Experimed 2023; 13(2): 103-108

ORIGINAL ARTICLE

DOI: 10.26650/experimed.1284215

Comparison of Gene Expression Levels in the p53 Pathway in Blood and Bone Marrow of Healthy Individuals

Aynur Daglar Aday[1], Gozde Oztan[2], Ilknur Suer[1,3]

[1]Division of Medical Genetics, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkiye
[2]Department of Medical Biology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkiye
[3]Department of Medical Genetics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkiye

ORCID ID: A.D.A. 0000-0001-8072-0646; G.O. 0000-0002-2970-1834; I.S. 0000-0003-1954-4190

Cite this article as: Daglar Aday A, Oztan G, Suer I. Comparison of gene expression levels in the p53 pathway in blood and bone marrow of healthy individuals. Experimed 2023; 13(2): 103-108.

ABSTRACT

Objective: A bone marrow (BM) sample is largely used in the diagnosis and prognosis follow-up of many hematological malignancies. BM aspiration is a more risky and laborious technique compared to blood collection. Together with publications in which the expression levels in BM and peripheral blood (PB) are correlated for many genes, there are also conflicting publications. This may also be due to the physiological and disease state. In this study, we aimed to compare the BM and PB expression levels of genes in the p53 pathway in healthy individuals.

Materials and Methods: The study comprised 23 healthy individuals. The expressions of 22 genes in the p53 pathway were analyzed using the RT^2-profiler polymerase chain reaction (PCR) array. The expression levels were normalized to the reference gene β-actin. Then the mRNA expression levels between PB and BM sample groups were compared.

Results: The expression levels of the 20 genes studied were similar between the two groups. Only *GADD45* and *PTX3* genes were differentially expressed between PB and BM sample groups (p=0.003 and p=0.033, respectively) and those two gene expression levels were strongly correlated (r=0.886, p<0.0001).

Conclusion: When the expressions of 20 genes other than the GADD45 and PTX3 in our panel were evaluated, we suggest that PB largely reflects the p53 pathway gene expression levels in the BM. Therefore, PB may be preferred as an alternative to invasive BM in the analysis of these 20 genes in patients with hematological malignancies.

Keywords: p53 pathway, bone marrow, peripheral blood

INTRODUCTION

The canonical functions of p53 in cell division, DNA repair, cellular senescence, and cell death are well-known (1). Recent studies have shown that wild-type and mutant p53 are involved in amino acid, nucleotide, and lipid metabolism, as well as other major metabolisms such as oxidative phosphorylation, glycolysis, and redox homeostasis (2, 3). From a metabolic point of view, the p53 pathway should be considered as a non-linear pathway. Furthermore, the complex metabolic network controlled by p53 regulators and the function of p53 in these mechanisms is not fully understood (3).

Peripheral blood (PB) material includes plasma and blood cells (erythrocytes, platelets, leukocytes). Apart from blood cells, plasma contains sugar, fat, salt, and water. Blood carries nutrients and oxygen to the cells, as well as removing waste from the cells (4). PB is used in many diagnostic tests because it can be collected less invasively than most other

Corresponding Author: Gözde Öztan **E-mail:** gozdeoztan@istanbul.edu.tr
Submitted: 16.04.2023 **Revision Requested:** 23.05.2023 **Last Revision Received:** 26.05.2023 **Accepted:** 16.06.2023 **Published Online:** 07.08.2023

body materials and obtaining blood is both easier and less risky compared to bone marrow (BM) collection (5). BM is localized within the bone and is responsible for the production of blood cells. Hip and scapula bones are frequently preferred sites for

Table 1. Comparison of expressions of p53 pathway genes between bone marrow and peripheral blood samples.

Gene	Groups	Number of participants	Relative expression (mean ± SD)	Fold change	p-value
BAX	BM	8	0.3273 ± 0.91941	1.15	0.353
	PB	15	0.0036 ± 0.00072		
CDKN2A	BM	8	0.0005 ± 0.00138	0.72	0.330
	PB	15	0.0000 ± 0.00001		
APAF1	BM	8	0.0084 ± 0.01071	1.94	0.456
	PB	15	0.0054 ± 0.00073		
ATM	BM	8	0.0021 ± 0.00414	2.03	0.430
	PB	15	0.0009 ± 0.00034		
ATR	BM	8	0.0016 ± 0.00342	1.13	0.309
	PB	15	0.0003 ± 0.00008		
CASP9	BM	8	0.0026 ± 0.00513	1.46	0.432
	PB	15	0.0011 ± 0.00016		
CDK4	BM	8	0.0036 ± 0.00623	0.68	0.249
	PB	15	0.0009 ± 0.00021		
CDKN1A	BM	8	0.0021 ± 0.00273	2.47	0.850
	PB	15	0.0019 ± 0.00060		
CHEK2	BM	8	0.0031 ± 0.00763	0.40	0.316
	PB	15	0.0002 ± 0.00005		
E2F1	BM	8	0.0007 ± 0.00081	0.46	0.066
	PB	15	0.0001 ± 0.00006		
E2F3	BM	8	0.0021 ± 0.00126	0.99	0.286
	PB	15	0.0016 ± 0.00023		
MCL1	BM	8	0.0781 ± 0.05242	0.98	0.350
	PB	15	0.0593 ± 0.01336		
MDM2	BM	8	0.0165 ± 0.03737	1.09	0.393
	PB	15	0.0045 ± 0.00103		
MDM4	BM	8	0.0013 ± 0.00183	1.31	0.555
	PB	15	0.0009 ± 0.00031		
PTEN	BM	8	0.0196 ± 0.01991	0.91	0.362
	PB	15	0.0127 ± 0.00146		
RB1	BM	8	0.0281 ± 0.07244	0.42	0.336
	PB	15	0.0016 ± 0.00036		
P53	BM	8	0.0482 ± 0.12947	0.64	0.353
	PB	15	0.0027 ± 0.00052		
BCL2	BM	8	0.3217 ± 0.90720	0.38	0.351
	PB	15	0.0009 ± 0.00035		
CHEK1	BM	8	0.0091 ± 0.02359	0.09	0.315
	PB	15	0.0001 ± 0.00002		
GADD45	BM	8	0.0011 ± 0.00063	0.10	**0.003**
	PB	15	0.0001 ± 0.00002		
PCNA	BM	8	0.0263 ± 0.04768	0.23	0.202
	PB	15	0.0026 ± 0.00059		
PTX3	BM	8	0.0035 ± 0.00357	0.06	**0.033**
	PB	15	0.0002 ± 0.00009		

PB: Peripheral blood; BM: Bone marrow

BM extraction (6). BM aspiration from these regions is highly invasive and local anesthesia is applied during the procedure. It has been reported that these anesthetics may have side effects that lead to various neurodevelopmental disorders, particularly in children (7). Allogeneic hematopoietic stem cell transplantation in adults with hematological malignancies is increasingly performed using PB-derived stem cells rather than BM. It is possible to donate PB-derived stem cells for convenience and safety reasons as well as logistical reasons, which have been behind the growth of this stem cell source (8).

Gene expression analyses in samples from PB mononuclear cells and different tissues are not always the same. Results from a single tissue are not sufficient to explain how expression changes affect complex biological systems in human beings (9). Limited studies compare PB and BM samples in terms of expression patterns. As a result of our detailed investigation, no study was present in the literature comparing the *p53* pathway gene expression levels in healthy individuals. *HMG-CoA reductase gene (HMGCR)* and *low-density lipoprotein receptor (LDLR)* gene expressions in the PB and BM samples of myelodysplastic syndrome (MDS) patients have been reported to be upregulated similarly when compared to blood samples of healthy controls (10). Apoptosis stimulating effect of p53 protein 2 (*ASPP2)* gene expression in PB and BM samples from chronic lymphoblastic leukemia (CLL) patients has been reported to be downregulated in the same way when compared to blood samples from healthy controls. In the same study, it was shown that the level of gene expression in the PB and BM samples of the patients were similar (11).

The p53 pathway genes, mainly p53, respond to stress during cell division (12). However, tumor protein p53 (TP53) is the most frequently genetically altered gene in both solid and hematological cancers (13). Other genes involved in this pathway have not been elucidated as p53. In order to understand the similar and different aspects of PB and BM aspirate materials in terms of p53 pathway genes, we aimed to compare the differential expression patterns of 22 genes ATM serine/threonine kinase *(ATM)*, Bcl-2 associated X-protein (*BAX*), cyclin-dependent kinase 4 *(CDK4)*, cyclin dependent kinase inhibitor 2A *(CDKN2A),* checkpoint kinase 1 *(CHEK1),* checkpoint kinase 2 *(CHEK2),* cyclin dependent kinase inhibitor 1A *(CDKN1A),* Ataxia Telangiectasia and Rad3 related *(ATR),* growth arrest and DNA damage inducible alpha *(GADD45A),* mouse double minute 2 homolog *(MDM2),* mouse double minute 4 *(MDM4),* proliferating cell nuclear antigen *(PCNA),* retinoblastoma 1 *(RB1),* caspase 9 *(CASP9),* tumor protein P53 *(TP53)*, B-cell lymphoma 2 *(BCL2),* apoptotic peptidase activating factor 1 *(APAF1),* E2F transcription factor 1 *(E2F1),* E2F transcription factor 3 *(E2F3),* myeloid cell leukemia 1 *(MCL1),* pentraxin 3 *(PTX3),* phosphatase and tensin homolog *(PTEN)* selected from the p53 pathway involved in cell growth, proliferation, differentiation, DNA repair and apoptosis processes.

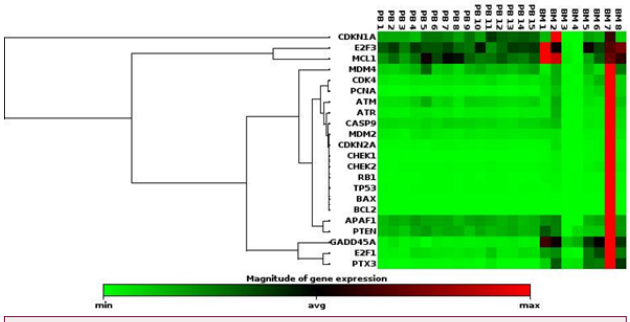

Figure 1. The average of the fold change for PB and BM samples were shown in heatmap graphs. The heat map is a graphical representation of the RT^2-PCR array's findings about the differential regulation of gene expression between the peripheral blood and bone marrow samples. The intensity of the colors reveals the degree of change in gene expression. Low gene expression (ratio<1) in PB samples is shown in green. Genes with a ratio close to 1 are shown as black squares. Gene expression in the red squares is greater than in the BM samples (ratio>1).

MATERIALS AND METHODS

Samples

PB and BM samples were collected in sterile tubes containing EDTA, after obtaining written informed consent from 23 healthy volunteers. PB samples were taken from healthy hospital personnel without a history of leukemia, and BM samples were taken from BM transplantation donor candidates in the Istanbul University Faculty of Medicine, Department of Hematology. The median age of 50.95 years was observed among 10 males (43.4%) and 13 females (56.5%). The study protocol was designed in accordance with the Declaration of

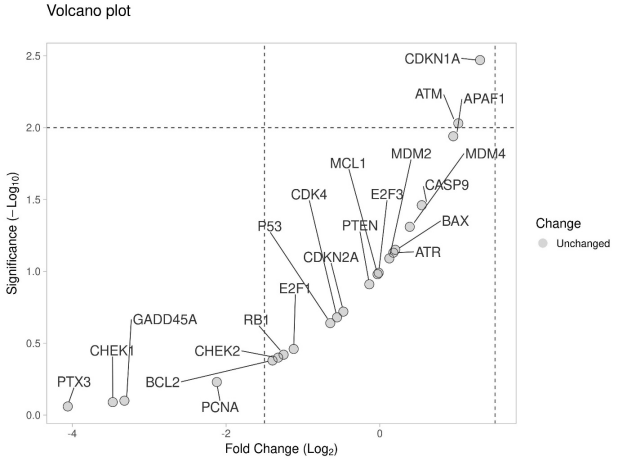

Figure 2. A volcano plot was generated showing the gene expressions of BM samples versus PB samples. Distributions of fold changes in gene expression are shown using volcano plots. BM samples compared with PM samples. p-values less than 0.05 and absolute fold changes of 2 were considered significant. No significant variation in fold alterations of genes was observed.

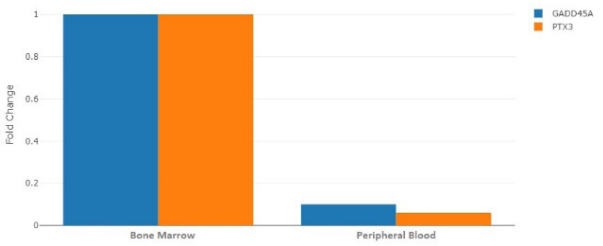

Figure 3. Comparison of the *GADD45* and *PTX3* gene expression in PB and BM samples. Fold-change ($2^{-\Delta\Delta CT}$) is the ratio of the normalized gene expression ($2^{-\Delta CT}$) in the PB sample to the normalized gene expression ($2^{-\Delta CT}$) in the BM sample. Fold-change values higher than one indicate a positive regulation, also known as an up-regulation, whereas fold-change values lower than one indicate a negative regulation, also known as a down-regulation.

Helsinki. The study was conducted with the ethical approval obtained from the Clinical Research Ethics Committee of Istanbul University Faculty of Medicine (E-29624016-050.99-876968/ May 9, 2022).

RNA Isolation and cDNA Synthesis

Total RNA from whole blood and BM samples were extracted using the QiaAmp RNA Blood Mini Kit (Qiagen, USA). RNA quality and quantity were measured using NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, USA). A template of 1 µg of total RNA was used in cDNA synthesis. cDNA synthesis was performed on a LightCycler 480 II platform using Qiagen RT²HT First Strand Kit (Qiagen, USA).

Expression Analysis via qRT-PCR Array

qRT-PCR array using a custom RT² - Profiler PCR array (CAPH_133446F; cat no. 330131/12 plate) was conducted to analyze the mRNA expressions of 22 genes involved in proliferation, differentiation, cell cycle, DNA repair, and apoptosis processes intervened by the p53 pathway. The study was carried out on a LightCycler 480 II platform using SYBR Green master mix and 1 µl cDNA sample. The gene expression levels were analyzed and normalized with the β-actin housekeeping gene. The Livak method was used to calculate relative gene expression levels (14).

Statistical Analysis

Statistical analysis was carried out using the SPSS package program, version 21. Statistical analysis of the expression levels of the genes in the BM aspirate and PB was carried out using the Student's t-test. Pearson correlation analysis was conducted to determine the expression correlations of genes that were statistically significant between the groups. $p<0.05$ was determined as the cut-off value for statistical significance.

RESULTS

Two of the p53 pathway genes *(GADD45* and *PTX3*) we investigated in our study were found to have different expression levels between BM and PB. The fold change in expression of these two genes between the groups (BM/PB) was 0.1 and 0.06, respectively. It was found that *GADD45A* and *PTX3* gene expressions were significantly decreased in BM samples compared to PB samples ($p=0.003$ and $p=0.033$, respectively) (Table 1). However, there was no statistical difference in the expression levels of *APAF1, ATM, BAX, CDKN1A, CDKN2A, MDM2, MCL1, MDM4, PTEN, CASP9, ATR, CHEK2, E2F1, E2F3, RB1, TP53, BCL2, CDK4, CHEK1,* and *PCNA* genes between the two groups (Table 1). The averages of the fold change for PB and BM samples were shown in heatmap graphs (Figure 1). A volcano plot was generated showing the gene expressions of BM samples versus PB samples (Figure 2). Comparison of the gene expressions of the genes that are differentially expressed (*GADD45, PTX3*) are shown in the bar graph (Figure 3).

According to the results of the Pearson correlation analysis, it was observed that the *GADD45* gene showed a high correlation with the expressions of the *APAF1, ATR, CDK4, E2F1, PTEN, PCNA, PTX3* genes ($r=0.7$; $p<0.001$). In addition, the *PTX3* gene showed a high correlation with the expressions of *BAX, CDKN2A, APAF1, ATM, ATR, CASP9, CDK4, CHECK2, E2F1, MDM2, MDM4, PTEN, RB1, TP53, BCL2, CHECK1, GADD45* and *PCNA* genes ($r=0.7$; $p<0.001$). The correlation between *GADD45* and *PTX3* was quite high ($r=0.886$, $p<0.0001$).

DISCUSSION

Transcription factor p53, which is one of the major tumor suppressor genes, affects the expression of many genes by targeting more than thousands of sites (15). p53 plays a role in the regulation of many cellular metabolic functions. In addition, p53 is also involved in various processes, including the regulation of growth factors and reactive oxygen species, which have an impact on cancer pathogenesis (16). Disturbances in the p53 pathway play a more active role in some hematological cancers like chronic lymphoblastic leukemia (CLL) and multiple myeloma (17, 18). Hematological cancers are malignancies of BM-derived cells. BM aspiration biopsy, which is important in the diagnosis and routine follow-up of patients, is an invasive technique that is very uncomfortable for the patient and has risks compared to PB collection. It is very important to determine the expression patterns of p53 pathway genes in PB and BM, as they may contribute to the same mechanisms. To the best of our knowledge, our study is the first to compare the differences in mRNA levels and correlations of p53 pathway genes between PB and BM samples.

However, there are various studies in the literature investigating different gene expression states in PB and BM samples of patients with hematological cancers. Crassini et al. examined the expression profile of 260 genes in PB, BM, and lymph node-derived CLL cells. They reported that approximately half of these

genes were reduced in PB-induced CLL cells compared to other groups (19). In another study comparing the expression levels of PB and BM samples taken from CLL patients, it was stated that there was not much difference in *Bcl-2, ADAM29, Mcl-1*, *ZAP70,* and *LPL* genes in this sense (20). In their study on acute myeloid leukemia patients, Sakhinia et al. did not find any difference in the expression of some genes *(leptin receptor, CD33, adipsin, proteoglycan 1, MB- 1, cyclin D3, hSNF2b, proteasome iota, HkrT-1,* and *E2A),* but they found significant changes in the expression of some other genes *c-myb, HOXA9, LYN, cystatin c* and *LTC4s* (21). In a study conducted on patients with chronic myeloid leukemia, it was reported that BCR-ABL transcript levels were correlated in PB and BM samples, and PB could be used instead of BM in routine monitoring (22). Moreover, van Leeuwen-Kerkhoff et al. reported that *MRC1, CSF3R, XCR1, CLEC9A* and *IRF8KI* gene expressions were correlative in BM and PB-derived myeloid dendritic cell subgroups (23).

Low fold change value detected in *GADD45* and *PTX3* genes and the presence of insignificant gene expression levels in other p53 pathway genes may indicate the similarity of PB and BM with respect to p53 pathway gene expressions.

Members of the GADD45 family, which are defined as stress sensors, are triggered by environmental stress such as inflammatory cytokines and genotoxic agents (24, 25). They also regulate genomic stability, senescence, cell survival and apoptosis (24). Apoptosis is induced when DNA damage is fatal or GADD45A arrests cell cycle progression. The hematopoietic system might benefit from GADD45A's ability to induce terminal differentiation in damaged stem and progenitor cells, as well as DNA repair and genomic stabilization (26). The impact of GADD45 proteins on tumor growth depends on the molecular structure of the activated oncogene, as well as the cell type in which it is expressed and the signaling pathways with which it is currently interacting (25). Exemplarily, GADD45a is both expressed independently of p53 and is a p53 target gene (27).

The second gene, *PTX3* which is a multifunctional protein, plays an important role in immunity, inflammation, and extracellular matrix organization/remodeling (28). In studies investigating the role of *PTX*3, it has been reported that it is expressed in different cells such as macrophages, neutrophils, and smooth muscle cells (29). According to the data we obtained from our study, a strong correlation was identified between *GADD45* and *PTX3* gene expression levels. Because of the similar mRNA levels between PB and BM, we think that PB may reflect the BM expression pattern for the other p53 pathway genes we analyzed.

As a limitation of our current study, the number of the participants was relatively small, that's why it should be considered as a preliminary study and should be confirmed by further studies encompassing larger PB and BM groups.

In this present study that aimed to compare the expression levels of the important genes in the p53 pathway, we detected a statistically significant difference between the expression patterns of only two genes (*GADD45A, PTX3)* in the PB and BM out of 22 genes. The fact that no statistically significant difference was observed in the expression of the other 20 genes in both groups suggested that these two groups may have similar characteristics in terms of *p53* pathway genes. Therefore, a PB sample, which is easier and less invasive to obtain, may be a convenient alternative to examine the expressions of genes in the p53 pathway instead of the BM sample.

Ethics Committee Approval: This study was approved by Clinical Research Ethic Committee of Istanbul Faculty of Medicine (E-29624016-050.99-876968/ May 9, 2022).

Authors' Contributions: Conception/Design of Study – A.D.A., G.O., I.S.; Data Acquisition – A.D.A., G.O., I.S.; Data Analysis/Interpretation – A.D.A., G.O., I.S.; Drafting Manuscript– A.D.A., G.O., I.S.; Critical Revision of Manuscript- A.D.A., G.O., I.S.; Final Approval and Accountability– A.D.A., G.O., I.S.

Note: All authors have contributed equally to this work.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Kruiswijk F, Labuschagne CF, Vousden KH. p53 in survival, death and metabolic health: a lifeguard with a licence to kill. Nat Rev Mol Cell Biol 2015; 16(7): 393-405.
2. Lacroix M, Riscal R, Arena G, Linares LK, Le Cam L. Metabolic functions of the tumor suppressor p53: Implications in normal physiology, metabolic disorders, and cancer. Mol Metab 2020; 33: 2-22.
3. Lahalle A, Lacroix M, De Blasio C, Cissé MY, Linares LK, Le Cam L. The p53 pathway and metabolism: The tree that hides the forest. Cancers (Basel) 2021; 13(1): 133.
4. Cowin SC, Cardoso L. Blood and interstitial flow in the hierarchical pore space architecture of bone tissue. J Biomech 2015; 48(5): 842-54.
5. Schraw JM, Woodhouse JP, Bernhardt MB, Taylor OA, Horton TM, Scheurer ME, et al. Comparison of the blood, bone marrow, and cerebrospinal fluid metabolomes in children with b-cell acute lymphoblastic leukemia. Sci Rep 2021; 11(1): 19613.
6. Lucas D. Structural organization of the bone marrow and its role in hematopoiesis. Curr Opin Hematol 2021; 28(1): 36-42.
7. Banerjee P, Rossi MG, Anghelescu DL, Liu W, Breazeale AM, Reddick WE, et al. Association between anesthesia exposure and neurocognitive and neuroimaging outcomes in long-term survivors of childhood acute lymphoblastic leukemia. JAMA Oncol 2019; 5(10): 1456-63.
8. Holtick U, Albrecht M, Chemnitz JM, Theurich S, Shimabukuro-Vornhagen A, Skoetz N, et al. Comparison of bone marrow versus peripheral blood allogeneic hematopoietic stem cell transplantation for hematological malignancies in adults - a systematic review and meta-analysis. Crit Rev Oncol Hematol 2015; 94(2): 179-88.
9. Pinhel MAS, Noronha NY, Nicoletti CF, Quinhoneiro DCG, Oliveira BAP, Cortes-Oliveira C, et al. Comparison of gene expression profile between blood cells and white adipose tissue of patients with obesity. Nutr Hosp 2017; 34(3): 608-12.

10. Ellis MH, Baraf L, Shaish A, Har-Zahav A, Harats D, Ashur-Fabian O. Alteration of lipids and the transcription of lipid-related genes in myelodysplastic syndromes via a TP53-related pathway. Exp Hematol 2012; 40(7): 540-7.
11. Schittenhelm MM, Illing B, Ahmut F, Rasp KH, Blumenstock G, Döhner K, et al. Attenuated expression of apoptosis stimulating protein of p53-2 (ASPP2) in human acute leukemia is associated with therapy failure. PLoS One 2013; 8(11): e80193.
12. Harris SL, Levine AJ. The p53 pathway: positive and negative feedback loops. Oncogene 2005; 24(17): 2899-908.
13. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. Nature 2013; 502(7471): 333-9.
14. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods 2001; 25(4): 402-8.
15. Simabuco FM, Morale MG, Pavan ICB, Morelli AP, Silva FR, Tamura RE. p53 and metabolism: from mechanism to therapeutics. Oncotarget 2018; 9(34): 23780-823.
16. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100(1): 57-70.
17. Ilknur S, Aynur A, Sariman M, Mesut A, Hindilerden IY, Ekmekci SS, et al. Dysregulation of MS4A3 and PRDX5 gene expression in multiple myeloma patients. Int J Hem Oncol 2021; 31(4): 205-13.
18. Öztan G, Aktan M, Palanduz S, İşsever H, Öztürk S, Nikerel E, et al. Relationship between chromosomal aberrations and gene expressions in the p53 pathway in chronic lymphocytic leukemia. Balkan J Med Genet 2020; 23(1): 15-24.
19. Crassini KR, Shen Y, Christopherson R, Stevenson WS, Mulligan S, Best OG. Analysis of mRNA expression in peripheral, bone marrow and lymph node dervied CLL Cells using the nanosting ncounter platform. Blood 2017; 130(1): 4279.
20. Wiestner A, Marti GE, Billings EM, Liu H, Lee E, White T, et al. Differential gene expression in CLL cells from bone marrow and peripheral blood suggests a role of bone marrow stroma in leukemic cell proliferation. Blood 2005; 106(11): 708.
21. Sakhinia E, Farahangpour M, Tholouli E, Liu Yin JA, Hoyland JA, Byers RJ. Comparison of gene-expression profiles in parallel bone marrow and peripheral blood samples in acute myeloid leukaemia by real-time polymerase chain reaction. J Clin Pathol 2006; 59(10): 1059-65.
22. Jiang Q, Zhao XY, Qin YZ, Liu YR, Lai YY, Jiang B, et al. The differences and correlations of BCR-ABL transcripts between peripheral blood and bone marrow assays are associated with the molecular responses in the bone marrow for chronic myelogenous leukemia. Am J Hematol 2012; 87(12): 1065-9.
23. Van Leeuwen-Kerkhoff N, Lundberg K, Westers TM, Kordasti S, Bontkes HJ, Lindstedt M, et al. Human bone marrow-derived myeloid dendritic cells show an immature transcriptional and functional profile compared to their peripheral blood counterparts and separate from Slan+ non-classical monocytes. Front Immunol 2018; 9: 1619.
24. Guo D, Zhao Y, Wang N, You N, Zhu W, Zhang P, et al. GADD45g acts as a novel tumor suppressor, and its activation suggests new combination regimens for the treatment of AML. Blood 2021; 138(6): 464-79.
25. Liebermann DA, Tront JS, Sha X, Mukherjee K, Mohamed-Hadley A, Hoffman B. Gadd45 stress sensors in malignancy and leukemia. Crit Rev Oncog 2011; 16(1-2): 129-40.
26. Wingert S, Thalheimer FB, Haetscher N, Rehage M, Schroeder T, Rieger MA. DNA-damage response gene GADD45A induces differentiation in hematopoietic stem cells without inhibiting cell cycle or survival. Stem Cells 2016; 34(3): 699-710.
27. Yamasawa K, Nio Y, Dong M, Yamaguchi K, Itakura M. Clinicopathological significance of abnormalities in Gadd45 expression and its relationship to p53 in human pancreatic cancer. Clin Cancer Res 2002; 8(8): 2563-9.
28. Garlanda C, Bottazzi B, Magrini E, Inforzato A, Mantovani A. PTX3, a humoral pattern recognition molecule, in innate immunity, Tissue Repair, and Cancer. Physiol Rev 2018; 98(2): 623-39.
29. Inoue K, Kodama T, Daida H. Pentraxin 3: A novel biomarker for inflammatory cardiovascular disease. Int J Vasc Med 2012; 2012: 657025.