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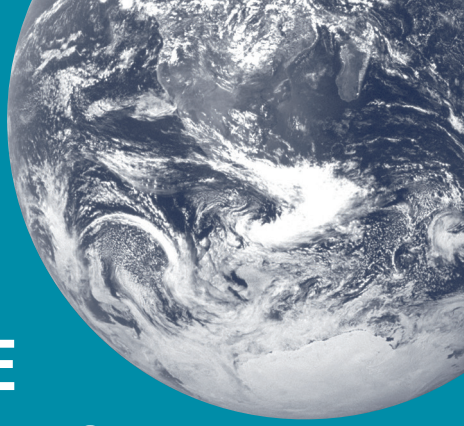

THE EXPRESSION OF THE TP53 GENE IN VARIOUS CLASSES OF ACUTE MYELOID LEUKEMIA

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Abstract – *Objective:* *Investigation of the underlying mechanisms involved in disease pathogenesis can open new insights into therapeutic strategies for patients with acute myeloblastic leukemia. A genetic mutation in TP53 (Tumor Protein 53) gene is detected in most malignancies and considered a key element in the determination of treatment planning due to its prognostic value; however, there are insufficient data for the evaluation of the amount of p53 expression as the product of the TP53 gene especially in hematologic malignancies such as acute myeloid leukemia (AML). The aim of this study was to evaluate p53 expression deregulation, according to different subtypes of acute myeloid leukemia.*

Patients and Methods: *Eighty-two new cases of AML and twelve healthy, normal control volunteers entered into this study with informed consent. The levels of p53 expression were examined using relative quantitative Real-time PCR (polymerase chain reaction). Statistical analyses were performed by t-test, one-way ANOVA and Tukey test using SPSS software.*

Results: *M3 and non M3 groups had a significant decrease in p53 expression in comparison with normal controls (30% and 20% of normal levels, respectively). Also, M3 patients showed apparently higher levels of p53 expression compared with other subtypes of AML.*

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Conclusions: *According to the results of the present study, there is an overall reduction in the level of p53 expression in patients with AML, meanwhile p53 showed differential expression in AML subtypes and M3 subtype showed higher expression in comparison with other AML subtypes. It suggests that p53 expression has a possible relation with granulocyte maturation and prognosis. Further investigations are needed to clarify the exact role of p53 expression fluctuations in AML patients as basic molecular events in malignant cells.*

KEYWORDS: *Acute myeloid leukemia, p53, Gene expression.*

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal disorder of hematopoietic system resulted from genetic and epigenetic abnormalities in hematopoietic stem cells[1,2]. This condition can alter gene expression and disrupt normal cell growth and differentiation. Since most of the deregulated genes belong to tumor suppressor or oncogene families; all vital aspects of the cell function such as cell cycle, differentiation, survival, and cell signaling will be changed in the direction of cancer formation[3-7]. Detection of the underlying mechanisms of AML pathogenesis is the basis of prognosis determination and risk stratification of patients which are essential in choosing appropriate therapeutic approaches[8,9]. In this regard, 17 p 13.1 deletions that usually affect tumor suppressor gene TP53 (encoding the p53 protein) are of the most critical factors in the risk stratification of AML patients although these mutations are infrequent in these patients[10,11]. Moreover, till now studies proved that P53 has a crucial role in all vital aspects of cell biology, including cell cycle, apoptosis, autophagy and DNA repair[12,13]. Genetic alterations of the p53 gene such as mutations are also commonly found in different types of cancer, such as lung, esophageal, colorectal, ovarian cancers, and leukemia[14,15]. While the appearance of destructive mutations is the main way for tumorigenesis in solid tumors; it seems that these genetic abnormalities do not have the same importance in leukemogenesis[16-18]. On the other hand, epigenetic modifications seem to be essentially involved in leukemia formation and development in accompany with the gene mutation. In this way, different mutations of TP53 (especially TP53 deletions) have been observed in approximately half of the human tumors, although they are detected in just 11 % of hematologic malignancies[19,20]. Insofar TP53 mutations have been demonstrated in 4.5-15 % of different AML sub-classes, although interestingly, they have not been reported in acute promyelocytic leukemia (APL) [5]. In addition, recent studies have demonstrated a deregulated pattern of expression of key genes involved in hematopoiesis in hematologic malignancies[21-27]. Despite the importance of p53 mutations in the formation and progression of different kinds of malignancies and their association with poor overall survival (OS) in AML patients, the significance of the deregulated expression of p53 has not been considered well in patients with AML[28-30]. In this study, we showed that p53 has deregulated expression in acute myeloid leukemia patients and it has a somewhat different expression in different subclasses of AML.

PATIENTS AND METHODS

Patients and risk stratification

These study examinations were conducted on 82 AML patients and 12 bone marrow (were obtained from bone marrow (BM) banking) and peripheral blood (PB) samples (from healthy volunteers) which were considered as normal controls. Mononuclear cells were collected from the BM and PB samples of patients and control groups.

QRT-PCR (synthetized by RevertAid First Strand cDNA Synthesis Kit)

Real-time PCR assay was carried out using SYBR™ Green Real-time PCR Master Mixes (Amplicon, Denmark). The primer sequences were P53 forward: AGGCTGTGTTCAAGTGGTTCTGA, P53 Reverse: ACAAAAATTAGCGGGGCGTGG. ABL (housekeeping gene for normalization) forward: AGTCTCAGGATGCAGGTGCT and ABL reverse: TAGGCTGGGGCTTTTTGTAA. RNA was isolated from mononuclear bone marrow and peripheral blood cells by Raeasy Kit (Qiagen, Hilden, Germany). The cDNA (cDNA was synthetise by RevertAid First Strand cDNA Synthesis Kit) products were amplified by PCR for p53 gene in conditions: 10 min at 95°C, then 40 cycles at 95°C for 15 s and 60°C for 30 s. The expression level of target genes was analyzed by the $2^{-\Delta\Delta CT}$ method and p53 gene expression was normalized against ABL as a reference gene.

The ethical issue

The study was approved by the Institutional Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1395.58). The protocols are in agreement with the Helsinki Decla-

ration. The written informed consent was obtained from each patient before inclusion. Patients were classified according to French-American-British (FAB).

Statistical analysis

Gene expression levels were calculated using $2^{-\Delta\Delta Ct}$ and Livak formula. The normal distribution of the genes was confirmed by the Shapiro-Vilk and Kolmogorov-Smirnov tests. Statistical analysis was performed using the SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) and the level of significance was considered as $p < 0.05$. Data means differences among patients and control groups were analyzed using the *t*-test. According to the patient's classification, a one-way ANOVA test was used for normal distributions. Dunnett sample was used to test the relationship between subgroups individually with the control group. Tukey test was also used to examine the relationship between subgroups.

RESULTS

Profile of patient sample specifications

This study was performed using 82 samples obtained from *de novo* AML patients of different genders and ages and 12 normal controls from healthy volunteers with an informed context (Table I). Patients were divided into different subtypes according to FAB/WHO classification as follows: 9 cases of M0, 18 cases of M1, 12 cases of M2, 27 cases of M3, 10 cases of M4, 6 cases of M5. There were no cases of M6 and M7 in this study (Table I).

P53 expression in AML and healthy patients

The mean Ct values (± SD) of ABL and p53 were 30.49 ± 1.64 and 25.38 ± 1.80 in normal samples, respectively. We also measured the ABL and p53 expression in 82 *de novo* AML patients using the same technique. The obtained values of ABL and p53 were 28.78 ± 3.44 and 25.35 ± 2.30, respectively. The Ct values obtained are indicative of strong positive reactions with abundant target nucleic acids. Subsequently, the Ct values obtained from p53 were normalized against the internal reference gene and ABL for both AML positive and normal control group samples. A statistical comparison was then made between the normalized values of AML-positive and normal control group samples, which revealed a significant difference ($p < 0.0000023$) between p53 expression and healthy patients (Figure 1). The mean expression level (± SD) measured of p53 for the AML-positive cases and the normal controls were 7.88 ± 2.12 and 30.22 ± 3.10, respectively. The expression level in the range of 95 % confidence interval, defined for the p53 average expression level in the healthy population, was considered at 17.36 - 43.03 and this analysis revealed that 12.19% of AML positive patients carried an intermediate p53 gene expression. Expression levels that fell below the threshold of the intermediate ranges for p53 were defined as low expression levels, 0.0041–0.79 in p53 and observed in 87.81% of AML-positive patients.

TABLE 1. Characteristics of patients.

Data	*Characteristics*
Genus	45 male/ 37 female
Age	2-87 years
Classification (FAB)	N
M0	9
M1	18
M2	12
M3	27
M4	10
M5	6
Grouping (based on differentiation)	N
Without differentiation	39
Granulocyte differentiation	27
Monocyte differentiation	16

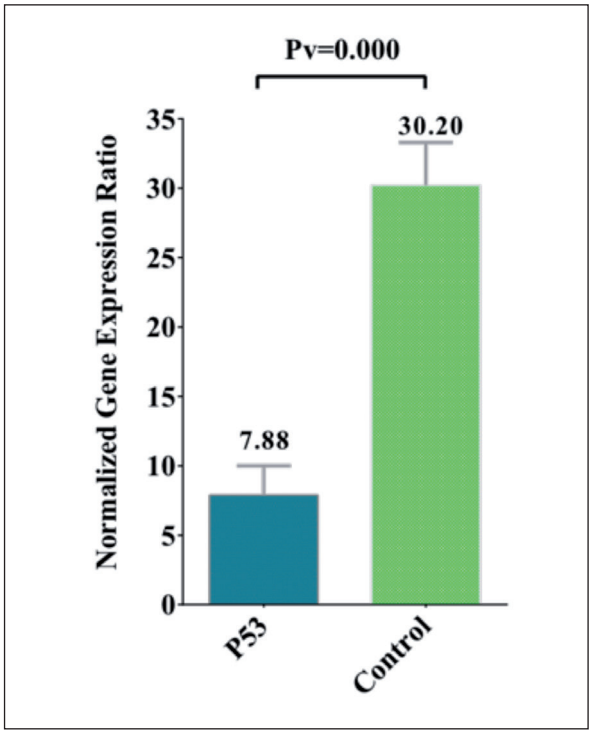

Fig. 1. Relative expression of p53 in 82 AML patients and 13 healthy patients was measured from Ct values and normalized against a reference gene (ABL). A significant difference ($p<0.0001$) between p53 expression in AML patients and healthy patients was identified. A relative p53 expression level of 7.88 ± 2.12 (SD) was measured in AML patients in comparison to 30.22 ± 3.10 (SD) in the normal control group. *P*v=*p*-value, *P*v<0.05 is significant.

Differential expression of p53 in FAB subtypes of AML

The differential expression of p53 between the different FAB subtypes expressed in AML patient samples was evaluated by the ANOVA test. Statistically, there was no significant difference between the different FAB subgroups, but it was intuitively different; the low expression of p53 (± SEM) was observed in M3 (9.29 ± 4.32) and non-M3 (6.64 ± 2.21) respectively. However, in comparison to the normal control group, these subgroups show a significant reduction ($p < 0.0001$ and $p = 0.002$, respectively), without any correlation between these subgroups together (Figure 2). The lowest expression was seen in M0 and the highest expression was seen in M5 in the non-M3 patient (without M3). The mean of gene expression was higher in non-M3 sub-group, although the difference was no significant (Figure 2).

DISCUSSION

Since the disruption of p53 pathway components is highly frequent in initiation and progression of different malignancies[13,15,21,28,29], it's crucial to evaluate

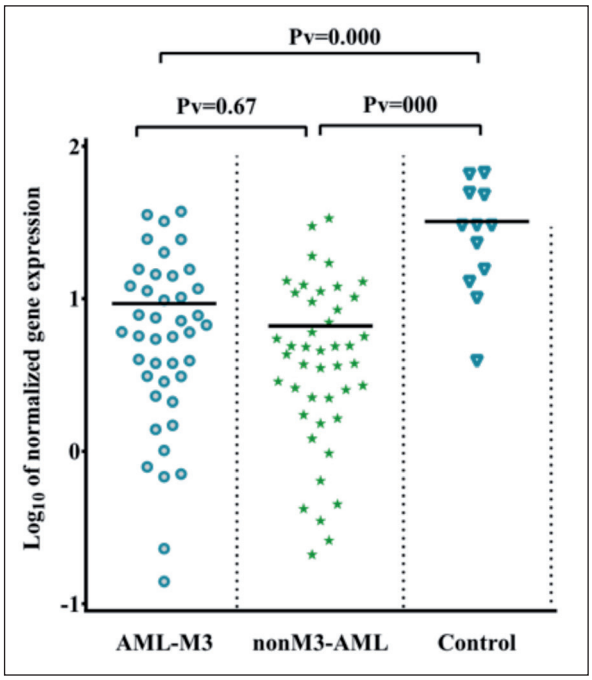

Fig. 2. The relative expression of p53 measured in 82 AML patients are grouped by their corresponding FAB subgroup and analysis by means of the ANOVA test determines that there is no significant difference in expression between these subgroups. The relative expression of p53 was measured at 9.29 ± 4.32 (SEM) in the nonM3 subgroup and at 6.64 ± 21 (SD) in the M3 subgroup. The M3 and non-M3 subgroups have a significant reduction in comparison to the normal control group ($p<0.000$ for both of them). There is no significant difference in p53 expression between these subgroups. *Pv*=*p*-value, $P<0.05$ is significant.

p53 gene and all its relevant aspects in neoplastic cells. In this study, gene expression levels of p53 reduced in both M3 and non-M3 AML patients (0.30741 and 0.21972 fold, respectively). Although previous studies detected p53 gene mutations in different kinds of human malignancies and p53 mutations have been reported in a significant number of human cancers; the frequency of mutations was unexpectedly lower in AML patients in comparison with other human cancers[16,31]. Due to the crucial role of the p53 pathway in maintaining cell integrity, it is strongly suggested that the rate of p53 abnormalities should be limited to gene mutations while the gene expression abnormalities can cause the same effect as well, but unfortunately it has been neglected. Moreover, studies demonstrated that patients with p53 mutations have a poor prognosis, refractory disease and short-term survival[32,33]. In spite of the critical role of p53 abnormalities in cancer development and its strong prognostic impacts, there is no comprehensive study on p53 expression, especially in hematologic malignancies. In this regard, the results of the present study declared that the p53 gene expression decreased in 87.81% of patients; these data clearly indicate that gene expression abnormality may be more important than gene mutation as our data showed p53 expression reduction in the majority of AML patients and universally in all subtypes of AML. Despite the fact that we detected an overall reduction in p53 expression in AML patients, different studies performed on the cell line or non-clinical samples showed somewhat different results. For instance, Shikami et al[34] reported the decreased level of p53 protein in t(8;21) positive AML cells but they observed no changes in mRNA level. However, we did not evaluate the p53 protein level in our samples, but it is supposed to have lower levels of p53 protein in patients with reduced p53 mRNA levels. On the other hand, while we showed an overall reduction of the p53 in non-M3 patients, Fu et al[35] indicated that after ectopic expression of AML1-ETO fusion genes, the AML1-ETO fusion protein attaches to AML1 binding site and induces the early growth response gene 1 (EGR1) expression and, thereafter, p53 and PTEN expression. Nevertheless, these studies were done in different contexts or using cell lines, which were basically different from our evaluation. In another study, Bellodi et al[36] claimed that PML/RARa fusion gene inhibits p53 transcription and subsequently, eradicates the growth suppression and apoptosis effects of p53[36]. Though in the present study, there was a bit more p53 expression level in M3 patients, it seems that patients with PML-RARα mutation (M3 subtype) exhibit a lower reduction of tumor suppressor genes such as p53 compared to the non-M3 group. Since there is a high relevance between PML-RARα modification and differentia-

tion procedure, it could be proposed that apparently higher level of p53 gene expression in AML-M3 patients suggest the role of p53 in differentiation progress. In addition, it can be expressed that p53 level may also be related to the overall survival and response to therapy because of the good prognosis for the PML-RARα mutation[21,37]. Therefore, p53 expression could also be considered as a possible invaluable prognostic marker and an indicator of relapse risk that may yield new therapeutic options. However, it needs to be evaluated in a larger patient group in a different context.

CONCLUSIONS

The results of the present study showed that there is an overall reduction in the level of p53 expression in AML patients, meanwhile, p53 had differential expression in AML subtypes and M3 patients demonstrated higher expression compared to other AML subtypes. So, it suggests that the p53 expression has a possible relation with granulocyte maturation and prognosis. Further investigations are needed to clarify the exact role of p53 expression fluctuations in AML patients as basic molecular events in malignant cells.

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Abbreviations

AML: Acute myeloid leukemia, APL: Acute Promyelocytic Leukemia

Author contribution

All authors contributed to the design of the research. AA, MHM, FM, HAN, SP, MRK and MAF collected the Data. AA, MHM, FM, HAN, SP, MRK, MAF and ZKH conducted analysis and interpretation of data. AA, MHM, FM, HAN, SP, MRK and MAF edited the first draft. All authors reviewed, commented and approved the final draft.

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Ethical approval

All the procedures performed in the studies involving human participants were in accordance with the Ethical standards of the Local Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1395.58) as well as 1964 Helsinki Declaration. Written informed consent was obtained from all patients and normal subjects.

Conflict of interest

The authors declare that they have no conflict of interest.

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