Downregulation of Stearoyl-CoA Desaturase 1 (SCD-1) Promotes Resistance to Imatinib in Chronic Myeloid Leukemia

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Abstract. Chronic myeloid leukemia (CML) is a malignant hematopoietic stem cell disease resulting in the fusion of BCR and ABL genes and characterized by the presence of the reciprocal translocation t(9;22)(q34;q11). BCR-ABL, a product of the BCR-ABL fusion gene, is a structurally active tyrosine kinase and plays an important role in CML disease pathogenesis. Imatinib mesylate (IMA) is a strong and selective BCR-ABL tyrosine kinase inhibitor. Although IMA therapy is an effective treatment, patients may develop resistance to IMA therapy over time. This study investigated the possible genetic resistance mechanisms in patients developing resistance to IMA. We did DNA sequencing in order to detect BCR-ABL mutations, which are responsible for IMA resistance. Moreover, we analyzed the mRNA expression levels of genes responsible for apoptosis, such as BCL-2, P53, and other genes (SCD-1, PTEN). In a group of CML patients resistant to IMA, when compared with IMA-sensitive CML patients, a decrease in SCD-1 gene expression levels and an increase in BCL-2 gene expression levels was observed. In this case, the SCD-1 gene was thought to act as a tumor suppressor. The present study aimed to investigate the mechanisms involved in IMA resistance in CML patients and determine new targets that can be beneficial in choosing the effective treatment. Finally, the study suggests that the SCD-1 and BCL-2 genes may be mechanisms responsible for resistance.

Keywords: CML; Imatinib resistance; BCR-ABL mutations; SCD-1.


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Introduction. Chronic myeloid leukemia (CML) is a neoplastic disease characterized by the Philadelphia chromosome. Philadelphia chromosome results from the reciprocal translocation between chromosomes t (9;22) (q34; q11) that fuses the BCR and ABL genes and is present in 95% of patients with CML.1,2 BCR-ABL
fusión has a consistent tyrosine kinase activity that leads to unregulated proliferation and apoptosis inhibition. CML can be classified into three phases, chronic phase (CP), accelerated phase (AP), and blast phase (BP). Most patients have CML in the chronic phase when diagnosed, but if they are not given treatment, it can advance and, after 3-5 years, reach the more deadly accelerated phase or terminal blast crisis.

Patients with chronic phase CML typically present with an increase in immature and mature myeloid components and retention of hematological differentiation. Anemia, leukocytosis, splenomegaly, and infrequently leukostasis symptoms are seen in the CP of the disease. Compared to CP, accelerated and blast crisis CML phenotypes are more variable and aggressive. A significant decline in cellular differentiation and the replacement of mature cells by immature blasts defines these two phases. More than 50% of patients have a myeloid blast stage similar to acute myeloid leukemia (AML) during a blast crisis.

IMA is a tyrosine kinase inhibitor (TKI) introduced as a first-line therapy for patients in all phases of CML. Although IMA is an efficient therapy and increases the survival rate in patients with CML, IMA resistance becomes an obstacle in therapy, leading to therapeutic failure and relapse.

Different mechanisms are involved in IMA resistance in CML. IMA resistance mechanisms are classified into two main groups: i) BCR-ABL dependent and ii) BCR-ABL independent mechanisms. The development of point mutations in the BCR-ABL tyrosine kinase domain and overexpression of the BCR-ABL gene are the most common BCR-ABL-dependent mechanisms. BCR-ABL independent mechanisms include apoptosis inhibition, overexpression of efflux drug transporters, DNA repair, autophagy, and metabolic pathways. Recent studies have shown that fatty acid metabolism affects cancer development and drug resistance. Fatty acids (FAs) are crucial for cancer cell membrane biosynthesis and provide energy source during proliferation and metabolic stress conditions. Therefore, viable cells should sustain the ratio of saturated to unsaturated FAs to maintain membrane fluidity.

Stearoyl-CoA desaturases (SCDs) are endoplasmic reticulum enzymes involved in FA desaturation in an oxygen-dependent manner. SCD-1 is an important enzyme responsible for FA desaturation and is detected in all human tissues. SCD-1 converts saturated FAs into monounsaturated FAs to enhance unsaturated FAs levels. SCD-1 is upregulated in different cancer types, including lung, breast, prostate, liver, and kidney, and correlates with aggressiveness and oncogenesis.

According to the cancer type, SCD-1 plays different roles in regulating cell proliferation, survival, and apoptosis. In mouse models, a decreased expression level of SCD-1 regulated apoptosis through modulation of PTEN, P53, and BCL-2 expression at the transcriptional and/or posttranscriptional level. Several studies indicate a link between P53 and PTEN as tumor suppressors and regulate cell proliferation and death.

This study investigated the mechanisms that affect IMA resistance in patients with CML and identified new targets for an effective treatment method. We found that the expression levels of the SCD-1 gene decreased in IMA resistance patients with CML and K562r (IMA-resistant) cell lines. However, we discovered higher expression levels of the BCL-2 gene in patients and K562r cells compared to the control groups. The downregulation of SCD-1 and upregulation of BCL-2 genes might be responsible for the IMA resistance in CML independent of point mutations in the BCR-ABL tyrosine kinase domain.

Materials and Methods.

Patients. In this investigation, bone marrow/blood samples from 10 patients responsive to IMA and 12 resistant to IMA, with CML diagnosis from the basic oncology branch at Hacettepe University, were studied. Bone marrow samples obtained from 5 healthy individuals were used as the control with no previous malignant disease diagnosis. IM resistance was documented with both cytogenetic and molecular tests. In addition, the patients who were changed to another TKI were followed up with BCR-ABL. Each sample was included in the study after informed consent forms were obtained and Hacettepe University Faculty of Medicine's Institutional Ethics Committee approved the study (approval no. GO 13/20). Bone marrow (BM) samples were collected from the 10 patients responsive to IMA (median age 40 years, 7 females and 3 males) and 12 patients resistant to IMA (median age 44 years, 4 females and 8 males). The control group comprised 5 healthy individuals (median age 35 years, 1 female and 4 males).

Gene Expression Omnibus analysis. The SCD-1 gene expression levels were studied using the Gene expression Omnibus database (GSE5550). The microarray data of GSE5550 downloaded from the GEO database (GPL201 Affymetrix Human HG-Focus Target Array) includes 8 healthy controls and 9 patients with newly diagnosed CML who were untreated in the chronic phase.

Cell Lines and Cell Cultures. For the IMA-resistant CML cell line, cells from the K562 susceptible cell line obtained from exposure to increasing IMA doses were used. K562s (IMA sensitive) and K562r (IMA resistant) CML cell lines were incubated using RPMI 1640 medium containing 1% penicillin/streptomycin, 5% L-glutamine, and 10% fetal bovine serum in an incubator at 37 °C with 5% CO2. For the K562r cell line, a medium containing 5 mM IMA was used.
Sequence Analysis. BCR-ABL mutations responsible for resistance to IMA (F317L, T315I, M351T, E355G, F359V, M244V, L248V, G250E, Q252H, Y253F, E255K, M343T) were analyzed with the DNA sequencing method. RNA isolation was performed from the samples using a triazole reagent. From the isolated RNA samples, cDNA was synthesized using the iScript cDNA synthesis kit (Biorad, Hercules, CA) according to the kit protocol. Using the P210 PCR product proliferated from the cDNA, the fourth and sixth exons were proliferated with nested PCR (Table 1). PCR samples passed through purification stages by the Promega A9281 Wizard SV Gel and PCR Clean-Up System kit protocol (Promega, Madison, Wis., USA). After purification, cycle sequencing was performed by the Big Dye Terminator v3.1 Cycle sequencing kit protocol (Applied Biosystems, Foster City, CA, USA). For DNA sequence analysis of the samples, an ABI 310 Genetic Analyzer (Applied Biosystems) Sequence device was used. DNA sequence analysis results were assessed in terms of mutations in each sample using the Chromas program.

Quantitative Real-Time PCR. The expression levels of SCD-1, BCL-2, P53, PTEN and HPRT (hypoxyanthine-guanine phosphoribosyltransferase) genes related to IMA resistance were analyzed quantitatively using the qRT-PCR (quantitative real-time PCR) method. Experiments were performed with 3 biological triplicates. Primer sequences are given in Table 2. Primer sequences used for real-time quantitative PCR.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer</th>
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<tr>
<td>P210</td>
<td>F: 5'-AGA TGC TGA CCA ACT CGT G-3'</td>
</tr>
<tr>
<td>ABL (4. exon)</td>
<td>R: 5'-GCC ATA GGT AGC AAT TTC CCA-3'</td>
</tr>
<tr>
<td>ABL (6. exon)</td>
<td>R: 5'-ATCACACCAGCTCATTATC-3'</td>
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Statistics. The experimental results were all reported as mean SD (standard deviation). GraphPad Prism statistical software was employed for the analysis. The means of the two groups were compared by performing the one-sample t-test, and ANOVA was used to analyze the means of numerous samples. Statistical significance was defined as p < 0.05 and p < 0.001.

Results

Patients clinical data. This study included 22 patients at least 18 years old with Philadelphia-positive chronic phase CML who followed in the Hacettepe University Department of Hematology. The diagnosis was established based on bone marrow examination, also cytogenetic and molecular studies. All patients were followed for at least 3 months, and a complete blood count and molecular study for BCR-ABL was conducted on every visit of the patients. The chronic phase (CP) was defined according to standard criteria. Cytogenetics and molecular responses to TKIs were rated according to the European Leukemia Net (ELN) guidelines. The principle of the molecular response depends upon the measurement of the BCR-ABL transcript levels relative to a control gene. All patients initiated IMA 400 mg/day as first-line treatment. IMA was maintained in 10 patients (47.8%), while 7 (30.4%) were treated with two TKIs and the remainder with >2 TKIs. Twelve patients who failed IMA treatment were treated with Dasatinib or Nilotinib as second-line treatment in a median of 26.4 months (2.5-172.5). Nine patients and the remaining 3 received Dasatinib 100 mg/day and 400 mg BID, respectively. A total of 5 failed Dasatinib treatments were changed to Nilotinib in a median of 19 months (13-47.4). In addition, 3 patients underwent allogeneic hematopoietic stem cell transplantation from a human leukocyte antigen-fully matched sibling donor.

Analysis of ABL Kinase mutations in BCR-ABL gene causing IMA resistance in patients with CML and cell lines. The presence of mutations responsible for resistance in patients with CML unresponsive to IMA and in K562s and K562r (5 μM) cell lines was researched using the DNA sequence analysis method. None of the patients resistant to IMA had mutations encountered (Figure 1). Furthermore, our previous study found no mutations in K562s and K562r cell lines.

Gene expression levels of SCD-1 in patients. Gene expression levels were determined by qRT-PCR in patients. Firstly, we analyzed the gene expression levels of SCD-1 in all CML patients and the control group. The SCD-1 gene expression levels increased 5-fold in IMA-resistant patients and 8-fold in IMA-sensitive patients compared to the control group (Figure 2). Later, we classified CML patients into 2 groups as patients sensitive to IMA and patients resistant to IMA.
therapy and resistant to therapy, and investigated the SCD-1 gene expression levels in these groups. As shown in Figure 2, SCD-1 gene expressions were significantly lower in IMA-resistant CML patients than in IMA-sensitive patients (p<0.001). Furthermore, SCD-1 gene expression in CML patients was compared to healthy controls using a gene expression dataset (GSE5550), and similar to the results of our study, a notable difference was detected in SCD-1 expression between CML patients and controls (p<0.0003) (Figure 3).

Expression levels of apoptotic genes in patients.
Figure 2 SCD-1 is downregulated in IMA-resistant CML patients. ** p<0.005, ***p<0.001.

Figure 3. SCD-1 gene expression was analyzed in CML patients compared to healthy controls using a publically accessible gene expression dataset (GSE5550). ***p< 0.0003.

Apoptotic gene expressions (BCL-2, PTEN, and P53) were significantly higher in IMA-resistant CML patients than in IMA-sensitive patients (Figure 4 a, b and c).

Expressions levels of genes (SCD-1, PTEN, BCL-2) in K562s and K562r cell lines. In K562r cells, there was a statistically significant reduction in SCD-1 gene expression levels (p=0.0082, p<0.05) and an increase in BCL-2 gene expression levels (p=0.0452, p<0.05) compared to K562s cells, in parallel to the situation in IMA-resistant patients with CML (Figure 5). No difference was identified between K562r and K562s cells for PTEN gene expression levels. Both cell lines undergo deletion in the P53 gene region.

Figure 4. a: BCL-2 is upregulated in IMA-resistant CML patients. b: PTEN is upregulated in IMA-resistant CML patients) c: P53 is upregulated in IMA-resistant CML patients. ***p<0.0005, *p<0.05.
we targeted BCR-ABL-dependent mechanisms. We have key roles in CML drug resistance. First, involvement in CML could be an epiphenomenon. SCD-1 plays an active role in CML in the literature; his P53, and BCL-2 pathways, there is no evidence that little is known about the relationship between SCD-1, therapy and overcoming IM resistance in patients. As so results may represent a clinical significance in CML bone marrow samples of CML patients. This study's biology of CML and its effect on IM resistance using study is the first to demonstrate the role of SCD-1 in the existing BCR-ABL kinase domain mutations.

polymorphisms, multi-drug resistance genes, and leukemic stem cells, next-generation genomics, genetic field of CML are gene expression profile, CML-TKI option. The primary topics of novel findings in the development of CML patients, the success rate has decreased due to resistance to imatinib. Mutations in the BCR-ABL kinase region are the most important cause of developing resistance. Therefore, identifying CML patients more likely to experience disease progression or develop resistance is crucial, as this affects the primary TKI option. The primary topics of novel findings in the field of CML are gene expression profile, CML-leukemic stem cells, next-generation genomics, genetic polymorphisms, multi-drug resistance genes, and existing BCR-ABL kinase domain mutations. Our study is the first to demonstrate the role of SCD-1 in the biology of CML and its effect on IM resistance using bone marrow samples of CML patients. This study's results may represent a clinical significance in CML therapy and overcoming IM resistance in patients. As so little is known about the relationship between SCD-1, P53, and BCL-2 pathways, there is no evidence that SCD-1 plays an active role in CML in the literature; his involvement in CML could be an epiphenomenon.

BCR-ABL-dependent and independent molecular mechanisms have key roles in CML drug resistance. First, we targeted BCR-ABL-dependent mechanisms. We examined mutations using DNA sequencing for this aim, and we found no point mutations in the BCR-ABL tyrosine kinase domain in patients with CML resistant to IMA. These findings suggested that BCR-ABL independent mechanisms, such as activation of alternative signaling pathways (such as apoptotic and metabolic pathways), influence drug resistance in CML patients.

Studies show that cancer and metabolism are tightly linked. Cancer cells display changes in fatty acid metabolism. Lipid metabolism changes impact tumor cell growth, spread, and chemotherapeutic treatment resistance. In various cancer types, key genes for fatty acid metabolism are defined as prognostic biomarkers related to relapse or survival.

One of these key genes is SCD-1. SCD-1, a transmembrane protein in the endoplasmic reticulum (ER) organelle, synthesizes saturated fatty acid from stearic acid and unsaturated fatty acid oleic acid. SCD-1 is necessary to stimulate lipid biosynthesis to ensure new phospholipids for cell membrane biogenesis in the mitosis cell cycle process.

The presence of SCD-1 was detected in almost every tissue, while disrupted expression levels of this gene were identified in many cancer types.

Several studies have proposed that SCD-1 is a new biomarker for pulmonary cancer and that excessive expression of SCD-1 associated with clinical symptoms is observed more frequently in patients with advanced-stage lung cancer and causes poor prognosis.

Similarly, SCD-1 levels are high in the tissues of colorectal cancer patients, and the literature states that SCD-1 is a biomarker for colorectal cancer and may be used for therapeutic purposes. In vivo and in vitro pharmacological studies revealed that SCD-1 inhibition stopped the growth of colorectal tumors through cellular ceramide production, mitochondrial dysfunction, and induction of apoptosis in colorectal cancer cells.

Recent studies showed that higher levels of SCD-1 expression in human bladder cancers were associated with disease stage, lymph node metastasis, and low survival percentage. High levels of SCD-1 expression predict poor prognosis in stomach cancer patients, and the potential of Scd-1 was shown in the literature as a biological biomarker for the early detection of stomach cancer.

When clinical targeting of the SCD-1 gene with antileukemic and anti-lymphoma treatments was studied for the first time in the literature, the administration of Bezafibrate and Medroxyprogesterone acetate combined therapy to acute myeloid leukemia (AML) and Burkitt lymphoma cell lines, causing reduced SCD-1 levels, showed anticancer activity.

In the literature, SCD-1 was shown to regulate the proliferation and survival of cancer cells; at the same time, the knock-down of SCD-1 by siRNA was stated to significantly reduce the survival of multiple human tumor cell lines. According to a recent study, SCD-1 was shown to affect leukemic metabolism changes impact tumor cell growth, spread, and chemotherapeutic treatment resistance. In various cancer types, key genes for fatty acid metabolism are defined as prognostic biomarkers related to relapse or survival. One of these key genes is SCD-1. SCD-1, a transmembrane protein in the endoplasmic reticulum (ER) organelle, synthesizes saturated fatty acid from stearic acid and unsaturated fatty acid oleic acid. SCD-1 is necessary to stimulate lipid biosynthesis to ensure new phospholipids for cell membrane biogenesis in the mitosis cell cycle process. The presence of SCD-1 was detected in almost every tissue, while disrupted expression levels of this gene were identified in many cancer types.

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Discussion. Chronic myelogenous leukemia (CML) is a clonal hematopoietic disorder that results from the balanced translocation of the ABL1 gene on chromosome 9 to the BCR region on chromosome 22, leading to the arise of the fusion protein BCR-ABL1, which contains an activated tyrosine kinase domain that is responsible for the clonal transformation. The first-line standard treatment of CML is the administration of a TKI-class drug. Imatinib is currently accepted as first-line agent with a high impact on allowing a deep molecular response. Although imatinib has shown very high success in CML patients, the success rate has decreased due to resistance to imatinib. Mutations in the BCR-ABL kinase region are the most important cause of developing resistance. Therefore, identifying CML patients more likely to experience disease progression or develop resistance is crucial, as this affects the primary TKI option. The primary topics of novel findings in the field of CML are gene expression profile, CML-leukemic stem cells, next-generation genomics, genetic polymorphisms, multi-drug resistance genes, and existing BCR-ABL kinase domain mutations. Our study is the first to demonstrate the role of SCD-1 in the biology of CML and its effect on IM resistance using bone marrow samples of CML patients. This study's results may represent a clinical significance in CML therapy and overcoming IM resistance in patients. As so little is known about the relationship between SCD-1, P53, and BCL-2 pathways, there is no evidence that SCD-1 plays an active role in CML in the literature; his involvement in CML could be an epiphenomenon.

Fig. 5 Genes expression levels in K562r cells compared to K562s cells. *p<0.05.
stem cells in mice and play a critical role in CML development. Contrary to studies conducted with various cancer types, Zhang et al. (2012) found that SCD-1 regulated apoptosis of leukemic stem cells (LSC) and acted as a tumor suppressor in leukemic cells. This situation shows that SCD-1 may play different roles in different cancers. Additionally, while the absence of SCD-1 accelerates CML development, Ph+ B-ALL remains undisrupted. For this reason, SCD-1 has different roles in leukemia subtypes and acts in a way specific to the cell type. Additionally, according to Zhang et al., the deficiency of SCD-1 in leukemic stem cells causes disrupted expression of genes associated with apoptosis, resulting in reduced PTEN, P53, and increased BCL-2 expression. According to these results in the literature, PTEN, P53, and BCL-2 transcriptional and/or posttranscriptional levels were shown to be regulated by SCD-1.13

In our study, we first used the GEO database to identify the SCD-1 gene expression levels of all CML patients. Second, we analyzed the mRNA expression levels of apoptotic (BCL-2, P53) and other genes (SCD-1, PTEN), which can be responsible for the IMA resistance of patients with CML and K562 cells. According to the transcriptome analysis in the gene microarray database (GSE5550), the SCD-1 gene expression levels in CML patients were elevated compared to the control group; these data are similar to our findings. When the IMA-resistant CML patient group with a large LSC population was compared with the IMA-sensitive patients with CML, there was a reduction in SCD-1 gene expression levels and an increase in BCL-2 gene expression levels, parallel to the study by Zhang et al. This situation suggests that the SCD-1 gene acts like a tumor suppressor in patients with CML resistant to IMA. The upregulation of BCL-2 gene expression in patients resistant to IMA increases the proliferation of leukemic cells and ensures their survival. In our study, the K562r cell line and IMA-resistant CML patient group were found to have similar results in terms of SCD-1 and BCL-2 gene expressions. In the literature, similar studies were conducted to reveal the role of BCL-2 in CML. In a mouse model, when BCL-2 was administered alone or combined with TKIs, the inhibition effect increased, the antileukemic effect developed, and survival durations increased. Combined inhibition of BCL-2 and BCR-ABL tyrosine kinase was shown to have significant potential for response and treatment rates in the chronic phase and blast crisis stages in CML.29 Studies with K562 cells similarly identified that BCL-2 and TKI combined treatments prevented IMA resistance related to BCL-2 increase or BIM or BAD loss.30 In this situation, it was concluded that the BCL-2 gene might be a key survival factor for CML.28 In our study, increases were identified in PTEN and P53 expression levels, 2 important genes playing roles in the cell cycle in patients with CML developing resistance to IMA. Yunes et al. found that cells carrying P53 loss of function mutations and overexpression P53 protein were chemotherapy-resistant and displayed increasing amounts of ABCB1 (ATP-dependent translocase) and MRPI/ABCC1 (Multidrug Resistance Protein 1).31 Contrary to our study, in the literature, PTEN was shown to act as a tumor suppressor inhibiting LSCs. Overexpression of PTEN reduced the percentage of bone marrow LSCs; thus, it was considered that PTEN inhibited LSCs.32,33 The increase in PTEN gene expression levels in our patients developing resistance to IMA leads to the consideration that the cell cycle slowing could be studied. No significant difference was found between the PTEN gene expression levels in the K562r and K562s cell lines.

Conclusions. In our study, apart from ABL kinase mutations responsible for resistance, SCD-1, and BCL-2 genes might be mechanisms responsible for resistance. In conclusion, for the first time in this study, variations in SCD-1 gene expression were illustrated in CML patient samples. Furthermore, increasing BCL-2 expression linked to suppressing the SCD-1 gene may develop IMA resistance in the patient. This supports the view that IMA and BCL-2 inhibitor combinations should be added to treatment protocols for patients with CML. Additionally, there is a need for more research in the future about detailed mechanisms of how SCD-1 regulates PTEN, P53, and BCL-2 expression.

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