Clin. Lab. 2021;67:1110-1118
©Copyright

REVIEW ARTICLE

Sirtuin1 and Chronic Myeloid Leukemia: a Comprehensive Glance at Drug Resistance

Sadegh Abbasian [1, 4], Negin Shokrgozar [2], Gholamhossein Tamaddon [3]

[1] *Department of Hematology and Blood Banking, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran*
[2] *Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[3] *Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran*
[4] *Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran*

SUMMARY

Background: **Chronic myeloid leukemia (CML) is a myeloproliferative disorder, which is caused by BCR-ABL fusion that has tyrosine kinase activity. The emergence of the first generation of tyrosine kinase inhibitors increased survival in patients. CML patients remain in silent phase for a long time by using drugs such as imatinib. Resistance to imatinib causes relapse of disease after using it. Different factors such as mutations, epigenetic factors, and changes in the drug's receptor can play an important role in drug resistance. SIRT1 is an NAD-dependent deacetylase that has a role in regulation of metabolic activities. It has been recently considered as a key regulator of drug resistance in malignancies such as CML.**
Methods: **The resources of this study are from different sites and journals such as ncbi.nlm.nih.gov/pubmed, scopus.com, American Journal of Hematology, International Journal of Hematology, etc.**
Results: **Expression of SIRT1 is increased in patients with imatinib resistance. The mechanism of this resistance is not exactly understood. The inhibition of SIRT1 in CML causes increased sensitivity to imatinib.**
Conclusions: **Recognition of drug resistance factors, reduction or neutralization of them is so important in patients' survival. This study indicates the role of SIRT1 as one of the most common causes of drug resistance in many cancers such as CML.**
(Clin. Lab. 2021;67:1110-1118. DOI: 10.7754/Clin.Lab.2020.200835)

Correspondence:
Gholamhossein Tamaddon
Diagnostic Laboratory Sciences and
Technology Research Center
School of Paramedical Sciences
Shiraz University of
Medical Sciences
Shiraz
Iran
Phone: +98 9151417043
Email: tamaddon.g@gmail.com

Review Article accepted October 3, 2020

KEY WORDS

chronic myeloid leukemia, imatinib, sirtuin1, drug resistance

LIST OF ABBREVIATIONS

CML - Chronic myeloid leukemia
SIRT1 - Sirtuin1
TKI - Tyrosine kinase inhibitor
FISH - Fluorescence In Situ Hybridization
RT-PCR - Real-time polymerase chain reaction
CP - Chronic phase
AP - Accelerated phase
BP - Blastic phase
ABC - ATP binding cassette
MDR-1 - Multi drug resistance-1

MRD - Minimal residual disease
Tregs - Regulatory T cells
NHEJ - Non-homologous end joining

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm, which is identified with the Philadelphia chromosome. This disease is usually observed in individuals in range of 65 - 75 years old [1]. In new cases, tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib, dasatinib, and bosutinib are used as the first line of treatment. At the beginning of treatment, imatinib is administered for the patients and if drug resistance is observed, other TKIs will be used [2]. Due to the fact that imatinib plays an important role in increasing the survival of patients, drug resistance is a challenge in treatment. Different studies have investigated the various factors as drug inhibitors. This study provides an overview of different factors, which are involved in drug resistance and introduces sirtuin1 (SIRT1) as a new factor in drug resistance.

1. Chronic myeloid leukemia

1a) Epidemiology

The incidence rate of chronic myeloid leukemia (CML) varies between 0.5 - 1.5% per 100,000 world-wide and it is approximately 0.8% per 100,000 in Asian countries [3,4]. In Iran, the number of patients with CML is estimated to be about 500 per year and its incidence in men is higher than women [5,6]. New drugs such as tyrosine kinase inhibitors (TKIs) increased survival in CML patients about 80 - 90% in Asian countries [7,8].

1b) Etiology

CML is a clonal myeloproliferative disease that is caused by a chromosomal abnormality due to the integration of BCR and ABL genes that is called the Philadelphia chromosome [9]. ABL and BCR genes are located on the long arms of chromosome 9 (ch9) and 22 (ch22), respectively [10]. This fusion is positioned between ch9 and ch22, which is shown as t (9; 22). BCR-ABL fusion has the property of tyrosine kinase [11]. Also, lifestyle affects the rate of CML, including smoking, high body mass index, exposure to ionizing radiation, and benzene, which are considered as risk factors for CML [12].

1c) Diagnosis

The leukocyte count is usually more than 5 x 10^9/L and may more than 30 x 10^9/L. The peripheral blood smear shows a complete spectrum of granulocytic cells, from myeloblast to neutrophils. Basophilia is seen in all patients with CML, and eosinophilia is present in about 90% of them [13]. According to WHO criteria, not only hematological findings but also genetic findings are required for diagnosis. Different methods such as FISH or RT-PCR are used in order to determine the presence of the Philadelphia chromosome. Biopsy of bone marrow is used to identify the number of blasts and granulocytic hyperplasia and to evaluate other cytogenetic abnormalities [14].

CML has three clinical phases: chronic phase (CP), accelerated phase (AP), and blastic phase (BP). According to WHO classification in BP, more than 20% blasts are seen in bone marrow or peripheral blood (Table 1). AP has one of the following characteristics: 10 - 19% blast, ≥ 20% basophil, platelet count less than 100,000/µL and no response to treatment with splenomegaly and increased WBC count. AP is more aggressive than CP and most of the patients in developed countries enter the CP (Table 1) [15].

1d) Treatment

Since the 19th century, different treatments have been taken for CML and first arsenic compounds were used [16]. In the early 20th century, splenic irradiation was used to reduce the degree of splenomegaly, but it was replaced by the alkylating agents such as busulfan [17, 18]. After that, busulfan was replaced by hydroxycarbamide, a ribonucleotide reductase inhibitor, due to the mutagenicity of busulfan and stimulation of blast crisis [19].

In 1970, interferon α and allogeneic stem cell transplantation were used for treatment leading to prolonged survival of patients [20]. Interferon α, in contrast to busulfan and hydroxycarbamide, increases median life expectancy and, in combination with cytarabine, has more positive effects, but leads to increased toxicity [21,22]. In 1996, Druker and colleagues reported the first data about TKIs [23]. Studies gradually showed that the reduction in BCR-ABL transcript levels was higher in patients treated with TKIs such as imatinib, compared to interferon α and cytarabine [24].

2. Tyrosine kinase inhibitors

TKIs inhibit the activity of tyrosine kinase-associated proteins by binding to their ATP position [25]. Imatinib is the first generation of TKIs that were used to treat CML for the first time. The chemical name of the drug is methyl amino pyrimidine, which was first examined in 1998. Imatinib plays its inhibitory role by occupying the position of ATP kinase in BCR-ABL oncogene. This drug causes cytogenetic responses in about 80% of patients [26]. The daily dose is 400 mg orally, but in the absence of expected response, 600 to 800 mg is also administered. The side effects of this drug are headache, skin rashes, edema, and bone pains. The toxic effects are determined by increasing serum transaminases. A small group of patients also experience neutropenia and thrombocytopenia [27].

Second generation of TKIs such as nilotinib, dasatinib, and bosutinib are used for the patients who do not respond to imatinib. Use of these drugs causes complete cytogenetic and molecular responses [28]. Nilotinib is a modified form of imatinib with an increase in drug activity and a daily dose of 400 mg. Dasatinib is chemi-

cally and structurally different from imatinib but with similar function and daily dose of 70 mg twice a day, and bosutinib acts in a wide range of tyrosine kinases and the side effects of this drug include severe diarrhea (Table 2) [29].

3. Drug resistance

Drug resistance is an innate and acquired response to treatment, and multiple mechanisms such as internal and external factors contribute to it. Innate resistance is defined as an inherited ability of cancer to develop resistance to drugs and the following factors are involved in this resistance: increased drug release to the outside of the cell, which is the responsibility of an ATP-dependent pump called ABC (ATP binding cassette). One type of ABC is ABCB-1, which is known as MDR-1 (multi drug resistance-1) or the drug resistance protein-1. Other factors such as multiple drug resistance-dependent proteins and toxin depletion system such as cytochrome P450, superoxide dismutase, and glutathione peroxidase are involved in this process. Acquired drug resistance is defined as the development of cancer after the initial recovery of the patient. In contrast to the innate drug resistance, acquired drug resistance is produced by several mechanisms such as genetic mutations and gene amplification. The molecular mechanisms of acquired drug resistance through mutations are not completely understood due to inadequate studies [30-32] (Figure 1).

4. Drug resistance to imatinib and treatment strategy

Imatinib resistance may be primary or secondary. After treatment, small groups of patients do not show hematologic and cytogenetic responses to the drug, despite the fact that most of them have appropriate responses. Secondary drug resistance occurs 2 years after initiation of the treatment. The cause of the primary drug resistance is still unknown, but it probably reflects the heterogeneity of the disease at the time of diagnosis. Resistance to TKIs may be in correlation with different mechanisms, including overexpression of BCR-ABL proto-oncogene, dissemination of drug to the outside of the cell or generation of point mutations in the domains of ABL-1 kinase. Today, about 50 point mutations in patients with positive Philadelphia chromosome are observed with varying degrees of drug resistance [33]. Each mutation causes the coding of different amino acids that are in the sections of the BCR-ABL proto-oncogene and its kinase part. The substitution of an amino acid such as T315I induces drug resistance to all TKIs. Consumers of TKI should be examined every three months for the gene involved in order to reach the desired MRD (minimal residual disease) [34].

Several biomarkers have been identified in order to indicate resistance to imatinib, which is the result of study on K562-R cells, a cell line resistant to drugs. These biomarkers include epigenetic changes such as methylation of THAP2, FEM1B, RPRM, and MLH1 genes or changes in different micro-RNAs such as miR-221, miR-379, miR-548, miR-603, and miR-658, and in these situations, nilotinib is used as the second line of treatment [35,36].

Using histone deacetylase inhibitors such as hydroxamic acid-based drugs including zolinza in combination with imatinib can significantly reduce the chance of relapse of the disease and cause the disease to remain silent [37].

ADAM8 is a metalloproteinase and using its inhibitors can be useful in patients who are receiving imatinib as the first line treatment but they are resistant to imatinib. In this situation, the rate of relapse due to drug resistance is reduced [38].

Using PI3K-AKT-mTOR pathway inhibitors accompanied with autophagy inhibitors may present a new treatment role in patients with resistance to imatinib. Combined drugs such as the simultaneous use of NVP-BEZ-235 and hydroxychloroquine can greatly reduce the growth of imatinib-resistant CML cells [39].

5. SIRT1

5a) Historical background

About a century ago, Peyton Rous discovered a protein called sirtuin, which had beneficial effects on limiting body calories [40]. Sirtuin family has seven members in mammals, SIRT1-7, which regulates metabolism in different tissues. SIRT1 is an NAD-dependent deacetylase and the function of this protein is related to deacetylation and ADP ribosyl transferase. This protein plays an important role in apoptosis, cell cycle, mitochondria function, metabolism, and metabolic functions [41].

5b) Structure and classification

Sirtuin is classified into four classes (I - IV) according to molecular polygenetic analysis of different types of organisms and domain sequences. SIRT1, SIRT2, and SIRT3 are known as Class I sirtuins, SIRT4 is a member of the Class II, SIRT5 is a part of the Class III, SIRT6 and SIRT7 are a subset of Class IV [42].

SIRT has two specific domains: small domain, which includes a helical module and a Zn^{2+}-binding module and the large domain is a Rossmann fold. The position of NAD connection is between these two domains [43].

5c) Tissue distribution

SIRT is expressed in a wide range of tissues and organs such as liver, heart, pancreas, muscle, adipose tissues and some parts of the brain. There is a high level of SIRT in embryonic tissues and less in the spleen, kidney, lung, thymus, testis, and ovary [41].

5d) Cellular distribution

Cellular distribution is dependent on cell type, stress status, and molecular reactions. SIRT1 has been seen in both nucleus and cytoplasm regions [44] (Figure 2).

5e) Cellular regulation and signaling pathway

SIRT1 acts on different substrates such as histone and

non-histone proteins. SIRT1 has a deacetylation activity that plays an important role in metabolism, inflammation, and regulation of DNA damage (Table 3) [45]. SIRT1 is responsible for the chemical reactions and deacetylation of lysine residues. This reaction consumes NAD^+ and converts it to nicotinamide. These NAD-dependent reactions are performed in 6 steps simultaneously. In the first step of deacetylation, NAD^+ is broken down and produces nicotinamide and 2′-O-acetyl-ADP ribose. Also, the NAD^+ dependent SIRT1 deacetylase reaction is inhibited by Sirtinol [41].

SIRT1 regulates regulatory T cells (Tregs) through the signaling pathway of NF-KB/AP1. Inactivation of SIRT1 in animal models causes inflammation and high sensitivity to oxidative stress due to defects in this signaling pathway. For regulation of this pathway, SIRT1 reacts to a subunit of NF-KB called ReIA/p65 and the result of this reaction is suppression of transcription and a reduction in the target gene expression [46]. Smac/NF-KB signaling pathway plays an important role in some tumors such as lung cancer. In this situation, SIRT1 expression reduces the sensitivity of cancer cells to radiation [47].

SIRT1 is activated in hematological malignancies such as AML, CML, and lymphoma. In CML patients, this activation occurs by the BCR-ABL oncogene, which exacerbates the progression of disease. SIRT1 promotes the mutant leukemic cells to increase drug resistance through a change in the DNA repair and the error-prone NHEJ (non-homologous end joining) repair, a pathway that repairs double-strand breaks in DNA [48]. Therefore, SIRT1 may result in the lack of intracellular penetration of the drug to the cell through different signaling pathways [49].

Most of the sirtuins are related to the signaling pathways associated with the lifetime of the hematopoietic stem cells. These signaling pathways include DNA repair, mTOR, FOXO, NF-KB, and P53 (non-histone proteins). In normal situations, sirtuin is involved in activating these signaling and regulatory pathways by acetylating these agents. In abnormal situations, SIRT1 and 7 can deacetylate these genes such as P53 and reduce its activity. This gene has an important role in cell cycle and apoptosis. In the same conditions, SIRT1 and 2 inhibit the autoacetylation of P300 or TIP60. Excessive activation of the error-prone NHEJ repair pathway in hematopoietic stem cells by SIRT may explain the cause of mutations in these cells [50].

SIRT1 regulatory pathways can be disrupted by miR-9. Due to the fact that miR-9 directly attaches to the 3′-untranslated region of SIRT1 and reduces the activity of the deacetylation function of it, this disorder is justifiable in sirtuin-dependent regulatory pathways [51].

6. SIRT1 and drug resistance in cancers

SIRT1 has two faces in cancer biology; it can act as a tumor suppressor or an oncogene. This gene plays its oncogenic role by deactivating tumor suppressor genes such as P53, E2F1, etc. Therefore, its overexpression is observed in prostate cancer, breast cancer, and leukemia [52-54]. The tumor suppressive role of SIRT1 is performed by inhibiting oncogenes and it is observed in some cancers such as sarcomas, lymphomas, and lung tumors [52].

Autophagy is a mechanism for life and survival of cells and also has a role in apoptosis. SIRT1 can play a role in creating drug resistance or increasing carcinogenesis by influencing this pathway. SIRT1 plays this role by deacetylating ATG, which is an autophagy-dependent factor [55].

SIRT1 has an important role in regulating lipid metabolism as a regulator of metabolic activities. In cancer cells, SIRT1 reduces lipid metabolism by activating transcription factors such as FOXO1 and PGC-1a or by inhibiting SREBP-1c. Autophagy or m-TOR pathways may also be involved in lipid homeostasis. SIRT1 affects m-TOR pathways through deacetylation and decreases it. Also, SIRT1 prevents the growth of tumor cells in different cancers [56].

7. SIRT1 and drug resistance in CML

Some studies have indicated that patients with higher expression of SIRT1 are more prone to drug resistance [57]. CML is a cancer with increased expression of SIRT1, which causes drug resistance, and increased expression of this gene has been investigated in cell-lines such as KCL-22 [58]. Evaluation of this gene expression in samples of CML patients has also indicated that SIRT1 expression is higher in imatinib-resistant compared with imatinib-sensitive patients [59].

DISCUSSION

Recently, resistance to imatinib is a major challenge in CML patients. The usefulness of imatinib in survival of patients is undeniable, but when there is drug resistance, the use of second and third generation TKIs such as nilotinib is an appropriate solution. The role of known agents such as mutations occurring in the BCR-ABL proto-oncogene causes no effect of imatinib on patients. Factors affecting epigenetics such as SIRT1 and even the role of autophagy in drug resistance in these patients have been underestimated. Most studies on animal models or cell culture confirm the role of SIRT1 in drug resistance, while there are few patient-based studies. Still, a precise mechanism that demonstrates how SIRT plays a role in drug resistance is not mentioned. However, this article discussed the latest developments about the role of SIRT1 in drug resistance.

In a study performed by Guanglin Qiu et al., the role of SIRT1 was emphasized as influencing the autophagy pathway in gastrointestinal cancers [55]. Other review studies have discussed less about the role of SIRT1 in resistance in CML patients. However, a study carried out by Ling Li and colleagues on CML patients specifically focused on the role of this factor in drug resistance and has shown that inhibiting the expression of the

Table 1. Characteristics of clinical phases of CML.

Parameter	Chronic phase	Accelerated phase	Blast crisis
BM blasts	< 5%	10 - 19%	≥ 20%
Basophils	< 20%	≥ 20%	Is different in leukemias
Platelets	↑ or normal	↓ or ↑ *	↓ *
Marrow cellularity	↑	↑	↑
Cytogenetic	Ph^+ *	Ph^+	Ph^+

Abbreviations: BM - bone marrow.
*** ↑ - increase, ↓ - decrease, Ph^+ - Philadelphia positive.**

Table 2. TKIs dosing and risk profiles.

TKIs	Dosing in chronic phase	Adverse effects
Imatinib	400 mg/day	edema, diarrhea, muscle cramps
Nilotinib	300 mg twice a day	skin rash, hyperglycemia
Dasatinib	100 mg/day	fluid retention, skin rash, headache
Bosutinib	500 mg/day	diarrhea, nausea, fatigue, skin rash, thrombocytopenia

Table 3. The molecules that are targeted for SIRT1.

Targeted molecules	Physiologic role	Effects of deacetylation by SIRT1
Histones	compressing DNA and chromatin	contribution to DNA compression
P53	cell cycle, DNA repair and apoptosis	inactivation by sirt1 and prevention DNA repair
KU70	DNA repair, regulation of transcription and recombination	prevention of apoptosis
FOXO	cell cycle and apoptosis	promotion of the expression of FOXO target genes involved in stress resistance and decreasing the transcription of genes involved in apoptosis
P300	histone acetyl transferase	inhibition of P300
TIP60	histone acetyl transferase and increased apoptosis	inhibition of apoptosis
NF-KB	immunity, inflammation, and apoptosis	suppression of the transcription activity of NF-KB

SIRT1 gene through activating the P53 causes elimination of leukemic cells in patients who are resistant to imatinib [60].

Based on the current approaches, considering the efficacy of imatinib in keeping patients in silent phase, elimination of factors that cause drug resistance instead of using alternative drugs can be an appropriate method to reduce or neutralize drug resistance. Using the technology to remove or modify the gene in cases where mutations exist, such as CRISPR/Cas9 editing, can also be a new way to counteract drug resistance.

Given that signaling pathway is performed through mTOR and AMPK, using drugs that can inhibit these pathways can be used to reduce SIRT1 activity when it is necessary.

At the gene expression level, the interfering miRNA can be used to prevent the synthesis of SIRT1 during translation at the mRNA level.

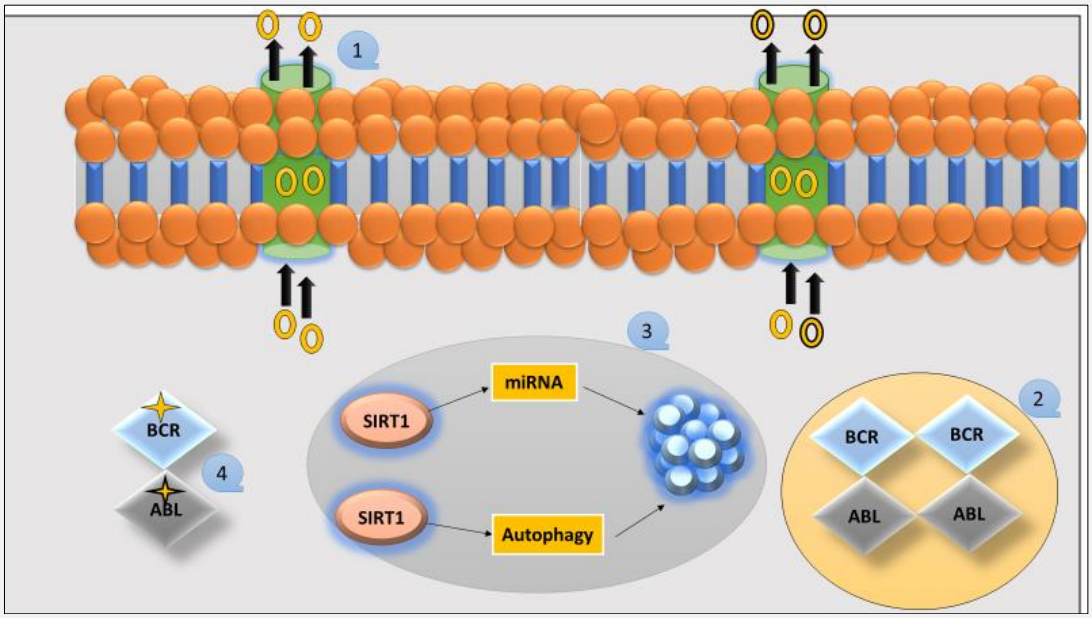

Figure 1. Mechanism of drug resistance.

1. Drug influx (MDR1), 2. Gene amplification, 3. Survival of leukemic cells by SIRT1, 4. Mutation in BCR-ABL.

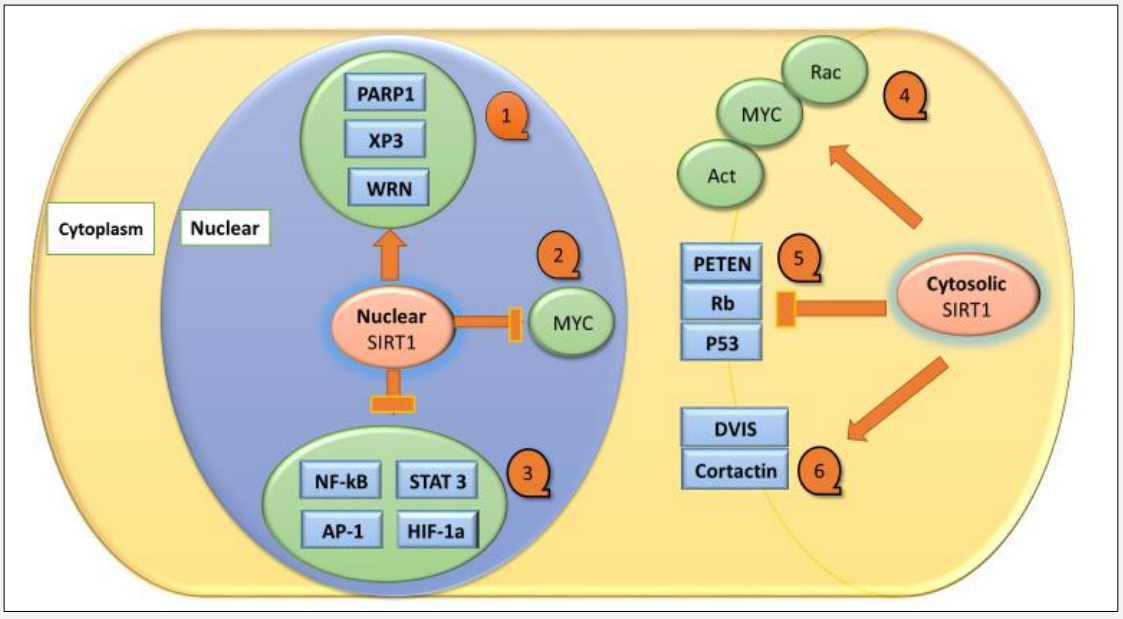

Figure 2. SIRT1 plays different roles in the nucleus and cytoplasm.

In the cytoplasm, it is more commonly used as a tumor suppressor, while in the nucleus, it is responsible for genome repair. 1. DNA repair, 2. Oncoproteins, 3. Transcription factor related to inflammation, 4. Oncoproteins, 5. Tumor suppressor, 6. Proteins with migration role in cell.

Cancer cells require NAD for proliferation, and the NAD concentration is increased in tumors. Different enzymes have roles in NAD production, and SIRT1 plays a role as a mediator in this pathway. Identifying the factors that reduce the energy of cancer cells or the production of NAD in tumors can reduce the growth of cancer cells.

The main activity of SIRT1 is influencing acetylation on the level of transcription factors and epigenetics. Using drugs that can block the active site of the enzyme or interfere with the active site by competitive mechanism may be beneficial in the presence of drug resistance and when there is no suitable alternative for the drug.

CONCLUSION

Drug resistance is a major challenge in treatment of cancer. Factors such as epigenetic factors, mutations in the drug receptor or disturbances in the signaling of the drug can contribute to the development of various drug resistances in cancers. Using a new drug or controlling the factors affecting the signaling pathway of the drug can help to improve the effectiveness of the drug when drug resistance is present. SIRT1 has been identified as an important and effective factor in drug resistance. SIRT1 can contribute to drug resistance in many cancers by interfering with epigenetic or signaling pathways, and also, it can cause drug resistance in CML when TKI is used.

Declaration of Interest:

The authors declare that there are no conflicts of interest.

References:

1. Heim D, Ebnöther M, Favre G. [Chronic myeloid leukemia-update 2020]. Ther Umsch. 2019;76(9):503-9 (PMID: 32157969).
2. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol 2018;93(3): 442-59 (PMID: 29411417).
3. Kim DW, Banavali SD, Bunworasate U, et al. Chronic myeloid leukemia in the Asia-Pacific region: current practice, challenges and opportunities in the targeted therapy era. Leuk Res 2010; 34(11):1459-71 (PMID: 20430443).
4. Au WY, Caguioa PB, Chuah C, et al. Chronic myeloid leukemia in Asia. Int J Hematol 2009;89(1):14-23 (PMID: 19101781).
5. Daroudi R, Mirzania M, Nikravanfard N, Sadighi S, Sedighi Z, Zendehdel K. Estimation of the prevalence and direct medical costs of chronic myeloid leukemia in the IR of Iran in the era of tyrosine kinase inhibitors. Asia Pac J Clin Oncol 2017;13(5): e416-22 (PMID: 26990676).
6. Malani PN. Harrison's principles of internal medicine. JAMA 2012;308(17):1813-4. https://jamanetwork.com/journals/jama/article-abstract/1389591
7. Mendizabal AM, Garcia-Gonzalez P, Levine PH. Regional variations in age at diagnosis and overall survival among patients with chronic myeloid leukemia from low and middle income countries. Cancer Epidemiol 2013;37(3):247-54 (PMID: 23411044).
8. Jalaeikhoo H, Ahmadzadeh A, Toogeh G, et al. Six-year follow up of imatinib therapy for newly diagnosed chronic myeloid leukemia in Iranian patients. Arch Iran Med 2011;14(6):378-80 (PMID: 22039840).
9. Rohrbacher M, Hasford J: Epidemiology and Etiology of Chronic Myeloid Leukemia; Neoplastic Diseases of the Blood. Springer, 2018:9-17. https://link.springer.com/chapter/10.1007/978-3-319-64263-5_2
10. Lichtman MA. Is There an Entity of Chemically Induced BCR-ABL-Positive Chronic Myelogenous Leukemia? Oncologist 2008;13(6):645-54 (PMID: 18586919).
11. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243(5405):290-3 (PMID: 4126434).
12. Kabat GC, Wu JW, Moore SC, et al. Lifestyle and dietary factors in relation to risk of chronic myeloid leukemia in the NIH-AARP Diet and Health Study. Cancer Epidemiol Biomarkers Prev 2013; 22(5):848-54 (PMID: 23625904).
13. Spiers A, Bain BJ, Turner JE. The Peripheral Blood in Chronic Granulocytic Leukaemia: Study of 50 Untreated Philadelphia-Positive Cases. Scand J Haematol 1977;18(1):25-38 (PMID: 265093).
14. Radich JP, Deininger M, Abboud CN, et al. Chronic myeloid leukemia, version 1.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018;16(9):1108-35 (PMID: 30181422).
15. Heibl S, Gisslinger B, Jäger E, et al. Clinical, Hematologic, Biologic and Molecular Characteristics of Patients with Myeloproliferative Neoplasms and a Chronic Myelomonocytic Leukemia-Like Phenotype. Cancers (Basel). 2020 Jul;12(7):1891 (PMID: 32674283).
16. Hoonjan M, Jadhav V, Bhatt P. Arsenic trioxide: insights into its evolution to an anticancer agent. J Biol Inorg Chem 2018 May 1;23(3):313-29 (PMID: 29396610).
17. Zaorsky NG, Williams GR, Barta SK, et al. Splenic irradiation for splenomegaly: A systematic review. Cancer Treat Rev 2017; 53:47-52 (PMID: 28063304).
18. Copelan EA, Avalos B, Ahn KW, et al. Comparison of Outcomes of Allogeneic Transplantation for CML with Cyclophosphamide in Combination with Intravenous Busulfan, Oral Busulfan or total body irradiation. Biol Blood Marrow Transplant 2015;21(3):552-8 (PMID: 25528388).
19. Mughal TI, Radich JP, Deininger MW, et al. Chronic myeloid leukemia: reminiscences and dreams. Haematologica 2016; 101(5):541-58 (PMID: 27132280).
20. Bonifazi F, de Vivo A, Rosti G, et al. Chronic myeloid leukemia and interferon-α: a study of complete cytogenetic responders. Blood 2001;98(10):3074-81 (PMID: 11698293).
21. Abecasis M, Cross NC, Brito M, et al. Is cancer latency an outdated concept? Lessons from chronic myeloid leukemia. Leukemia. 2020 Jul 6:1-6 (PMID: 32632094).

22. Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. N Engl J Med 1997;337(4):223-9 (PMID: 9227927).

23. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2(5):561-6 (PMID: 8616716).

24. Hughes TP, Kaeda J, Branford S, 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(15):1423-32 (PMID: 14534335).

25. Natoli C, Perrucci B, Perrotti F, Falchi L, Iacobelli S. Tyrosine kinase inhibitors. Curr Cancer Drug Targets 2010;10(5):462-83 (PMID: 20384577).

26. Goldman JM. How I treat chronic myeloid leukemia in the imatinib era. Blood 2007;110(8):2828-37 (PMID: 17626839).

27. Pushpam D, Bakhshi S. Pharmacology of tyrosine kinase inhibitors in chronic myeloid leukemia; a clinician's perspective. Daru. 2020 Jan 3:1-5 (PMID: 31900888).

28. Hoffmann VS, Hasford J, Deininger M, Cortes J, Baccarani M, Hehlmann R. Systematic review and meta-analysis of standard-dose imatinib vs. high-dose imatinib and second generation tyrosine kinase inhibitors for chronic myeloid leukemia. J Cancer Res Clinical Oncol 2017;143(7):1311-8 (PMID: 28275866).

29. Lu X, Smaill JB, Ding K. New Promise and Opportunities for Allosteric Kinase Inhibitors. Angew Chem Int Ed Engl. 2020 Apr 1 (PMID: 31889388).

30. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer 2013;13(10):714-26 (PMID: 24060863).

31. Griess B, Tom E, Domann F, Teoh-Fitzgerald M. Extracellular superoxide dismutase and its role in cancer. Free Radic Biol Med 2017;112:464-79 (PMID: 28842347).

32. Brown R, Curry E, Magnani L, Wilhelm-Benartzi CS, Borley J. Poised epigenetic states and acquired drug resistance in cancer. Nat Rev Cancer 2014;14(11):747-53 (PMID: 25253389).

33. Lewandowski K, Warzocha K, Hellmann A, et al. Frequency of BCR-ABL gene mutations in Polish patients with chronic myeloid leukemia treated with imatinib: a final report of the MAP-TEST study. Pol Arch Med Wewn 2009;119(12):789-94 (PMID: 20010464).

34. Soverini S, Branford S, Nicolini FE, et al. Implications of BCR-ABL1 kinase domain-mediated resistance in chronic myeloid leukemia. Leuk Res 2014;38(1):10-20 (PMID: 24131888).

35. Loscocco F, Visani G, Galimberti S, Curti A, Isidori A. BCR-ABL independent mechanisms of resistance in chronic myeloid leukemia. Front Oncol. 2019;9:939 (PMID: 31612105).

36. Di Stefano C, Mirone G, Perna S, Marfe G. The roles of microRNAs in the pathogenesis and drug resistance of chronic myelogenous leukemia (Review). Oncol Rep. 2016 Feb 1;35(2):614-24 (PMID: 26718125).

37. Zhang B, Strauss AC, Chu S, et al. Effective targeting of quiescent chronic myelogenous leukemia stem cells by histone deacetylase inhibitors in combination with imatinib mesylate. Cancer Cell 2010;17(5):427-42 (PMID: 20478526).

38. Miyauchi M, Koya J, Arai S, et al. ADAM8 Is an Antigen of Tyrosine Kinase Inhibitor-Resistant Chronic Myeloid Leukemia Cells Identified by Patient-Derived Induced Pluripotent Stem Cells. Stem Cell Reports 2018;10(3):1115-30 (PMID: 29429960).

39. Mitchell R, Hopcroft LE, Baquero P, et al Targeting BCR-ABL-independent TKI resistance in chronic myeloid leukemia by mTOR and autophagy inhibition. J Natl Cancer Inst 2018 May 1;110(5):467-78 (PMID: 29165716).

40. Rous P. The influence of diet on transplanted and spontaneous mouse tumors. J Exp Med 1914;20(5):433-51 (PMID: 19867833).

41. Chang HC, Guarente L. SIRT1 and other sirtuins in metabolism. Trends Endocrinol Metab 2014;25(3):138-45 (PMID: 24388149).

42. Michan S, Sinclair D. Sirtuins in mammals: insights into their biological function. Biochem J 2007;404(1):1-13 (PMID: 17447894).

43. Davenport AM, Huber FM, Hoelz A. Structural and functional analysis of human SIRT1. J Mol Biol 2014;426(3):526-41 (PMID: 24120939).

44. Chung S, Yao H, Caito S, Hwang JW, Arunachalam G, Rahman I. Regulation of SIRT1 in cellular functions: role of polyphenols. Arch biochem Biophys 2010; 501(1): 79-90 (PMID: 20450879).

45. Milner J. Cellular regulation of SIRT1. Curr Pharml Des 2009; 15(1):39-44 (PMID: 19149601).

46. Kauppinen A, Suuronen T, Ojala J, Kaarniranta K, Salminen A. Antagonistic crosstalk between NF-κB and SIRT1 in the regulation of inflammation and metabolic disorders. Cell Signal 2013; 25(10):1939-48 (PMID: 23770291).

47. Ji K, Sun X, Liu Y, et al. Regulation of Apoptosis and Radiation Sensitization in Lung Cancer Cells via the Sirt1/NF-κB/Smac Pathway. Cell Physiol Biochem 2018;48(1):304-16 (PMID: 30016782).

48. Tian WL, Guo R, Wang F, et al. The IRF9-SIRT1-P53 axis is involved in the growth of human acute myeloid leukemia. Exp Cell Res 2018;365(2):185-93 (PMID: 29501566).

49. Roth M, Wang Z, Chen W. Sirtuins in hematological aging and malignancy. Crit Rev Oncog 2013;18(6):531-47 (PMID: 24579733).

50. Liang R, Ghaffari S. Mitochondria and FOXO3 in stem cell homeostasis, a window into hematopoietic stem cell fate determination. J Bioenerg Biomembr 2017;49(4):343-6 (PMID: 28639090).

51. Zhou L, Fu L, Lv N, et al. A minicircuitry comprised of microRNA-9 and SIRT1 contributes to leukemogenesis in t (8;21) acute myeloid leukemia. Eur Rev Med Pharmacol Sci 2017; 21(4):786-94 (PMID: 28272704).

52. Chalkiadaki A, Guarente L. The multifaceted functions of sirtuins in cancer. Nat Rev Cancer 2015;15(10):608-24 (PMID: 26383140).

53. Stünkel W, Peh BK, Tan YC, et al. Function of the SIRT1 protein deacetylase in cancer. Biotechnol J 2007;2(11):1360-8 (PMID: 17806102).

54. Huffman DM, Grizzle WE, Bamman MM, et al. SIRT1 is significantly elevated in mouse and human prostate cancer. Cancer Res 2007;67(14):6612-8 (PMID: 17638871).

55. Alves-Fernandes DK, Jasiulionis MG. The role of SIRT1 on DNA damage response and epigenetic alterations in cancer. Int J Mol Sci 2019 Jan;20(13):3153 (PMID: 31261609).

56. Simmons GE Jr, Pruitt WM, Pruitt K. Diverse roles of SIRT1 in cancer biology and lipid metabolism. Int J Mol Sci 2015;16(1): 950-65 (PMID: 25569080).

57. Liu T, Liu PY, Marshall GM. The critical role of the class III histone deacetylase SIRT1 in cancer. Cancer Res 2009;69(5):1702-5 (PMID: 19244112).

58. Wang Z, Yuan H, Roth M, Stark JM, Bhatia R, Chen W. SIRT1 deacetylase promotes acquisition of genetic mutations for drug resistance in CML cells. Oncogene 2013;32(5):589-98 (PMID: 22 410779).

59. Teng YQ, Jin H, Liu ZY, et al. The Lyn-SIRT1 signaling pathway is involved in imatinib resistance in chronic myeloid leukaemia. Am J Transl Res 2020;12(6):2711-25 (PMID: 32655803).

60. Li L, Wang L, Li L, et al. Activation of p53 by SIRT1 inhibition enhances elimination of CML leukemia stem cells in combination with imatinib. Cancer cell 2012;21(2):266-81 (PMID: 22340598).