Original Article

ADAR1 Gene Polymorphism and Hematological Analysis in Responders and Relapse Patients with Chronic Myeloid Leukemia

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Abstract

Background: Chronic myeloid leukemia (CML) is defined by the Break point cluster region and Abelson Genes (BCR-ABL) fusion gene, which produces a continuously active tyrosine kinase known as the primary driver responsible for initiating and sustaining the disease. The RNA editing enzyme adenosine deaminase acting on double-stranded RNA 1 (ADAR1) converts adenosine into inosine in double-stranded RNA substrates. This enzymatic process is crucial in cellular RNA editing and can impact disease progression and therapeutic responses in CML. **Objective:** Analysis of ADAR1 gene polymorphisms, ADAR1 levels, and hematological parameters in Iraqi patients with CML. **Materials and Methods:** From January 2021 to February 2023, one hundred and twenty samples of whole blood were collected from patients with CML at the National Center of Hematology/Mustansiriyah University. The control group in this study comprised thirty samples of fresh whole blood. Total DNA genomic extraction was done to detect the ADAR1 gene polymorphism by sequencing. Furthermore, serum was used to detect ADAR1 enzyme level. **Results:** According to the age and male/female ratio, the patients' groups were matching with control group. A group of CML patients on treatment, 65 out of 100 patients were on imatinib, while 35 were treated with other tyrosine kinase inhibitors. The patient groups in terms of age and gender ratio were matched with the control group. Among CML patients receiving treatment, 65 out of 100 were using imatinib, while 35 were treated with other tyrosine kinase inhibitors. In the newly diagnosed CML group, ADAR mutations were present in 35% of cases, and among treated CML patients, this proportion was 36%, whereas the control group showed no mutations ($P < 0.001$). The distribution of DNA polymorphisms—A/G, G/T, and G/G—was 42%, 30%, and 28%, respectively, among patients with CML, compared to 34%, 20%, and 46%, respectively, in the control group. There are significant differences between different groups according to genotyping of ADAR1 ($P < 0.05$). Based on ADAR1 mutation, there is a significant difference observed between the newly diagnosed CML group and the CML patients in the treatment group compared to the control group ($P < 0.001$). Specifically, the differences between the new diagnosis CML group and the treatment group were not statistically significant ($P = 0.326$). Furthermore, both the new diagnosis CML group and the relapse group showed significant differences compared to the control group ($P < 0.001$). The P value associated with the correlation between ADAR mutation and these groups is <0.001, indicating a highly significant correlation. **Conclusion:** The current findings suggest that ADAR1 polymorphisms and ADAR1 enzyme levels in Iraqi patients with CML could potentially influence disease progression and deepen our understanding of its mechanisms. These factors may also contribute to disease development and affect how patients respond to treatment.

Keywords: Adenosine deaminase acting on double-stranded RNA 1 enzyme level, ADAR1 polymorphism, chronic myeloid leukemia, mutation, sequencing

Introduction

Although advanced malignancies are diverse in phenotype, they often exhibit stem-cell properties, including enhanced survival, differentiation, quiescence, and self-renewal potential.[1,2] Early insights into the molecular pathogenesis of cancer stemmed from the discovery of the Philadelphia chromosome (Ph+) and

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its constitutively active *BCR-ABL1* tyrosine kinase in chronic myeloid leukemia (CML).[3-5] Tyrosine kinase inhibitor (TKI) therapy targeting *BCR-ABL1* suppresses CML during the chronic phase (CP) of the disease in most patients able to tolerate long-term therapy.[6] Although the chronic phase of CML can often be managed effectively for extended periods using standard TKI therapies, additional genetic and epigenetic changes eventually drive the expansion of progenitor cells. This leads to the development of self-renewing leukemia stem cells, which contribute to disease progression, transformation into blast crisis, and resistance to TKIs.[7,8]

RNA editing is an important posttranscriptional process able to increase transcriptome and proteome.[9-11] In humans, the most common type of RNA editing is mediated by ADAR enzymes, which convert adenosine into inosine within double-stranded RNA (dsRNA). This modification is mediated by two adenosine deaminases acting on dsRNA: adenosine deaminase acting on dsRNA 1 (ADAR1) (ADAR) and ADAR2 (ADARB1), whose function is tightly regulated. ADAR1 has at least two protein isoforms, a constitutive p110 and an inducible p150. Although the p110 isoform is found in the nucleus, the p150 isoform, due to its nuclear export sequence, is also present in the cytoplasm.[12,13]

In particular, ADAR1 has been shown to be essential for the proliferation and differentiation of cells of both erythroid and myeloid lineage.[14,15] Lineage commitment toward myeloid differentiation is a complex, multistep mechanism marked by distinct transcriptional and translational changes, including the expression of specific cell surface markers and epigenetic modifications, leading to typical morphological changes.[16]

Furthermore, TKI discontinuation usually results in CML resurgence, suggesting that quiescent progenitors persist despite therapy.[17] Mutations in spliceosome genes and alternative splicing of coding and noncoding RNAs are increasingly recognized as significant contributors to transcriptomic diversity, driving leukemic progression and therapeutic resistance. Additionally, previous studies have shown extensive RNA editing in the human transcriptome, mainly in primate-specific Alu sequences. Alu sequences (Arthrobacter luteus restriction endonuclease elements) are the most abundant transposable elements, with over one million copies spread throughout the human genome, promoting splice isoform diversity.[18-20] RNA editing activity is mediated by the ADAR family of editases,[21] which includes ADAR1 (also known as ADAR), ADAR2 (ADARB1), and ADAR3 (ADARB2). ADAR1 and ADAR2 are active in embryonic cell types, and ADAR3 may play a nonenzymatic regulatory role in RNA editing activity.[22]

ADAR enzymes regulate fetal and adult hematopoietic stem cell maintenance and stem cell responses to inflammation.[23] ADAR-mediated adenosine-to-inosine (A-to-I) RNA editing in an Alu sequence containing dsRNA hairpin structures[20] can generate alternative donor or acceptor splice sites,[24] alter RNA structure,[21] modulate regulatory RNAs and gene silencing activities,[25] and introduce codon sequence alterations.[25] Interestingly, ADAR deregulation has been implicated in a variety of malignant cell types.[26] However, the functional effects of RNA editing in leukemia have not been elucidated.

This study aims to analyze the molecular characteristics of ADAR1 gene polymorphisms, investigate ADAR1 mutations, and measure the levels of the ADAR1 enzyme in patients with CML.

Materials and Methods

This case-control study involved 120 individuals diagnosed with CML from the National Center of Hematology. Of these, 20 were newly diagnosed CML patients, while the remaining 100 were patients who had been treated with TKIs. Sixty-five patients out of 100 were treated with imatinib and 35 CML patients were on other TKIs.Out of the 100 patients, 69 responded to treatment, while 31 did not. Additionally, 30 healthy individuals were included as the control group. The CML group and the control group were matched for age and gender. Blood samples of 5 milliliters were collected from both patients and controls. These samples were divided into 2 milliliters in an EDTA tube for detecting ADAR1 single-nucleotide polymorphism (SNP) and 3 milliliters of serum for measuring the ADAR1 enzyme levels. The inclusion criteria for the study were newly diagnosed CML patients and treated patients in the chronic phase (CP), some of whom were in remission, regardless of sex.

The study included patients newly diagnosed with chronic myeloid leukemia (CML) as well as those currently undergoing treatment, specifically those in the chronic phase (CP), including those in remission, regardless of gender. Participants aged 18 to 65 years who were receiving treatment with tyrosine kinase inhibitors (TKIs) were eligible. Excluded from the study were individuals under 18, pregnant or breastfeeding women, and patients with active systemic infections.

Study groups

Blood from each group of CML patients in the study should be collected and categorized into:

1. Group of blood samples from patients with CML
2. Blood of apparently healthy persons as the control group.

Sample collection

Blood samples were collected from CML patients and from apparently healthy individuals serving as the control group at the National Center of Hematology, Mustansiriyah University, between June 2022 and February 2023.

Detection of single-nucleotide polymorphism of adenosine deaminase acting on double-stranded RNA 1 by sequencing

Genomic DNA was extracted from the blood of both patients and control groups using a DNA extraction kit (G-SPIN-INTRON\KOREA).

Determining the hematological parameters

A complete blood count was conducted using a 5-part differential autoanalyzer hematology machine (Icon5 OP/ Hungary) for all patients and controls.

Estimation of serum adenosine deaminase acting on double-stranded RNA 1 enzyme level

The concentration of ADAR 1 enzyme level in serum is quantitatively evaluated through the utilization of a sandwich enzyme immunoassay technique known as ELISA. This approach involves the utilization of a kit provided by (My BioSource, USA).

Ethical permission was obtained for this investigation, ensuring adherence to the ethical principles derived from the Declaration of Helsinki. Before obtaining a sample, the patient's verbal and analytical consent was obtained.

Statistical analysis

To assess the significance of the variables under investigation in this study, the Chi-square test was employed. All statistical analyses were conducted using the SPSS Version 23 software ELISA kit (My BioSource, USA). $P < 0.05$ was deemed to indicate statistical significance.

Results

Age and sex distribution among groups

The age of the patient groups was matched with that of the control group ($P = 0.62$). The sex ratio in the newly diagnosed group was 1.5, and in the treated group, it was 1.08, both of which matched the sex ratio of 1.5 in the control group ($P = 0.56$) [Table 1].

Hematological and genetic abnormalities in chronic myeloid leukemia patients' group

At diagnosis, the white blood cell (WBC) count means 173.5 × 10^9/. Leukocytosis of more than 100 × 10^9/L was noted in 80% of cases. The mean hemoglobin (Hb) was 12.1 g/l.The average platelet count was 283 × 10^9/L. Among the CML patients receiving treatment, 65 out of 100 were taking imatinib, while the remaining 35 were treated with other TKIs such as nilotinib and bosutinib. WBC count means 7.75 × 10^9/. The mean Hb was 12.3 g/l. The mean platelet count was 323 × 10^9/L. In the newly diagnosed CML group, ADAR mutations were found in 35% of cases, whereas among CML patients undergoing treatment, ADAR mutations were present in 36% of cases, compared to a negative result finding in the control group [Table 2].

Results of adenosine deaminase acting on double-stranded RNA 1 sequencing among study groups

The exact position of the adenosine deaminase acting on the double-stranded RNA 1 gene

In this study, the ADAR1 genetic sequences were located on chromosome 6. The 480 bp amplicons of this gene were investigated, and using the NCBI BLAST engine, approximately 99.5% sequence similarity was observed between the sequenced samples and the intended reference target sequences. These sequences completely covered the exon-1 sequences for ADAR1, as annotated in previous human genome annotations (GenBank acc. rs201331183; rs747829977; rs766724113) as shown on Table 3.

The accurate positions and additional details of the retrieved PCR fragments were identified in Tables 4-6 by comparing the observed DNA sequences of the investigated samples with the retrieved DNA sequences (GenBank acc. rs201331183; rs747829977; rs766724113).

Table 1: Age and sex distribution between patients with chronic myeloid leukemia groups and controls groups

Parameters	Patients (*n*=120)		Controls (*n*=80)	*P*
	New diagnosis (*n*=20)	CML patients on treatment (*n*=100)		
Age±SD	35±12.1	51±11.89	44±13.7	0.62
Sex, *n* (%)				
Male	12 (60)	52 (52)	18 (60)	0.565
Female	8 (40)	48 (48)	12 (40)	
Male/female ratio	1.5:1	1.08	1.5	

CML: Chronic myeloid leukemia, SD: Standard deviation

Table 2: Hematological and molecular changes in chronic myeloid leukemia groups in comparison to the control group

Parameters	Patients (*n*=120)		Controls (*n*=30)
	New diagnosis (*n*=20)	CML patients on treatment (*n*=100)	
WBC±SD (×10^9/L)	173.5±88.13	7.7±5.47	6.6±0.75
Platelets±SD (×10^9/L)	283±138	323±312	246.6±56.3
Hb±SD (g/dL)	12.1±1.65	12.3±1.65	13.1±1.4
PCV±SD (%)	36.9±5.21	37.5±6.9	40.1±4.5
ADAR mutation			
Positive	7 (35)	36 (36)	0
Negative	13 (65)	64 (64)	30 (100)

CML: Chronic myeloid leukemia, SD: Standard deviation, ADAR: Adenosine deaminase acting on double-stranded RNA, WBC: White blood cell, Hb: Hemoglobin, PCV: Packed cell volume

Table 3: Observed DNA sequences of adenosine deaminase acting on double-stranded RNA 1 sample with the retrieved DNA sequences (GenBank acc. rs201331183; rs747829977; rs766724113)

SNPs	rs201331183	rs747829977	rs766724113
Clinical significance	Likely-benign	Not reported in clinvar	Not reported in clinvar
Wild	AA	AA	GG
Varaiation	A>G	A>G	G>T

SNPs: Single-nucleotide polymorphisms

Table 4: Genotyping of adenosine deaminase acting on double-stranded RNA 1 gene (480 bp) gene in comparison with the NCBI referring sequences (GenBank acc. no. NC_000012.12)

Zygosity status	CML, *n* (%)	Control, *n* (%)	Position in PCR fragment	Position in the reference genome	OR (95%)	SNP type	Significant	Variant summary
A/G	21 (42)	17 (34)		201331183	1.8 (0.40–2.43)	3′-UTR	0.04	201331183G/C
G/T	15 (30)	10 (20)	103	766724113	1.98 (0.41–3.77)	3′-UTR	0.03	rs766724113G/T
G/G	14 (28)	23 (46)		747829977	0.98 (0.41–3.77)	3′-UTR	0.06	rs747829977G/G
Totals	50	50						
Allele								
G	53	40			1.73 (0.65–1.89)		0.029	
T	47	60						

SNP: Single-nucleotide polymorphism, OR: Odds ratio, CML: Chronic myeloid leukemia, PCR: Polymerase chain reaction, NCBI: National Centre for Biotechnology Information

Table 5: Comparison between new chronic myeloid leukemia, treated patients and control groups according to adenosine deaminase acting on double-stranded RNA 1 enzyme level

Parameters	Patients (*n*=120)		Controls (*n*=30)	*P*
	New diagnosis (*n*=20)	On treatment (*n*=100)		
ADAR±SD enzyme	9.3±5.8	10.7±7.4	2.9±1.88	0.326* <0.001** <0.001***

*Comparison between new diagnosis CML and on treatment patients, **Comparison between new diagnosis CML patients and control group, ***Comparison between treated patients with CML and control subjects. CML: Chronic myeloid leukemia, SD: Standard deviation, ADAR: Adenosine deaminase acting on double-stranded RNA

Table 6: Comparison between new diagnosis chronic myeloid leukemia, patients in response state and on treatment relapse in adenosine deaminase acting on double-stranded RNA 1 enzyme level

Parameters	New diagnosis (*n*=20)	On treatment (*n*=100)		*P*
		Response to treatment (*n*=69)	Relapse (*n*=31)	
ADAR±SD enzyme	9.3±5.8	9.17±7.95	14.4±4.71	0.73* <0.001** <0.001***

*Comparison between new diagnosis CML and response to treatment patients, **Comparison between new diagnosis CML patients and relapse patients, ***Response to treatment patients and relapse patients. CML: Chronic myeloid leukemia, SD: Standard deviation, ADAR: Adenosine deaminase acting on double-stranded RNA

The sequencing chromatogram of the identified variation, as well as its detailed annotations, was documented, and the chromatogram of this sequence was shown according to its position in the PCR amplicon. With regard to G > T, it was demonstrated that this SNP was identified in a heterozygous (G/T) pattern as well as a homozygous variation (A/G) pattern.

Genotyping of adenosine deaminase acting on double-stranded RNA 1 polymorphism

According to the present findings, the distribution of DNA polymorphisms was as follows: A/G, G/T, and G/G accounted for 42%, 30%, and 28%, respectively, in patients with CML, and 34%, 20%, and 46%, respectively, in the control group. There are significant statistical differences ($P < 0.05$) between different groups according to genotyping of ADAR1 [Table 4 and Figure 1].

Nucleoide sequences of ADAR1 submission in NCBI

The samples were deposited in NCBI with the accession numbers LC775144, LC775145, LC775146, and LC775147 for the nucleotide sequences of ADAR1.

Comparison of ADAR1 enzyme levels between CML patient groups and a control group

The comparison between newly diagnosed patients and those on treatment ($p = 0.326$) indicates that there is no statistically significant difference in ADAR1 levels between these two patient subgroups. The ADAR1 levels in both the newly diagnosed group ($p < 0.001$) and the treatment group ($p < 0.001$) are significantly higher compared to the control group, indicating a statistically significant difference.

Comparison of ADAR1 enzyme levels among newly diagnosed CML patients and on-treatment patients (responders and relapse patients)

Regarding ADAR enzyme levels, there are statistically significant differences between the newly diagnosed CML group and both the relapse group and the control group ($P < 0.001$). However, there are no statistical differences between the newly diagnosed group and patients who are in response state and on treatment response ($P < 0.73$) [Table 6].

Comparison of ADAR1 enzyme levels among newly diagnosed CML patients and patients receiving different TKIs

To the ADAR enzyme level, there were no statistical significant differences between all groups [Table 7].

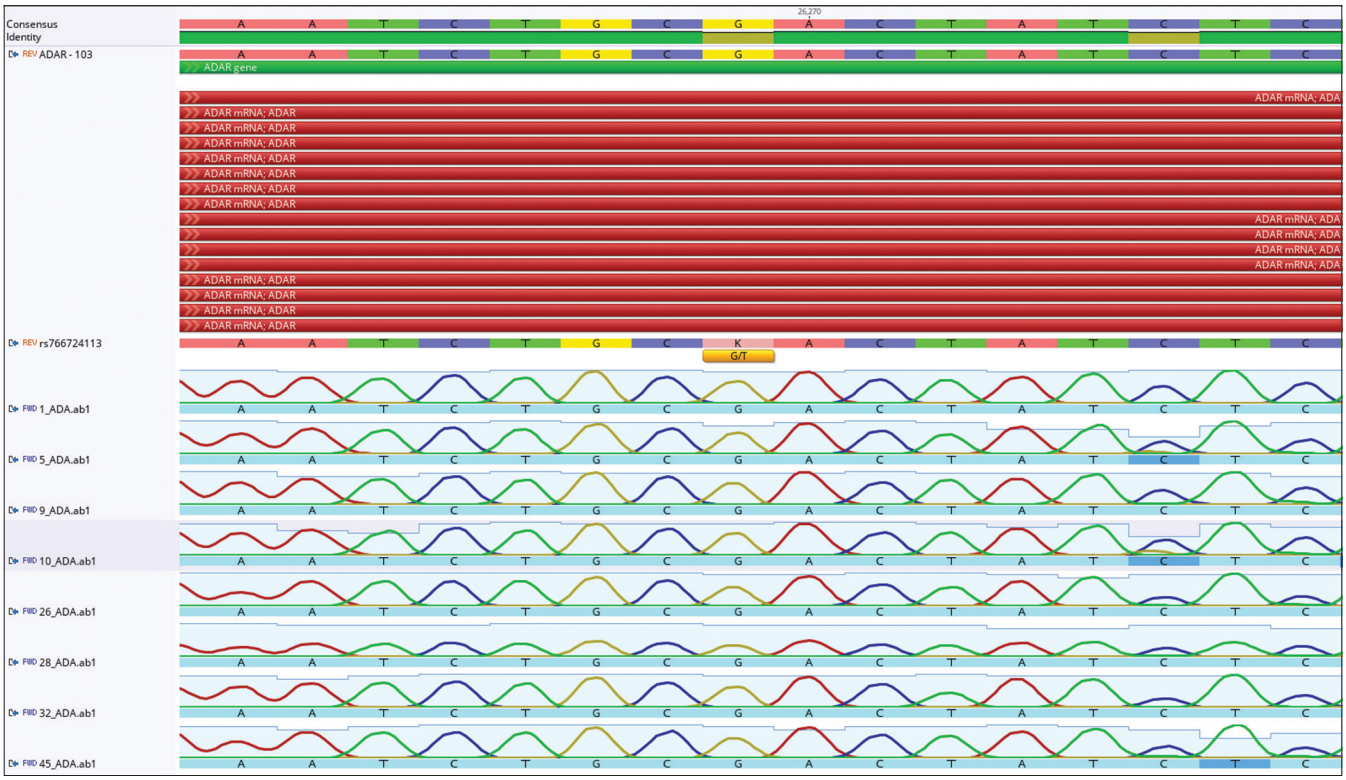

Figure 1: The single-nucleotide polymorphisms (SNP's) novelty checking of *ADAR1* genetic single-nucleotide polymorphisms using the dbSNP server. The identified 103G>T SNP. The GenBank acc. no. NC_ rs766724113 was used in the positioning of the highlighted substitution SNP. The position of the targeted sequences was found in the negative strand

Table 7: Comparison between new diagnosis chronic myeloid leukemia, patients on imatinib and patients on other tyrosine kinase inhibitors according to adenosine deaminase acting on double-stranded RNA 1 enzyme level

Parameters	New diagnosis (*n*=20)	CML patients on treatment (*n*=100)		*P*
		On imatinib (*n*=65)	Other tyrosine kinase inhibitors (*n*=35)	
ADAR±SD enzyme	9.3±5.8	10.19±8.4	11.9±5.1	0.663* 0.088** 0.272***

*Comparison between new diagnosis CML and patients on imatinib, **Comparison between new diagnosis CML patients and patients on other tyrosine kinase inhibitors, ***Comparison between patients on imatinib and patients on other tyrosine kinase inhibitors. CML: Chronic myeloid leukemia, SD: Standard deviation, ADAR: Adenosine deaminase acting on double-stranded RNA

Adenosine deaminase acting on double-stranded RNA 1 mutation distribution among study groups

The ADAR1 mutation was found in 7 (35%) out of 20 patients in new diagnosis CML patients and 36 patients (36%) had ADAR1 mutation out of 100. The *P* value associated with the correlation between ADAR mutation and the groups was <0.001, indicating a highly significant association [Table 8].

ADAR1 mutations were detected in 10 (14.5%) out of 69 CML patients who responded to treatment, compared to 26 patients (84%) with ADAR1 mutations among the 31 patients who did not respond to treatment. The P-value for the correlation between ADAR mutation and treatment response is < 0.001, indicating a highly significant association [Table 9].

Receiver operating characteristic curve to predict new chronic myeloid leukemia patients with control group

According to the Table 10 which summarizes the area under the curve (AUC) between new diagnosis CML patients, the ADAR enzyme variable shows a higher AUC of 0.705. The associated $P = 0.015$ suggests that the observed AUC is statistically. The associated $P = 0.015$ suggests that the observed AUC is statistically significant. The 95% confidence interval for the AUC ranges from 0.562 to 0.848 [Table 10]. In summary, the ADAR enzyme variable shows superior discriminatory capability.

Discussion

It is not generally clear whether ADAR1 and ADAR2 play the same or different roles in human cells. Our study focused on the role of ADAR enzymes in human myeloid leukemia cells, finding that they are both overexpressed in cells undergoing differentiation to monocyte/macrophage lineage. Our findings revealed distinct regulation patterns for the two ADARs during myeloid differentiation: ADAR1 is gradually modulated

Table 8: Distribution of adenosine deaminase acting on double-stranded RNA 1 mutation between chronic myeloid leukemia patient's groups

Mutations	New diagnosis (*n*=20)	CML patients on treatment (*n*=100)	*P*
ADAR1, *n* (%)			
Positive	7 (35)	36 (36)	<0.001
Negative	13 (65)	64 (64)	

CML: Chronic myeloid leukemia, ADAR1: Adenosine deaminase acting on double-stranded RNA 1

Table 9: Distribution of adenosine deaminase acting on double-stranded RNA 1 mutation between chronic myeloid leukemia patient's response to treatment and not respond

Mutations	CML patients on treatment (*n*=100)		*P*
	Responder (*n*=69)	Nonresponder (*n*=31)	
ADAR1, *n* (%)			
Positive	10 (14.5)	26 (84)	<0.001
Negative	59 (85.5)	5 (16)	

CML: Chronic myeloid leukemia, ADAR1: Adenosine deaminase acting on double-stranded RNA 1

Table 10: Summarized the area under curve between new diagnosis patients with chronic myeloid leukemia

	AUC			
Test result variable(s)	Area	*P*	Asymptotic 95% CI	
			Lower bound	Upper bound
ADAR enzyme	0.705	0.015	0.562	0.848

The test result variable(s): ADAR enzyme has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. AUC: Area under the curve, CI: Confidence interval, ADAR1: Adenosine deaminase acting on double-stranded RNA 1

throughout maturation, whereas ADAR2 experiences a sharp increase during differentiation. Of note, ADAR1 has been found to be required for normal hematopoiesis and for promoting malignant progenitor reprogramming in CML.[23,24,27] Consistently, we observed that primary myeloid leukemia blasts from 13 AML patients, as well as two myeloid leukemia cell lines, express detectable, albeit variable, levels of ADAR1.

However, when the ADAR1-silenced U-937 cells were PMA-differentiated *in vitro*, ADAR1 expression failed to increase without this interfering with the course of cell differentiation, indicating a lack of ADAR1 involvement within this process. This finding is further confirmed by the lack of increase in ADAR1 expression, which remained stable in leukemia blasts undergoing *in vitro* PMA differentiation. On the contrary, ADAR2 also in this case was strongly upregulated, as already observed in the two myeloid cell lines. The above observation indicates that, differently from ADAR1, ADAR2 is not necessary or even detrimental for blast homeostasis, as suggested by the observation that ADAR2 is eliminated through the ubiquitin–proteasome degradation pathway. However, ADAR2 might play some role afterward when cells stop duplicating and proceed through differentiation.[28]

ADAR-mediated RNA editing can control various molecular processes, such as RNA interference, microRNA function,[29] RNA stability, localization, nuclear retention, degradation, and alternative splicing.[30,31] Moreover, high levels of ADAR-mediated RNA editing activity may reflect a reversion to a primitive transcriptional program typical of embryonic stem cells.[18] A previous study demonstrated that ADAR1 was among the top 5% of genes expressed in the mutational evolution of lobular breast cancer,[32] indicating that activation of ADARs may correlate with disease progression in multiple malignant cell types.[30] While previous studies have demonstrated upregulation of ADAR1 p110 in a murine leukemia model and pediatric acute leukemias,[33] it is important to note that human hematopoietic tissues undergo significant changes during aging, influenced in part by increased inflammation and genomic instability.[34]

Conclusion

The current findings suggest that ADAR1 polymorphism and ADAR1 enzyme levels in a study of Iraqi patients with CML might influence the development and exacerbation of CML, potentially impacting treatment response as well.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jamieson C. The MLLgnant consequences of reverting to an embryonic transcriptional program. Cell Stem Cell 2009;4:97-8.
2. Eppert K, Takenaka K, Lechman ER, Waldron L, Nilsson B, van Galen P, *et al*. Stem cell gene expression programs influence clinical outcome in human leukemia. Nat Med 2011;17:1086-93.
3. Ben-Neriah Y, Daley GQ, Mes-Masson AM, Witte ON, Baltimore D. The chronic myelogenous leukemia-specific P210 protein is the product of the BCR/ABL hybrid gene. Science 1986;233:212-4.
4. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
5. Shtivelman E, Lifshitz B, Gale RP, Canaani E. Fused transcript of ABL and BCR genes in chronic myelogenous leukaemia. Nature 1985;315:550-4.
6. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, *et al*. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-32.
7. Abrahamsson AE, Geron I, Gotlib J, Dao KH, Barroga CF, Newton IG, *et al*. Glycogen synthase kinase 3beta missplicing contributes to leukemia stem cell generation. Proc Natl Acad Sci U S A 2009;106:3925-9.
8. Perrotti D, Jamieson C, Goldman J, Skorski T. Chronic myeloid leukemia: Mechanisms of blastic transformation. J Clin Invest 2010;120:2254-64.
9. Bass BL. RNA editing by adenosine deaminases that act on RNA. Annu

Rev Biochem 2002;71:817-46.
10. Wulff BE, Sakurai M, Nishikura K. Elucidating the inosinome: Global approaches to adenosine-to-inosine RNA editing. Nat Rev Genet 2011;12:81-5.
11. Nishikura K. Functions and regulation of RNA editing by ADAR deaminases. Annu Rev Biochem 2010;79:321-49.
12. Patterson JB, Samuel CE. Expression and regulation by interferon of a double-stranded-RNA-specific adenosine deaminase from human cells: Evidence for two forms of the deaminase. Mol Cell Biol 1995;15:5376-88.
13. Desterro JM, Keegan LP, Lafarga M, Berciano MT, O'Connell M, Carmo-Fonseca M. Dynamic association of RNA-editing enzymes with the nucleolus. J Cell Sci 2003;116:1805-18.
14. Wang Q, Khillan J, Gadue P, Nishikura K. Requirement of the RNA editing deaminase ADAR1 gene for embryonic erythropoiesis. Science 2000;290:1765-8.
15. Liddicoat BJ, Hartner JC, Piskol R, Ramaswami G, Chalk AM, Kingsley PD, *et al*. Adenosine-to-inosine RNA editing by ADAR1 is essential for normal murine erythropoiesis. Exp Hematol 2016;44:947-63.
16. Daigneault M, Preston JA, Marriott HM, Whyte MK, Dockrell DH. The identification of markers of macrophage differentiation in PMA-stimulated THP-1 cells and monocyte-derived macrophages. PLoS One 2010;5:e8668.
17. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer 2012;118:3123-7.
18. Ramaswami G, Lin W, Piskol R, Tan MH, Davis C, Li JB. Accurate identification of human Alu and non-Alu RNA editing sites. Nat Methods 2012;9:579 81.
19. Peng Z, Cheng Y, Tan BC, Kang L, Tian Z, Zhu Y, *et al*. Comprehensive analysis of RNA-Seq data reveals extensive RNA editing in a human transcriptome. Nat Biotechnol 2012;30:253-60.
20. Eisenberg E, Nemzer S, Kinar Y, Sorek R, Rechavi G, Levanon EY. Is abundant A-to-I RNA editing primate-specific? Trends Genet 2005;21:77-81.
21. Athanasiadis A, Rich A, Maas S. Widespread A-to-I RNA editing of Alu-containing mRNAs in the human transcriptome. PLoS Biol 2004;2:e391.
22. Bass BL, Weintraub H. An unwinding activity that covalently modifies its double-stranded RNA substrate. Cell 1988;55:1089-98.
23. Chen CX, Cho DS, Wang Q, Lai F, Carter KC, Nishikura K. A third member of the RNA-specific adenosine deaminase gene family, ADAR3, contains both single- and double-stranded RNA binding domains. RNA 2000;6:755-67.
24. Hartner JC, Walkley CR, Lu J, Orkin SH. ADAR1 is essential for the maintenance of hematopoiesis and suppression of interferon signaling. Nat Immunol 2009;10:109-15.
25. XuFeng R, Boyer MJ, Shen H, Li Y, Yu H, Gao Y, et al. ADAR1 is required for hematopoietic progenitor cell survival via RNA editing. Proc. Natl Acad Sci U S A 2009;106:17763-8.
26. Wang Q. RNA editing catalyzed by ADAR1 and its function in mammalian cells. Biochemistry (Mosc). 2011;76:900-11.
27. Nishikura K. Editor meets silencer: Crosstalk between RNA editing and RNA interference. Nat Rev Mol Cell Biol 2006;7:919-31.
28. Galeano F, Tomaselli S, Locatelli F, Gallo A. A-to-I RNA editing: The "ADAR" side of human cancer. Semin Cell Dev Biol 2012;23:244-50.
29. Jiang Q, Crews LA, Barrett CL, Chun HJ, Court AC, Isquith JM, *et al*. ADAR1 promotes malignant progenitor reprogramming in chronic myeloid leukemia. Proc Natl Acad Sci U S A 2013;110:1041-6.
30. Rossetti C, Picardi E, Ye M, Camilli G, D'Erchia AM, Cucina L, *et al*. RNA editing signature during myeloid leukemia cell differentiation. Leukemia 2017;31:2824-32.
31. Yang W, Chendrimada TP, Wang Q, Higuchi M, Seeburg PH, Shiekhattar R, *et al*. Modulation of microRNA processing and expression through RNA editing by ADAR deaminases. Nat Struct Mol Biol 2006;13:13-21.
32. Heale BS, Keegan LP, O'Connell MA. ADARs have effects beyond RNA editing. Cell Cycle 2009;8:4011-2.
33. Heale BS, Keegan LP, McGurk L, Michlewski G, Brindle J, Stanton CM, *et al*. Editing independent effects of ADARs on the miRNA/siRNA pathways. EMBO J 2009;28:3145-56.
34. Shah SP, Morin RD, Khattra J, Prentice L, Pugh T, Burleigh A, *et al*. Mutational evolution in a lobular breast tumour profiled at single nucleotide resolution. Nature 2009;461:809-13.