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RESEARCH ARTICLE

Upregulated Acute Systemic Inflammation-Related Genes based on Endotoxin Exposure Provide "Survival Benefit" or Create "High Risk of Death" in Leukaemia and Colon Cancer

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ABSTRACT

Objective: Although endotoxin exposure has been shown to trigger innate immune responses and promote cancer, it has also been shown to prevent cancer formation. In our study, survival analysis was performed to determine whether the upregulated genes triggered by endotoxins have hazardous effects on cancers or provide a survival benefit.

Materials and Methods: Gene intensity values of control and bacterial endotoxin-administered individuals were obtained from the Gene Expression Omnibus database. Using the R "Linear Models for Microarray Data" package, differentially expressed gene analyses were conducted to determine genes that differ between healthy and bacterial endotoxin-administered samples. "ShinyGo 0.80" web-based tool was used to determine the disease types indicated by these genes. The "Kaplan-Meier Plotter" web-based tool was used to conduct survival analysis.

Results: Genes that create an innate immune response to bacterial endotoxin exposure and are upregulated differently than in individuals without exposure were identified. According to gene enrichment analyses, the two main types of cancer identified were leukaemia/lymoma and colon cancer. We detected that *MLF1, STAT5B*, and *BCL3* genes led to poor survival; however, the *ARHGAP26* gene was protective for acute myeloid leukaemia patients. In the case of colon cancer, *SMAD7* and *TLR2* genes were determined as leading to "high risk of death".

Conclusion: Once the systemic inflammation-related genes identified in our study are confirmed through laboratory experiments in samples taken from solid tissue in the case of colon cancer and at the level of genes obtained from blood samples in leukemias, genetically targeted treatments will also be possible.

Keywords: Cancer, Endotoxin, Systemic inflammation, Bioinformatics, Survival

INTRODUCTION

Bacterial endotoxins (lipopolysaccharide, LPS) are a part of the outer wall of Gramme-negative bacteria with the biologically active part lipid-A. After the bacteria die and their bacterial outer walls disintegrate, they appear in materials containing cellulose, called organic dust, and appear in a way that we can even be exposed to in our daily lives.[1] Health problems that occur as a result of exposure to bacterial endotoxins vary depending on the LPS concentration. While septic shock and serious life-threatening effects may occur as a result of exposure to high doses of LPS, there are even cases where it can be considered beneficial for the host because of the low level of triggering of the innate immune system as a result of exposure to low doses.[2,3] In addition to studies showing that endotoxin-mediated inflammatory responses have a triggering effect on cancer, there are studies showing that they have host-protective effects on cancer. For example, in a study showing that LPS, which is more abundant in the colon flora compared with normal intestinal flora, regulates gene expression in human colon cancer cell lines, it was shown at the genetic level that LPS does not affect cell viability but contributes to inflammatory responses and cancer development.[4] In a study published in 2021, it was shown at the molecular level that LPS triggers metastasis in colorectal cancers using cell lines and clinical samples.[5] In addition, there are studies on the relationship of gut microbiota with many cancers other than colon cancer. Some studies have also shown that endotoxins (mainly LPS) have protective effects against cancer. For example, in a review article published in 2023, where current and comprehensive publications were scanned, publications sharing information on whether the gut

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microbiota, consisting of different types of bacteria, promote or inhibit cancers in different human and murine cancer models were summarized.[6] There are limited number of studies conducted on mouse models and mouse/human cell lines, showing that gut microbiota inhibits cancer formation in colorectal and colon cancers. It has been shown that mostly colorectal or colon cancer gut microbiota promote cancer.[6-9] In another study, it was shown that acute myeloid leukaemia (AML) caused cancer progression in vivo and in vitro through the effect of gut-derived LPS in mouse models.[10]

In clinics, local and systemic inflammation is decisive in the diagnostic phase of cancers and in terms of response to treatment.[11] Studies have shown that inflammatory responses play a role in tumour progression and survival in cancer patients. For example, in a study conducted in 2018 that included randomized clinical trials, the effect of systemic inflammatory responses on the survival rates of cancer patients was investigated. As seen in the study, a limited number of studies are possible in leukaemia and colon cancer patients.[12] In another study, we attempted to determine prediagnostic systemic inflammation markers for many types of cancer based on cancer incidence using UK Biobank data. These markers include the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio.[13] In another study in which meta-analyses were conducted in 2021, a study was conducted on the creation of a systemic inflammation response index in cancer patients.[14]

As can be seen from the studies summarized in the literature above, there is no research on how endotoxin-mediated systemic inflammation affects cancer formation and survival at the gene level. In this context, our study provides novel findings. Our aim in our study was to identify upregulated genes associated with systemic inflammation through bioinformatic analysis and to identify the cancers with which these genes are associated. In our study, the effect of genes upregulated in certain types of cancer on the survival (protective or triggering) of patients was also investigated.

MATERIALS AND METHODS

Data Acquisition and Processing

In this study, gene intensity values of control and bacterial endotoxin-administered individuals were obtained from the Gene Expression Omnibus (GEO) database (GSE3284) [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array (GPL96 and GPL97) platforms with 22.283 and 22645 probes, respectively. According to the overall design of the dataset, genes of blood leukocytes of individuals were analysed before (0 hour as an internal control) and at 2, 4, 6, 9, and 24 h upon bacterial endotoxin administration using Affymetrix GeneChip arrays.[15-18] Additionally, gene intensity values of 24 healthy individuals (from GSE9006) were used as the control for samples obtained from all bacterial endotoxin administered hours, including hour 0 from the GSE3284 dataset. Using these datasets, differentially expressed gene (DEG) analysis was achieved; thus, only genes that were commonly upregulated at 2, 4, 6, 9, and 24 h after bacterial endotoxin administration were identified.

Statistical Analysis

In this study, raw data of GSE3284 and GSE9006 (24 healthy controls) as CEL files were used, and "Robust Multi-Array Average" normalization was achieved using the Bioconductor R packages. Using the linear modelling method included in the R LIMMA (version 4.2.2) package separately for all datasets, genes that differed between healthy samples and bacterial endotoxin-administered samples were identified. A p-value of <0.01 was set as the threshold value for determining statistical significance. Following DEG analyses, upregulated genes were determined in bacterial endotoxin-administered individuals at 2, 4, 6, 9, and 24 h (GSE3284) (16 individuals for 2, 9, 24 h and 14 individuals for 4 and 9 h), which were different from the genes obtained from the other 16 control individuals (0 h before administration) and healthy individuals (obtained from GSE9006).

Gene Enrichment Analysis

"ShinyGo 0.80" web-based tool was used to determine the disease types indicated by the genes that are commonly upregulated in individuals who were administered bacterial endotoxin, according to healthy internal control and 0 h samples, by selecting the "Disease. OMIM.Disease" option (http://bioinformatics.sdstate.edu/go80/).[19]

Survival Analysis

The "Kaplan-Meier (KM) Plotter" web-based tool was used to determine how the genes found to be commonly upregulated in people administered bacterial endotoxin compared with healthy controls affected survival [event-free survival (EFS) for AML and multiple myeloma (MM); relapse-free survival (RFS) for colon cancer) in cancer types (leukaemia and colorectal cancers) determined in gene enrichment analysis (https://kmplot.com/analysis/).[20] Hazard Ratio (HR) is a ratio that indicates the probability of an event (in the case of survival, this is death) in a group of cancer patients relative to the probability in a control group over a unit of time. In our study, HR was obtained as a result of survival analysis, and HR greater than 1 in KM plots means that the relevant upregulated gene has a hazardous effect on survival. When HR is less than 1, the relevant upregulated gene provides survival benefit.

RESULTS

In our study, DEG analyses were performed to determine the genes that were upregulated in individuals administered bacterial endotoxin compared with controls. As a result of the DEG analysis performed with the gene intensity data obtained from both platforms in the GSE3284 dataset, there were 415 upregulated genes obtained from the GPL96 platform, whereas this number was 202 from the GPL97 platform. After the common genes were determined, this number was determined to be 617. Gene enrichment analysis was performed using the 617 genes obtained using the ShinyGo 0.80 "Disease. OMIM.Disease" option. According to our results, the most common cancer types are leukaemia, lymphoma, and colorectal cancer (Figure 1). As seen in Table 1, the genes indicated by the detected cancer types are *MLF1, ARHGAP26, BCL3, MYB, STAT5B, KIT,* and *IKZF1* genes for leukaemia and *BCL3* and *MAD1L1* genes for lymphoma. For colon cancer, *SMAD7, MLH3*, and *TLR2* genes were determined according to the results of gene enrichment analysis.

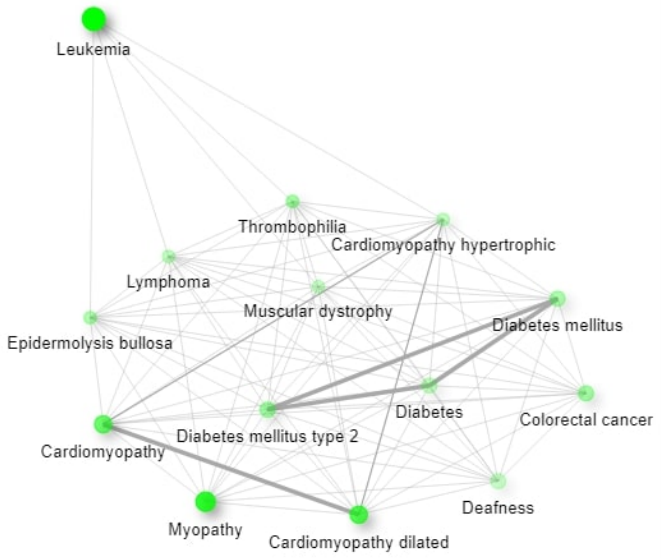

Figure 1. Upregulated acute systemic inflammation-related DEGs indicate various disease types, including cancers such as leukaemia, lymphoma, and colorectal cancers. The network figure obtained from ShinyGO 0.80 web-tool using the "Disease. OMIM.Disease" option mentioned mainly leukaemia, lymphoma, and colon cancers. In the interactive plot, two pathways (nodes) are connected if they share 20% (default) or more genes. Darker nodes are associated with more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapping genes (http://bioinformatics.sdstate.edu/go80/).

Table 1 shows the genes specific to leukaemia, lymphoma, and colorectal cancers obtained from gene enrichment analyses. The aim of our study was to determine whether genes specific to these cancers affect survival in cancer patients. Therefore, survival analysis was performed one by one for genes for AML, MM, and colon cancers using the "KM-Plotter" tool, which also includes high patient numbers. The number of patients and information about the relevant genes are shared in Table 2.

According to the results obtained from survival analysis, *SMAD7* and *TLR2*, among the three genes determined in colon cancer patients, affect survival (EFS) in a statistically significant way, and since HR value is above 1, its effect on survival is considered as "high risk of death" (Figure 2). In addition, it was determined that the *MLH3* gene did not significantly affect the survival of patients (data not shown).

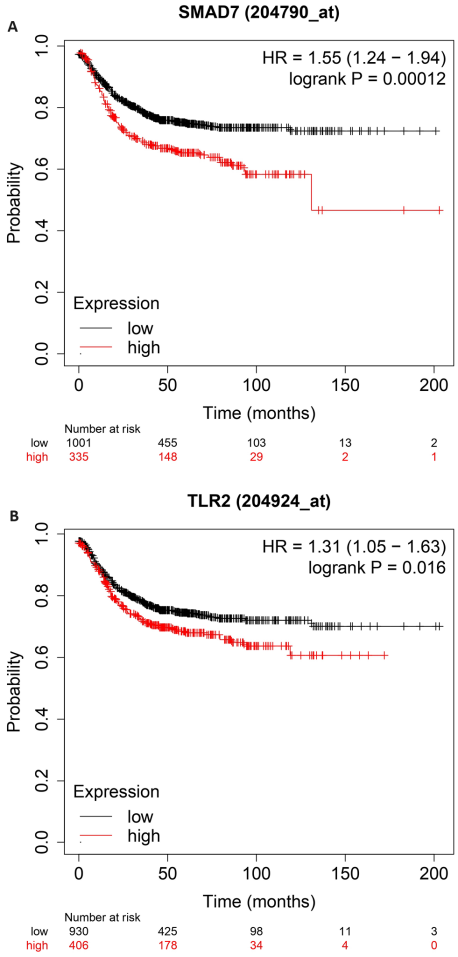

Figure 2. Upregulated *SMAD7* and *TLR2* genes indicate "high risk of death" in colon cancer patients. (A) Hazardous effect of *SMAD7* gene on RFS shown by Kaplan-Meier plot (B) Hazardous effect of *TLR2* gene on RFS shown by Kaplan-Meier plot HR > 1 means DEGs have hazardous effects on survival, HR<1 means DEGs lead to survival benefit in patients.

In our study, using the data of AML patients in KM-Plotter, survival analysis was performed with the genes determined for leukaemia according to the results of gene enrichment analyses. According to our results, while *MLF-1, STAT5B*, and *BCL3* genes had hazardous effects on survival in AML patients, *ARHGAP26* gene had a protective effect on survival (Figure 3). In addition, it was determined that the *PBT*, hlk-1 (IKZF1), and *MYB* genes did not significantly affect the survival of patients (data not shown).

Table 1. Leukaemia, lymphoma, and colorectal cancer-related upregulated genes in individuals with acute systemic inflammation.

Enrichment FDR	Number of Genes	Pathway Genes	Fold Enrichment	Pathway	Genes
3.65897672044697e-05	7	57	12.53132832	Leukemia	*MLF1, ARHGAP26, BCL3, MYB, STAT5B, KIT, IKZF1*
0.038128527	2	17	12.00480192	Lymphoma	*BCL3, MAD1L1*
0.016862797	3	31	9.874917709	Colorectal cancer	*SMAD7, MLH3,*

Explanations of all gene abbreviations are explained in Table-2.

Table 2. Number of cancer patients included in survival analysis of commonly upregulated genes in individuals with acute systemic inflammation.

	Genes and Affy IDs	Gene Description	Number of MM patients	Number of AML patients
AML and MM	*MLF1* (204783_at)	myeloid leukemia factor 1	801	525
	ARHGAP26 (226576_at)	Rho GTPase activating protein 26	559	353
	BCL3 (204907_s_at)	BCL3 transcription coactivator	801	525
	MYB (204798_at)	MYB proto-oncogene, transcription factor	801	525
	STAT5B (205026_at)	signal transducer and activator of transcription 5B	559	353
	KIT (PBT) (205051_s_at)	KIT ligand	801	525
	IKZF1 (hlk-1) (205039_s_at)	IKAROS family zinc finger 1	559	353
Colon Cancer	**Genes and Affy IDs**	**Gene Description**	**Number of CC patients**	
	SMAD7 (204790_at)	SMAD family member 7	1296	
	MLH3 (204838_s_at)	mutL homolog 3	1296	
	TLR2 (204924_at)	toll like receptor 2	1296	

MM: Multiple Myeloma; AML: Acute Myeloid Leukemia; CC: Colon Cancer; Affy IDs: Affymetrix probe IDs

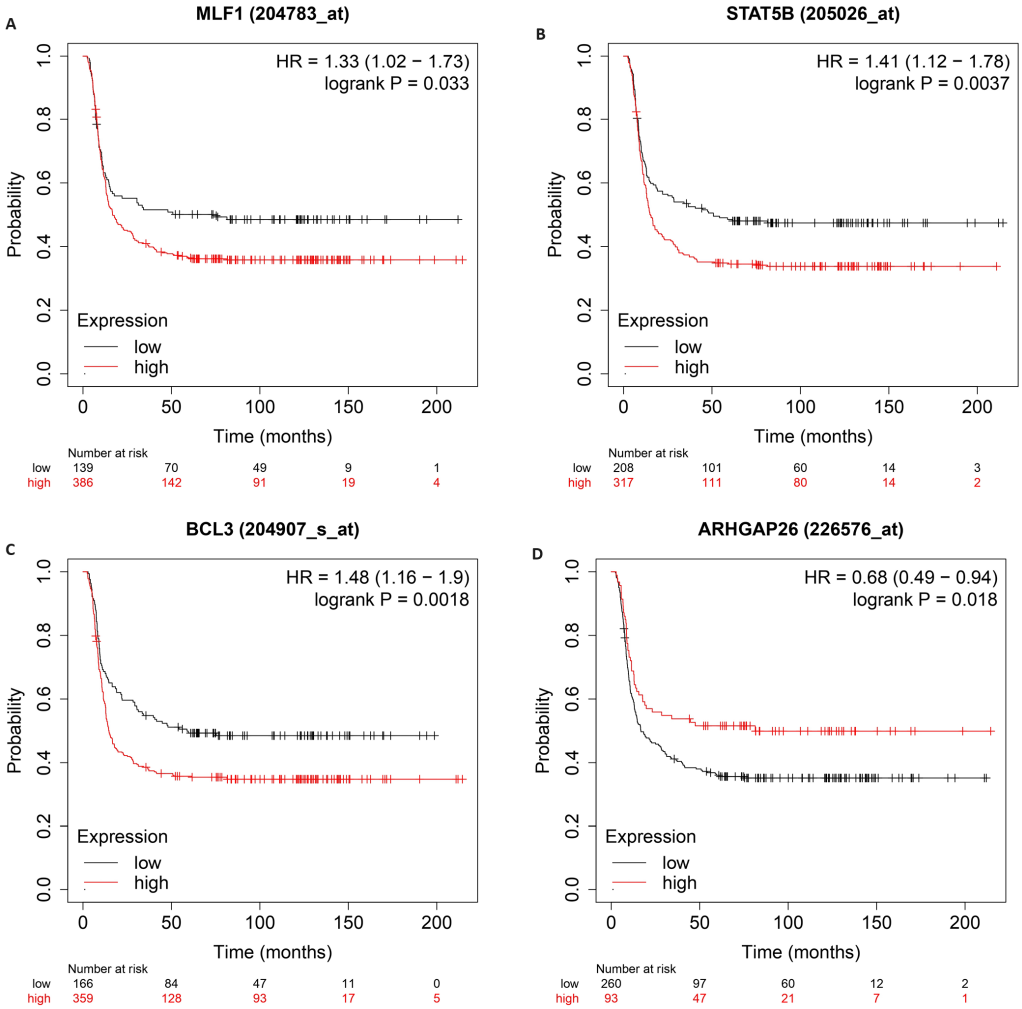

Figure 3. Upregulated *MLF-1, STAT5B*, and *BCL3* genes indicate a "high risk of death" and upregulated *ARHGAP26* gene provides "survival benefit" in AML patients. (A) Hazardous effect of *MLF1* gene on event-free survival (EFS) shown by Kaplan-Meier plot (B) Hazardous effect of *STAT5B* gene on EFS shown by Kaplan-Meier plot. (C) Hazardous effect of *BCL3* gene on EFS shown by Kaplan-Meier plot. (D) Protective effect of *ARHGAP26* gene on EFS shown by Kaplan-Meier plot. HR > 1 indicates that DEGs have hazardous effects on survival, HR<1 means DEGs lead to survival benefit in patients.

In our study, survival analysis was also performed using the genes determined for leukaemia, using the data of MM patients in KM-Plotter. According to our results, *BCL3*, *MYB*, and *IKZF1* genes had hazardous effects on survival in patients with MM, whereas *MLF-1, ARHGAP26, STSD5B*, and *PBT* genes were found to have a protective effect on survival (Figure 4).

DISCUSSION

The gene intensity data (GSE3284) of the people whose data were used in our study were originally taken from a study conducted on the genetic analysis of the acute systemic inflammation responses of human blood leukocyte cells after infection with bacterial endotoxin (LPS).[15] There are studies in literature examining the role of inflammatory responses caused by endotoxin exposure in cancer development. As summarised in a recent review article published by Jiaao Sun et al., it has been shown that endotoxin exposure triggers innate immune responses and promotes cancer in some cancers and inhibits it in some cancers.[6] In our study, the aim was to determine whether the upregulated genes triggered by endotoxins have a hazardous (high risk of death) effect on cancers or provide a survival benefit.

More than 100 trillion beneficial intestinal bacteria in the human body contribute to human health by maintaining metabolic balance. However, the situation changes when microbiome disturbance called dysbiosis occurs and exposure to crude microbial metabolites triggers cancer as well as some metabolic diseases (such as type 2 diabetes, non-alcoholic liver disease).[21-23] Studies have shown that the bacteria that make up our natural flora in the colon contribute positively or negatively to the formation and development of gastrointestinal cancers such as colon, hepatocellular and pancreatic cancers, and cholangiocarcinoma.[24] There are studies conducted on mouse models and mouse/human cell lines, albeit limited in number, showing that gut microbiota inhibits cancer formation in colorectal or colon cancers. On the other hand, it has also been

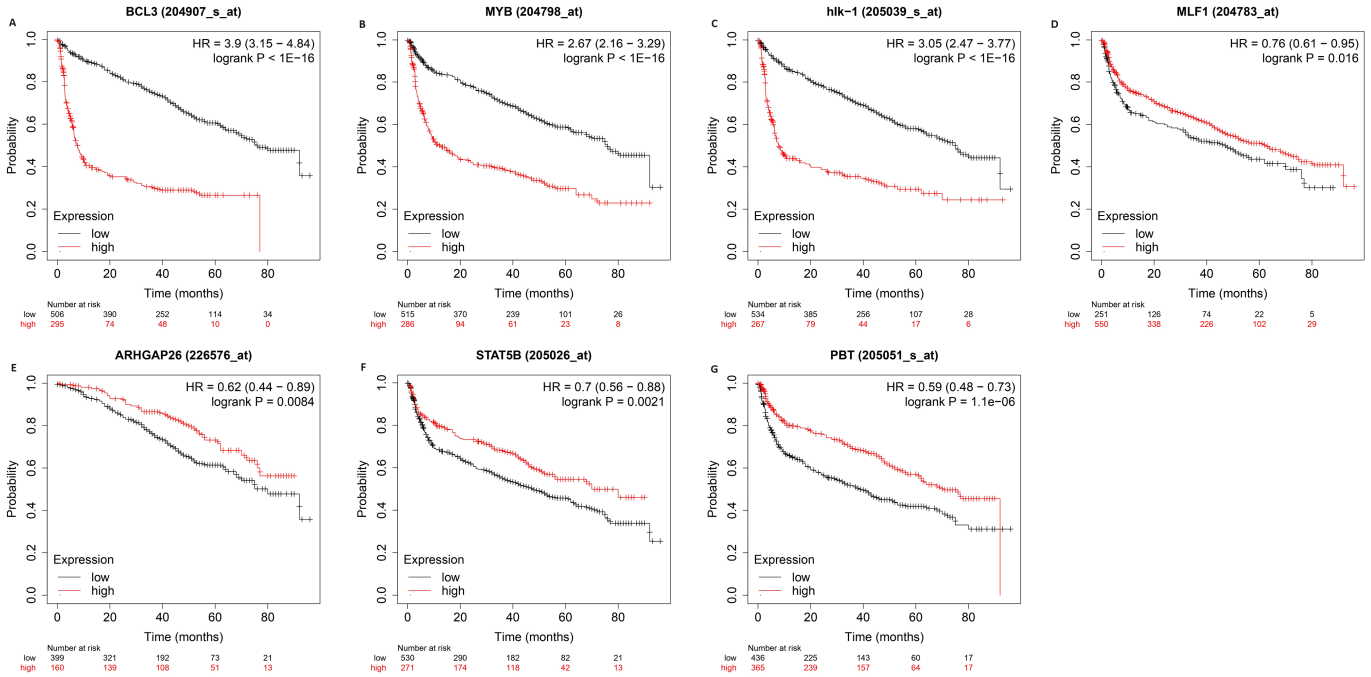

Figure 4. Upregulated *BCL3, MYB*, and *hlk-1 (IKZF1)* genes indicate "high risk of death" and upregulated *MLF-1, ARHGAP26, STSD5B*, and *PBT* genes provide "survival benefit" in MM patients. (A) Hazardous effect of *BCL3* gene on event-free survival (EFS) shown by Kaplan-Meier plot. (B) Hazardous effect of *MYB* gene on EFS shown by Kaplan-Meier plot. (C) Hazardous effect of *IKZF1 (hlk-1)* gene on EFS shown by Kaplan-Meier plot (D) Protective effect of *MLF1* gene on EFS shown by Kaplan-Meier plot (E) Protective effect of *ARHGAP26* gene on EFS shown by Kaplan-Meier plot (F) Protective effect of *STAT5B* gene on EFS shown by Kaplan-Meier plot (G) Protective effect of *PBT* gene on EFS shown by Kaplan-Meier plot HR>1 means DEGs has hazardous effects on survival, HR<1 means DEGs lead to survival benefit in patients.

shown that gut microbiota promotes cancer, mostly in colorectal cancers.[6-9] In our study, it was shown that among the genes that were upregulated in people with endotoxin exposure compared with people without endotoxin exposure, *SMAD7* and *TLR2* genes, which were found to be significant in colon cancer, negatively affected survival. Although how a gene affects survival does not mean how it affects cancer processes, it has been accepted that the detected upregulated genes have a hazardous effect on cancer development in colon cancer patients. It has been shown in the literature that the product of the *SMAD7* gene, known as an inhibitor of the transforming growth factor (TGF)-β1 signalling process in colon cancer, increases as a result of chronic intestinal inflammation and causes poorer survival.[25] In addition, while it was mentioned in this study that the *SMAD7* gene increased as a result of inflammatory bowel disease and contributed to cancer by this mechanism, its relationship with gut microflora and endotoxin exposure was not mentioned. In this respect, our study contains novel findings.[25] Another gene detected in our study is *TLR2*. In the literature, it has been shown that this gene, as a single component of the gut microbiota in mouse models, reduces the incidence of colitis-induced colon cancer by acting as a TLR agonist of *A. muciniphila*.[6,26] According to our findings, when the *TLR2* gene increases with endotoxin exposure, it causes a decrease in the survival rate of colon cancer patients; in other words, it has an increasing effect on the incidence of cancer. In addition, laboratory studies should be conducted to determine the effect of each type of bacteria in the gut microbiota on colon cancer.

According to our findings, the second type of cancer we focussed on is leukaemia. In this context, it has been shown in the literature that AML causes cancer progression *in vivo* and *in vitro* in mouse models with the effect of gut-derived LPS.[27] Additionally, restored and intact gut microbiota was found to protect genetically predisposed mice against leukemia.[28] Studies are limited to mouse models. In addition, as summarised in a review article published in 2023, it has been shown in Phase 2 clinical trials that dysbiosis complications can be prevented by transplantation of autologous gut microbiome in cancer treatments and AML, and restoration of the microbiota has been found to be important in the effectiveness of cancer therapies.[6] To the best of our knowledge, there are no studies in the literature that identify genetic levels between endotoxin exposure and leukaemia survival rate; therefore, the results of our study contain novel findings. Although *MLF-1, STAT5B*, and *BCL3* genes have not yet been related to endotoxin exposure in AML patients, alterations in these genes have contributed to survival rates of AML patients. For instance, Yuna Niu et al. indicated that *BCL3* gene overexpression is not only a promising potential prognostic marker for chronic lymphocytic leukaemia but also for AML.[29] Furthermore, *STAT* genes including *STAT5B* and its protein product have been shown to contribute to the malignancy of cells in AML patients. *STAT5B* and its protein

are also accepted as potential targets for therapies through the JAK/STAT pathway.[30,31] Furthermore, *MLF-1* gene may play roles in AML as either tumour suppressor gene or an oncogene depending on the context of the cell.[32] For instance, overexpression of *MLF-1* gene led to poor prognosis in AML.[33]

In our study, MM was also indicated as a result of gene enrichment analysis. Similar to AML patients[29], upregulated *BCL3* and *MYB* oncogenes have been associated with high proliferative capacity in myeloma cells of MM patients.[34,35] Lastly, high expression of the hlk-1 (*IKZF1*) gene has been associated with poor prognosis and low survival rates in MM patients.[36] These genes are also not related to endotoxin exposure, and further studies should be conducted.

Our study also has some limitations. For example, genes obtained from gene enrichment analyses indicate leukaemia/lymoma and colorectal cancers. However, survival analysis was performed for AML and MM cancers and colon cancer, for which data were available in the KM-plotter tool. Survival analysis should also be performed for other leukaemia types (e.g. lymphoma) and colorectal cancers for relevant genes.

CONCLUSION

In summary, the genes upregulated because of endotoxin exposure detected in our study may be targetable genes that can increase treatment efficiency in colon cancer and leukaemia, depending on how they affect survival. The genes triggered by immune responses as a result of systemic inflammation need to be confirmed by laboratory experiments in solid tissue samples in the case of colon cancer and at the level of genes obtained from peripheral blood mononuclear cells in leukaemia. Thus, treatments targeted at the genetic level will also be possible.

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