerability, film bound immunoglobulins go about as receptors, setting off the clonal multiplication and partition of B lymphocytes into immunoglobulin-emanating plasma cells considering the introduction of a particular antigen. Released immunoglobulins mediate during the effector phase of humoral invulnerability, which comes full circle in the clearing of bound antigens. The antigen limitation site is framed by the variable area of one weighty chain joined with that of its connected light chain. Subsequently, every immunoglobulin has two antigen-confining areas, every one of which has a solid partiality for a specific antigen. The antigen restricting site is framed by the variable spaces of one weighty chain and its related light chain. Subsequently, every immunoglobulin has two antigen restricting locales, one for every antigen. Variable areas are delivered by the V-(D)-J improvement process and can then be exposed to substantial hypermutations, which permit partiality development for a specific many more than one antigen openness and determination.

IgM antibodies assume a basic part in fundamental safeguarded systems. They've

been connected to early discovery of outside trespassers, for example, microorganisms and contaminations, cell squander, and an adjusted self, as well as early recognition and evacuation of precancerous and unsafe developments. Most typical B-cells have a layer bound structure notwithstanding IgD. The Src group of protein tyrosine kinases phosphorylate CD79A and CD79B when IgM is connected to a film. It can possibly set off apoptosis, or cell demise. It's additionally found in the dissolvable design, which represents around 30% of all out-serum immunoglobulins and is essentially found as a homopentamer. When the antigen associates with the B-cell receptor, it delivers a significant measure of antigen (26). The majority of the genes found in this study are significantly expressed in autoimmune illness and are linked to a strong immune response, according to the findings. As a result, cell suppression may result in diminished effects in sepsis patients. This study was the first to reveal a link between some of these genes and sepsis. Following network and pathway analysis, it was shown that these genes are linked to critical sepsis pathways. The T cell signaling pathway, the chemokine signaling pathway, and the notch signaling cAMP signaling pathway are all examples of these pathways. . The majority of these pathways are clearly linked to sepsis and other autoimmune diseases. As a result, we are able to favorably act in sepsis.

## Conclusion

In this study, it has been shown that suppression of NK cells may have important effects on patients with sepsis. The results are important indicators that NK cells response to sepsis directly or indirectly have an effect on the immune system response, and this effect may favor the host in fighting with sepsis. Most of the genes we identified have functions that cause high immune response. More in vitro and

in vivo studies are needed to demonstrate the role of natural killer cells in patients with sepsis.

## Authors' details

Ayriana Safari Baesmat, Faculty of Medicine, Lokman Hekim University, Ankara ,Turkey.

## References

- 1-Cao C, Yu M, Chai Y. Pathological alteration and therapeutic implications of sepsis-induced immune cell apoptosis. *Cell Death Dis.* 2019;10(10):782. Published 2019 Oct 14. doi:10.1038/s41419-019-2015-1
- 2- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-810. doi:10.1001/jama.2016.0287
- 3- Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41(2):580-637. doi:10.1097/CCM.0b013e31827e83af
- 4- Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A Review of Advances in Management. *Adv Ther.* 2017;34(11):2393-2411. doi:10.1007/s12325-017-0622-8)
- 5- Hotchkiss, R., Moldawer, L., Opal, S. et al. Sepsis and septic shock. *Nat Rev Dis Primers* 2, 16045 (2016). <https://doi.org/10.1038/nrdp.2016.45>
- 6- Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet.* 2018;392(10141):75-87. doi:10.1016/S0140-6736(18)30696-2
- 7- Purcarea A, Sovaila S. Sepsis, a 2020 review for the internist. *Rom J Intern Med.* 2020;58(3):129-137. doi:10.2478/rjim-2020-0012

- 8- Guo Y, Patil NK, Luan L, Bohannon JK, Sherwood ER. The biology of natural killer cells during sepsis. *Immunology*. 2018;153(2):190-202. doi:10.1111/imm.12854
- 9- Biassoni R, Coligan JE, Moretta L. Natural killer cells in healthy and diseased subjects. *J Biomed Biotechnol*. 2011;2011:795251. doi:10.1155/2011/795251
- 10- Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. *Immunity*. 2014;40(4):463-475. doi:10.1016/j.immuni.2014.04.001
- 11- Hildebrand D, Decker SO, Koch C, et al. Host-Derived Delta-Like Canonical Notch Ligand 1 as a Novel Diagnostic Biomarker for Bacterial Sepsis-Results From a Combinational Secondary Analysis. *Front Cell Infect Microbiol*. 2019;9:267. Published 2019 Jul 23. doi:10.3389/fcimb.2019.00267
- 12- Kuksin CA, Minter LM. The Link between Autoimmunity and Lymphoma: Does NOTCH Signaling Play a Contributing Role?. *Front Oncol*. 2015;5:51. Published 2015 Feb 24. doi:10.3389/fonc.2015.00051
- 13- de Serres F, Blanco I. Role of alpha-1 antitrypsin in human health and disease. *J Intern Med*. 2014;276(4):311-335. doi:10.1111/joim.12239
- 14- Song S. Alpha-1 Antitrypsin Therapy for Autoimmune Disorders. *Chronic Obstr Pulm Dis*. 2018;5(4):289-301. Published 2018 Oct 5. doi:10.15326/jcopdf.5.4.2018.0131
- 15- Grimstein, C., Choi, YK., Wasserfall, C.H. et al. Alpha-1 antitrypsin protein and gene therapies decrease autoimmunity and delay arthritis development in mouse model. *J Transl Med* 9, 21 (2011). <https://doi.org/10.1186/1479-5876-9-21>
- 16- Ye J, Liao YT, Jian YQ, et al. Alpha-1-antitrypsin for the improvement of autoimmunity and allograft rejection in beta cell transplantation. *Immunol Lett*. 2013;150(1-2):61-68. doi:10.1016/j.imlet.2013.01.009
- 17- Matsumoto N, Kon S, Nakatsuru T, et al. A Novel  $\alpha 9$  Integrin Ligand, XCL1/Lymphotactin, Is Involved in the Development of Murine Models of Autoimmune Diseases. *J Immunol*. 2017;199(1):82-90. doi:10.4049/jimmunol.1601329
- 18- Yeh PT, Lin FA, Lin CP, Yang CM, Chen MS, Yang CH. Expressions of lymphotactin and its receptor, XCR, in Lewis rats with experimental autoimmune anterior uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(12):1737-1747. doi:10.1007/s00417-010-1435-5
- 19- Hedrick JA, Zlotnik A. Lymphotactin. *Clin Immunol Immunopathol*. 1998;87(3):218-222. doi:10.1006/clin.1998.4546
- 20- Wang CR, Liu MF, Huang YH, Chen HC. Up-regulation of XCR1 expression in rheumatoid joints. *Rheumatology (Oxford)*. 2004;43(5):569-573. doi:10.1093/rheumatology/keh147
- 21- Müller K, Bischof S, Sommer F, Lohoff M, Solbach W, Laskay T. Differential production of macrophage inflammatory protein 1gamma (MIP-1gamma), lymphotactin, and MIP-2 by CD4(+) Th subsets polarized in vitro and in vivo. *Infect Immun*. 2003;71(11):6178-6183. doi:10.1128/IAI.71.11.6178-6183.2003
- 22- Lei Y, Takahama Y. XCL1 and XCR1 in the immune system. *Microbes Infect*. 2012;14(3):262-267. doi:10.1016/j.micinf.2011.10.003
- 23- Ohta T, Sugiyama M, Hemmi H, et al. Crucial roles of XCR1-expressing dendritic cells and the XCR1-XCL1 chemokine axis in intestinal immune homeostasis. *Sci Rep*. 2016;6:23505. Published 2016 Mar 23. doi:10.1038/srep23505

24- Gokturk B, Keles S, Kirac M, et al. CD3G gene defects in familial autoimmune thyroiditis. Scand J Immunol. 2014;80(5):354-361. doi:10.1111/sji.12200

25-Delmonte, O.M., Rowe, J.H., Dobbs, A.K. et al. Complete Absence of CD3 $\gamma$  Protein Expression Is Responsible for Combined Immunodeficiency with Autoimmunity Rather than SCID. J Clin Immunol 41, 482–485 (2021). <https://doi.org/10.1007/s10875-020-00918-z>

26- Picchianti Diamanti A, Rosado MM, Scarsella M, et al. Increased serum IgM, immunodeficiency, and autoimmunity: A clinical series. Int J Immunopathol Pharmacol. 2015;28(4):547-556. doi:10.1177/0394632015600231



