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Review

Effects of Metformin on Leukemia: Biological Mechanisms, Targets, and Treatment Possibilities

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Abstract

Metformin is a widely prescribed medication for managing diabetes, but it also affects cancer cell metabolism through both direct and indirect mechanisms. Cancer cells often divide rapidly, and this quick division, along with metabolic changes, increases intracellular free radicals and inhibits the enzyme hexokinase. This inhibition prevents the conversion of glucose to glucose-6-phosphate, leading to glucose deprivation and subsequently causing mitochondrial depolarization and apoptosis in cancer cells. KDM1A is an epigenetic regulator that plays a vital role in cancer development. Both KDM1A and metformin influence autophagy and cancer-related pathways, and their interaction could lead to new treatment strategies. Metformin reduces oxidative stress and activates ATM signaling, since the ATM gene encodes a tumor suppressor protein that helps repair DNA mutations during stress. Additionally, the drug enhances the recognition of damaged DNA by increasing ATM protein levels. In acute myeloid leukemia (AML), leukemic stem cells (LSCs) often develop resistance after chemotherapy, which greatly contributes to treatment failures. This article aims to explore how metformin affects LSCs, DNA repair gene expression, and related biological mechanisms, as well as its targets and therapeutic potential. This study reviews existing articles about metformin's mechanisms in leukemia. Metformin shows significant potential for reducing mortality rates associated with various cancers, including leukemia.

1. Metformin: A medication for leukemia and diabetes

Changes in lipid and adiponectin mechanisms, as well as the overactivation of inflammatory cytokines and signaling pathways, occur similarly in both diabetes and cancer (1-3). Obesity, body mass index (BMI), insulin resistance, and hyperglycemia in individuals with diabetes are directly associated with a higher risk of leukemia (4, 5). Additionally, individuals with underlying metabolic syndrome have a higher risk of developing leukemia compared to those without it (6,7). One indirect mechanism of metformin is its ability to inhibit the mitotic division of cancer cells, which is influenced by lipogenesis and hyperinsulinemia. In cancer patients, somatomedin C promotes the division of cancer cells (8-11). Metformin helps prevent the survival of cancer cells through an indirect mechanism by activating the insulin receptor and reducing glucose levels. Since cancer cells depend on

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glucose for their survival and metabolism, the activation of AMPK by metformin decreases its availability for them (12, 13). In the cell nucleus, the downstream signaling of the AKT-mTOR pathway is essential for regulating cell growth and proliferation. Metformin inhibits this AKT-mTOR signaling by activating AMPK, which in turn reduces cell proliferation. This mechanism may offer a potential therapeutic strategy for leukemia, as the AKT-mTOR pathway is a key regulator of cellular metabolism and growth. Disruptions in this pathway can result in abnormal growth of cancer cells (14-16).

Metformin can induce various types of cell death through multiple signaling pathways and may act as a pro-toxicity agent in cancer treatment (17-19). Atenolol (metformin) can lower blood levels of glutathione (GSH) due to the action of plasma xanthine oxidase. Additionally, metformin may enhance the activity of important enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which play a crucial role in neutralizing free radicals(20). GSH, a non-protein thiol and antioxidant, plays a significant role in maintaining redox balance. It has a dual function: it protects against cancer while also potentially supporting tumor growth (21-26). The three essential glutathione enzymes: glutathione reductase, glutathione transferase, and glutathione synthetase—function normally in healthy cells. However, in cancer cells subjected to higher toxicity from chemotherapy, the activity of these enzymes is often impaired. This impairment, along with deficiencies in glutathione (GSH) and DNA repair mechanisms, leads to widespread genomic alterations, resulting in genomic instability and the potential formation of tumors (27-29).

2. Gene expression in leukemia

Chemotherapy-resistant leukemia stem cells (LSCs) play a complex role in influencing treatment outcomes. When these cells are exposed to chemotherapy and radiation, an enzyme called HK2, located in the nucleus of the LSCs, repairs double-stranded DNA damage. This rapid repair process, aided by HK2, not only contributes to the cells' resistance to chemotherapy but also enables their continued proliferation (30-34). During chemotherapy, leukemic stem cells can take refuge in the protective environment of the bone marrow niche, which shields them from the harmful effects of chemotherapeutic agents. This protective microenvironment plays a significant role in the development of chemotherapy resistance, ultimately leading to the relapse of leukemia. Therefore, it is essential to conduct further research on the mechanisms that underlie the chemical resistance of leukemic stem cells (35-37). KDM1A is a demethylase that contains a SWIRM domain at its N-terminal end and is involved in the interactions between protein molecules. It interacts with the transcription factor TAL1, which has a dual role in regulating KDM1A expression. When TAL1 is phosphorylated, it separates from the KDM1A complex, which triggers the production of red blood cells and contributes to the development of leukemia. Initially, the interaction between KDM1A and TAL1 is diminished and disrupted, leading to the suppression of erythroid function (38-41). In cancer patients, there is a significant increase in KDM1A and BCL2 expression, along with elevated KDM1A activity in both the nucleus and cytoplasm (42). Cancer cells exhibit elevated levels of reactive oxygen species (ROS). Research has shown that metformin can help prevent the progression of cancer. In various cancers, mutations cause changes in the proteins of the electron transport chain, which leads to increased ROS production and resistance to apoptosis (programmed cell death). Metformin can protect these electron transport chain proteins. Additionally, metformin induces changes in DNA methylation and affects the activity of S-adenosylhomocysteine hydrolase (SAHH). Its regulation of S-adenosylhomocysteine (SAH) levels is associated with its impact on DNA methylation (43, 44).

3. An Overview of the Biological Mechanisms of Metformin and Its Connection to Leukemia

Tumor cells modify their metabolism by increasing glucose consumption and converting it to lactic acid, even in the presence of oxygen. This adaptation allows them to survive and proliferate more effectively. Glycolysis becomes the main source of ATP for cancer cells, enabling them to grow significantly faster than normal cells, a phenomenon known as the Warburg effect. Additionally, low oxygen levels, or hypoxia, increase the expression of hypoxia-inducible factors (HIF), which stimulate the formation of blood vessels around the tumor (45-49). Cancer stem cells possess self-renewing capabilities and are metabolically active. They generate new cancer cells that exhibit metabolic characteristics distinct from standard cancer cells. This distinction contributes to the tumor's resilience against harsh conditions, including chemotherapy (50-52). Metformin is a medication frequently used to lower blood glucose levels. It works by inhibiting oxidative phosphorylation, which reduces the amount of cellular ATP (adenosine triphosphate). This depletion of ATP affects the activation of cancer stem cells by increasing the concentration of AMP (adenosine monophosphate) in the cell. As ATP levels decrease, AMP levels rise, leading to the

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activation of AMP-activated protein kinase (AMPK) (53, 54).

AMPK functions as a cellular energy sensor and is crucial for regulating metabolism, stress responses, and inflammation by activating various pathways. In cancer, AMPK is connected to the abnormal protein BCR-ABL. By lowering blood glucose levels and activating AMPK, metformin inhibits the growth of BCR-ABL-positive acute lymphoblastic leukemia (ALL) cells. Additionally, metformin can enhance the effectiveness of chemotherapy by increasing the sensitivity of ALL cells to treatment (55-58). Metformin helps inhibit the proliferation of cancer cells through several mechanisms. It stimulates the immune system, reduces the signaling of growth factors, and promotes the apoptosis (programmed cell death) of tumor-infiltrating lymphocytes (TILs). Additionally, metformin increases the levels of interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), while also inhibiting GTPase activity. These actions collectively contribute to the anticancer effects of metformin (59, 60). Acute lymphoblastic leukemia (ALL) is a type of blood cancer that primarily affects children and adolescents, especially those aged 2 to 5 years. Unlike other cancers, leukemia does not create solid tumors that can be surgically removed; instead, it primarily develops in the bone marrow. There are several treatment options available for leukemia, including chemotherapy, biological therapy (immunotherapy), kinase inhibitors, and bone marrow transplantation (61-66). Metformin also has an antitumor mechanism that involves epigenetic modifications in metabolism. It functions as a significant therapeutic agent by altering cellular energy metabolism. Indirectly, it lowers insulin levels, while its direct effects include reducing energy levels and influencing tumor formation. The metabolic mechanisms through which metformin acts in diabetic patients are similar to those observed in pro-inflammatory and cancer cells, where immune cells and their modulation serve as metabolic inhibitors (67-70). E-cadherin is crucial in the process of cancer metastasis. Research has shown that metformin can increase the levels of E-cadherin, which helps to prevent cancer cells from migrating to other parts of the body. Additionally, metformin reduces hypoxia by positively affecting blood vessels and promoting the regeneration of abnormal vessels, thereby inhibiting angiogenesis, a process that facilitates the migration of cancer cells. Moreover, individuals with a mutated version of the ATM gene are more susceptible to various types of cancer, including leukemia (71-74).

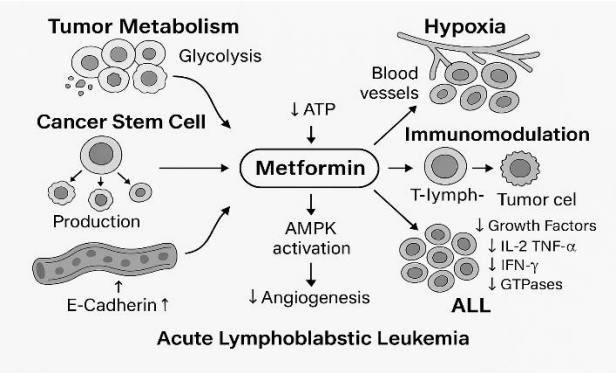

Figure 2. An Overview of the Biological Mechanisms of Metformin and Its Connection to Leukemia.

4. Metformin and Its Potential Role in Treating Leukemia

Metformin, an antidiabetic medication, has been studied as a potential cancer treatment over the past decade. Currently, chemotherapy is the main treatment for leukemia, but it often comes with numerous side effects. Therefore, it is essential to explore low-risk alternatives. Patients with acute leukemias typically have a very poor prognosis, highlighting the urgent need for new therapies and alternative treatment options (75-78). Metformin is a well-established medication that has been used for many years, instilling confidence in its application for cancer patients. In cases of leukemia, where traditional treatments like extensive surgery may not be feasible, and where bone marrow cells exhibit varying resistance patterns to chemotherapy, it is crucial to explore low-risk, continuous treatment options for these patients(79, 80). Modifying the metabolism of cancer cells offers a promising and low-risk approach to treatment. However, it is essential to note that metformin has not been thoroughly studied in children under 18 years of age. Acute lymphoblastic leukemia, which is prevalent among pediatric leukemia patients, necessitates that metformin be first researched for use in diabetic children. Only after this initial investigation should metformin be combined with chemotherapy for broader application in cancer treatment (80-82).

Acute lymphoblastic leukemia is more common in males. This may be attributed to factors such as lower levels of estrogen and progesterone, combined with higher levels of testosterone, which can promote increased cell proliferation and make men more susceptible to cancer. Additionally, the X chromosome contains several tumor suppressor genes, which could further influence this susceptibility (83, 84). Women have two X chromosomes, which may lead to higher expression levels of these genes

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compared to men, who possess only one X chromosome. This genetic difference may help explain why women are generally less likely to develop cancer (85-89). In a study conducted by Thomas Farg, researchers explored the effects of imatinib and metformin on chronic myeloid leukemia. The findings showed that metformin inhibits lactate excretion and glucose uptake by modulating lactate levels. This modulation leads to the accumulation of lactate, which ultimately results in cell death. Additionally, metformin inhibits the transporters MCT1 and MCT4 through AMPK phosphorylation, which suppresses mTORC1 activity and reduces HIF-1α expression. However, the induction of hypoxia allows cancer cells to restore their metabolic adaptation (90-93). New strategies are emerging to combat therapeutic resistance in leukemia. An effective and innovative approach is reprogramming the energy and cellular metabolism of cancer (94).

Several strategies for metabolic reprogramming aim to reverse drug resistance in cancer treatment. These include: 1. Immune Metabolism: This strategy involves the use of immunosuppressants and the activation of immune cells to enhance their effectiveness against cancer. 2. Targeting Mitochondrial Metabolism: This approach includes the use of inhibitors for mitochondrial complex I and ATP synthase to disrupt energy production in cancer cells. 3. Targeting Cancer Cell Attachment: This strategy employs glutaminase inhibitors and inhibitors of enzymes involved in the methionine cycle to impede cancer cell attachment and survival. These perspectives provide potential pathways to reverse drug resistance in cancer treatment (95). 4. Targeting epigenetic modifications involves using HDAC (histone deacetylase) and DNMT (DNA methyltransferase) inhibitors (96). 5. Manipulating the extracellular matrix: This approach utilizes inhibitors of HIF-1α. 6. Targeting glycolysis: This strategy employs inhibitors of glycolysis. 7. Addressing lipid metabolism disorders: This includes the use of FANS inhibitors, CD36 inhibitors, and CPT1 inhibitors. Together, these strategies aim to address the challenges of therapeutic resistance in leukemia (97-99).

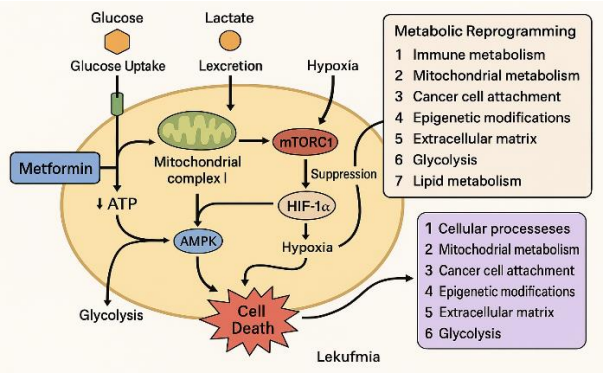

Figure 1. Metformin and Its Potential Role in Treating Leukemia.

5. Types of Leukemia and Challenges in Treatment

The term "leukemia" is derived from the Greek, combining "leukos," meaning "white," and "haima," meaning "blood." It refers to a group of blood cancers characterized by an excessive increase in white blood cells (100). Leukemia is categorized into four main types: 1. Acute Myeloid Leukemia (AML): This type involves abnormal myeloid cells and primarily affects adults. 2. Acute Lymphoblastic Leukemia: This type features abnormal lymphocytes and primarily occurs in children. 3. Chronic Lymphocytic Leukemia (CLL): This type involves abnormal lymphocytes and is most commonly found in older adults. 4. Chronic Myeloid Leukemia (CML): This type involves abnormal myeloid cells and can affect both adults and children (101-104). Leukemia cells possess a unique ability to migrate and invade tissues, allowing them to spread throughout the body without requiring genetic changes or mutations. Unlike solid tumors, which form secondary tumors in other parts of the body after separating from a primary tumor, leukemia metastasis is characterized by a rapid and progressive process that involves both tissues and the bloodstream. This invasive nature significantly contributes to the severity of leukemia as a disease (105-108). Hematopoietic stem cells (HSCs) are located in the protective niche of the bone marrow. While some of these cells remain inactive, others are mobile and circulate throughout the body. A specific subset of leukemia cells, known as leukemia stem cells (LSCs), can proliferate and divide. These LSCs can persist in a patient's body and regenerate even after treatment, which can lead to disease recurrence. This characteristic makes them significant in the context of metastasis (109-112). Various complex molecular components are involved in the metastatic stages of leukemia. One key component is selectin, whose ligands are present in different types of leukemia. Another vital group consists of integrins, which play crucial roles in cell anchoring and adhesion. Additionally, chemokines, cytokines, and growth factors help direct the movement of tumor cells and facilitate tumor invasion. Structural materials also significantly impact the metastasis process of leukemia and other cancers by influencing the adhesion and migration of cancer cells. Leukemic cells employ specific migratory strategies, such as amoeboid movement and the use of invasive pseudopods, which contribute to the spread of the disease (113-116). The treatment of Acute Myeloid Leukemia (AML) focuses on eliminating cancer cells and restoring normal bone marrow function, particularly by targeting resistant cells known as leukemia stem cells (LSCs). LSCs have diverse genetic profiles, making them difficult to identify and treat. Promising therapies, such as azacitidine and venetoclax, specifically target certain subsets of LSCs

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that are resistant to BCL-2. Additionally, BH3 mimetics are being utilized to overcome LSC resistance in AML treatment, representing a valuable and innovative approach (117-120).

6. The KDM1A and ATM genes

KDM1A is a complex molecule that interacts with protein complexes, playing a role in both gene activation and repression through its interactions with various transcription factor activators. It is recognized as a potential therapeutic target for cancer, as the expression of the KDM1A gene has been detected in both acinar and ductal adenocarcinomas of the prostate in men, as well as in estrogen receptor-negative breast cancer in women. Inhibiting KDM1A has been associated with improved treatment outcomes in leukemia and certain myeloid proliferative disorders (121-125). KDM1A interacts with various factors, including protein complexes, transcription factors, microRNAs, estrogen and androgen receptors, non-coding RNAs, and other proteins (126, 127). By influencing epigenetic changes, such as histone methylation, KDM1A regulates specific genes that help maintain the characteristics of stem cells. This regulation can contribute to resistance against common treatments like chemotherapy and radiation therapy (128-132). Histone modifications are vital in the development of various cancer types. In particular, histone methylation can inactivate tumor suppressor genes, impair DNA damage repair, lead to chromosomal instability, and increase the expression of oncogenes. KDM1A, a histone demethylase, acts as a negative regulator of oncogenic activity within cells. Effective pharmacological inhibitors of KDM1A can eliminate the clonal potential of leukemia cells and promote their differentiation (133-135). The ATM (ataxia-telangiectasia mutated) protein is crucial for repairing DNA double-strand breaks, which can result in cell malfunctions. The ATM gene functions similarly to the TP53 gene. As a pleiotropic protein, ATM prevents the processing of damaged DNA, regulates DNA repair functions, and triggers apoptosis if the DNA damage is persistent and remains unrepaired. This process is vital for maintaining genome integrity (136, 137). Deletions or mutations in the ATM gene are among the most common genetic abnormalities observed in patients with chronic lymphocytic leukemia (CLL). Structural changes in the ATM protein, especially point mutations, can impair its function and result in negative clinical outcomes for patients (138-140). Mutations such as R2691C and P2699S disrupt ATM kinase activity and are associated with serious biological disorders, particularly malignant neoplasms and an increased risk of leukemia. Heterozygous missense mutations significantly increase the likelihood of developing leukemia (141-143). Wilmore and colleagues demonstrated that mutations in the ATM gene can impair the function of DNA-PK, which negatively affects the repair of DNA double-strand breaks. They concluded that inhibiting DNA-PK in chronic lymphocytic leukemia (CLL) cells with mutated ATM can improve the effectiveness of chemotherapy. The close interaction between ATM and DNA-PK in the DNA repair process suggests a potential therapeutic strategy for treating CLL (144-147).

7. Conclusion

Metformin activates AMP-activated protein kinase (AMPK), which is a mechanism associated with cancer prevention. By inhibiting the mechanistic target of rapamycin (mTOR), the function of AMPK is stimulated (148, 149). Phenformin is a more potent biguanide than metformin; however, its use as a diabetes treatment was discontinued due to reports of lactic acid accumulation in the blood. In cases of acute lymphoblastic leukemia or lymphoma, phenformin has been shown to inhibit the proliferation of T cells. Metformin functions by inhibiting mitochondrial complex I, which subsequently leads to the activation of AMPK (150-152). Mitochondrial complex I plays a vital role in electron transport. Its inhibition decreases ATP (adenosine triphosphate) production and increases intracellular ADP (adenosine diphosphate) concentration. Consequently, AMP (adenosine monophosphate) levels rise, leading to the activation of AMPK (153-155). Recent studies indicate that metformin can activate AMPK via a lysosomal pathway known as the AXIN/LKB1-*v*-ATPase-Regulator pathway (155).

AMPK is a crucial regulator of several metabolic pathways, including glucose and lipid metabolism, as well as energy homeostasis. While metformin may possess anti-leukemic properties, it is vital to manage potential side effects carefully (156, 157). The way AMPK activates different signaling pathways in solid tumors as opposed to liquid tumors may clarify why metformin's effectiveness varies in preventing different types of cancer. Notably, its effectiveness is considerably lower in liquid cancers, such as leukemia, compared to its impact on solid tumors(14, 158). Metformin increases the levels of NKG2D and ICAM-1 proteins in cancer-infected cells, enhancing the binding affinity of killer T lymphocytes to these cells, which ultimately reduces tumor cell division and establishes it as an effective treatment for leukemia (159-161). Metformin modulates p53 activity and affects cellular metabolism by activating AMPK. It can also cause cancer cells to become

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resistant to cytotoxic lymphocytes by enhancing p53 expression or increasing levels of Bcl-xL (162-165). Metformin promotes senescence in liver cells, which could be a potential therapeutic strategy for cancer treatment. At low concentrations, it activates the AMPK pathway and increases p53 levels, leading to this senescence (166). Research has shown that metformin can target cancer stem cells. Metformin has shown promise in combating tumor growth and metastasis, highlighting the importance of its role in future studies related to leukemia. This medication helps prevent cancer cells from detaching from tumors, thus reducing the risk of metastasis to other tissues. This unique ability makes metformin a valuable tool in the fight against cancer. Furthermore, metformin significantly enhances the effectiveness of both radiotherapy and chemotherapy, underscoring its relevance in discussions about cancer treatment. It may also contribute to lowering the incidence of various types of leukemia. Considering that untreated leukemia often leads to an 80% mortality rate, there is an urgent need for effective and straightforward adjunctive therapies, with metformin emerging as a promising option (75, 167). Recent studies indicate that metformin may inhibit the growth of cancer cells with mutations in the DNMT3A gene, which is present in approximately one-sixth of cases of acute myeloid leukemia (AML) (168, 169). Empagliflozin is a diabetes medication that not only helps manage blood sugar levels but also significantly affects cardiovascular diseases, erectile dysfunction, and cancer. Ongoing research is exploring the impact of other antidiabetic drugs on various cancers, including leukemia (170, 171). These findings underscore the potential of metformin for cancer prevention and treatment, emphasizing the necessity for further research in this field. A graphical abstract summarizing the role of metformin in treatment of AML has been provided in **Figure 3.**

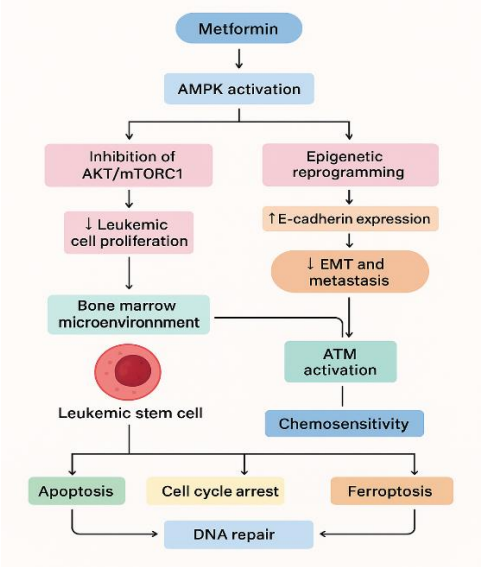

Figure 3. Graphical abstract.

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Conflict of interest

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Ethical statement

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