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Review

Glycolysis and immunosenescence: key players in the pathogenesis of acute myeloid leukemia and their therapeutic potential

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ABSTRACT

Acute myeloid leukemia (AML) is a hematopoietic progenitor cell-affected hematological malignancy, caused by the accumulation of genetic and epigenetic abnormalities leading to impaired cell differentiation, enhanced self-renewal capacity, and uncontrolled proliferation. Despite progress in understanding its biology and therapeutic strategies, the mortality rate remains high, with a five-year survival rate below 30%, and the clonal evolution of cells is complex, exhibiting genetic heterogeneity. Glycolysis plays a central role in the metabolic network of cancer cells. Cancer cells produce energy and substances through glycolysis, and their metabolic product, lactic acid, affects the tumor microenvironment (TME), leading to immune suppression, among other effects. Inhibition of glycolysis can enhance the sensitivity of AML to chemotherapeutic drugs. Aging is a risk factor for many diseases and leads to increased incidence and mortality rates of AML. Elderly patients exhibit greater heterogeneity. In AML, the dysfunction of T cells and NK cells is closely related to treatment responses. The process of T cell senescence is complex, involving various phenomena and mechanisms. Senescent T cells have weakened functions, affecting immune surveillance and TME, leading to reduced responses to chemotherapy. This review summarizes the significance of key glycolytic enzymes and aging in AML-related research.

KEYWORDS

acute myeloid leukemia (AML), glycolysis, aging, immunosenescence

1 Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy affecting hematopoietic progenitor cells, characterized by the accumulation of genetic and epigenetic abnormalities. These alterations result in impaired differentiation, enhanced self-renewal capacity, and uncontrolled proliferation [1, 2].

Over the past few decades, continuous advancements have been made in the biological understanding and therapeutic strategies for AML [3], however, the mortality rate remains alarmingly high, with a five-year survival rate of lower than 30% [4]. Additionally, the clonal evolution of AML cells is extensive, resulting in the emergence of leukemia cell subgroups with distinct mutation profiles. This genetic heterogeneity leads to the activation of complex signaling pathways, complicating AML treatment and necessitating individualized therapeutic approaches [5].

Metabolic reprogramming is recognized as a plausible contributor to the complexity of the disease, primarily involving glucose, fatty acid, amino acid, and mitochondrial metabolism. Among these, glycolysis holds a central role in the metabolic network of tumor cells, playing an irreplaceable role in tumorigenesis and progression [6]. Research on the mechanisms and clinical applications of glycolytic enzymes and products with altered expression levels in malignancies

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remains an active area of investigation [7]. Key enzymes in glycolysis are critical regulators of tumor metabolism. The altered expression levels of these enzymes in tumor cells, along with their interactions with other protein molecules, significantly impact disease progression [8]. The metabolic byproduct lactate contributes to the formation of an acidic tumor microenvironment, promoting the development of an immunosuppressive milieu, enhancing angiogenesis, impairing the function of immune cells within the tumor microenvironment (TME), and is associated with resistance to tumor immunotherapy [9, 10]. AML cells with high glycolytic activity exhibit low sensitivity to adriamycin (ADR), thus, targeting glycolytic regulation represents a promising strategy for treating AML [11].

Aging is a prominent risk factor for many chronic diseases. Senescent cells accumulate in normal tissues, leading to organ and tissue damage, and promoting tumor formation. Aging contributes to increased incidence of AML and mortality, with older AML patients exhibiting greater heterogeneity [12]. The prognosis for elderly AML patients is poor, with a median age of 68 years at diagnosis, and the five-year survival rate for patients over 60 ranges from 5% to 15% [13]. Aging-related genes frequently possess substantial clinical prognostic value for AML patients.

This review discusses the roles of glycolytic enzymes: hexokinase 2 (HK2), phosphofructokinase1 (PFK–1), pyruvate kinase M2 (PKM2), and immunosenescence in AML, and provides an overview of the research related to the clinical applications of glycolysis and immunosenescence.

2 The role of glycolysis in AML

2.1 The role of rate-limiting enzymes in glycolysis in AML

In the 1920s, the Warburg effect demonstrated that cancer cells predominantly rely on glycolysis for energy production, even in the presence of oxygen. This significant discovery highlighted an exceptional aspect of the glycolytic process in cancer cells [14]. Compared to oxidative phosphorylation (OXPHOS), tumor cells utilize substantial amounts of glucose through glycolysis to produce the necessary substances for cell proliferation and rapidly generate ATP to meet the energy demands during development [15]. Tumor cells usually exhibit the characteristics of low glucose levels and high lactate levels, and can absorb glucose from the environment competitively, thereby preventing its uptake by immune cells. This impairs the physiological activity of immune and stromal cells, increases glycolysis, and produces more lactate, which creates an acidic environment favorable for tumor growth [16]. For example, AML cells upregulate glycolysis and the pentose phosphate pathway to generate macromolecules such as amino acids and nucleotides, which are necessary for sustaining the leukemic state [17]. Studies have demonstrated that AML cells with rapid proliferation develop resistance to Ara-C by enhancing glucose metabolism [18]. Inhibiting glycolysis can increase AML's sensitivity to chemotherapeutic agents [19].

Enzymes that regulate the rate of glucose metabolism are critical for tumor growth. Tumor cells upregulate HK2 and glucose transporter 1 (GLUT1) to increase glucose uptake. Activation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) and PFK1 stimulates glycolysis and enhances the expression of lactate dehydrogenase A (LDHA), which catalyzes the conversion of pyruvate to lactate [20] (Fig. 1).

2.1.1 HK2

Hexokinase acts as the initial rate-limiting enzyme, catalyzing the entry of glucose into tumor cells and its phosphorylation to form glucose-6-phosphate (G-6-P) [21]. Currently, five major hexokinase isoforms are known in mammals. The role of the recently identified hexokinase domain-containing protein 1 (HKDC1) is not yet fully understood [22], while HK1, HK2, HK3, and HK4 are the four well-characterized hexokinase isoforms [23]. HK1 and HK3 exhibit catalytic activity solely at their C-terminal ends, whereas HK2 demonstrates catalytic activity at both the C-terminal and N-terminal ends under various physiological conditions [24]. In tumor cells, HK2 binds to voltage-dependent anion channel 1 (VDAC1), controlling the movement of the channel pore and inhibiting the transition of VDAC1 to the closed state, thereby

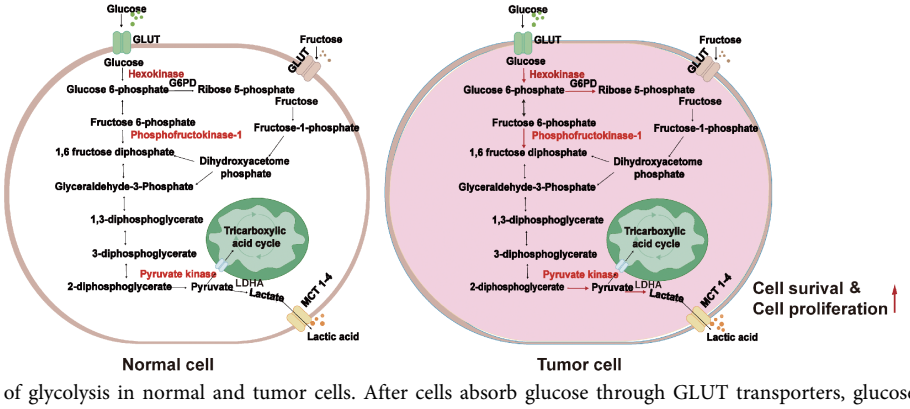

Figure 1 An overview of glycolysis in normal and tumor cells. After cells absorb glucose through GLUT transporters, glucose undergoes a series of enzymatic steps in the cytoplasm, ultimately producing pyruvate. When oxygen is abundant, pyruvate enters the mitochondria to participate in the tricarboxylic acid (TCA) cycle. In the absence of sufficient oxygen, under the catalytic effect of lactate dehydrogenase (LDH), pyruvate is converted into lactate, which is then excreted from the cells via the monocarboxylate transporter (MCT). Hexokinase, phosphofructokinase, and pyruvate kinase act as rate-limiting enzymes to regulate this metabolic process. Glucose-6-phosphate is catalyzed by glucose-6-phosphate dehydrogenase to produce pentose phosphate, NADPH, and carbon dioxide. Fructose enters the cells and ultimately participates in the glycolysis process in the forms of fructose-1,6-bisphosphate and glyceraldehyde-3-phosphate. In tumor cells, the glycolytic process is intensified, promoting cell survival and proliferation.

protecting cancer cells from apoptosis [25, 26]. Hypoxia-inducible factor 1 alpha (HIF1α) binds to the hypoxia response element (HRE) on the promoter of HK2, leading to increased expression of HK2 and accelerating glycolytic activity [27]. A combination of specific HK2 inhibition, partial OXPHOS inhibition, and partial fatty acid oxidation (FAO) inhibition offers a promising therapeutic strategy for treating $HK1^{-}HK2^{+}$ cancers, which may be well tolerated by normal tissues [28]. In addition to its glycolytic kinase activity, HK2 overexpression in the nucleus of leukemic stem cells interacts with nuclear proteins that regulate chromatin accessibility. This interaction enhances stemness and chromatin accessibility at DNA repair sites, independently of its metabolic functions, thereby increasing stemness, inhibiting differentiation, reducing double-strand breaks, and conferring chemoresistance to leukemic stem cells [29].

HK2 is the main subtype catalyzing the glycolytic process in AML cells, while HK3 exerts protective effects through non-glycolytic functions in myeloid cell survival. HK3 is significantly upregulated during the *in vitro* myeloid differentiation of healthy $CD34^{+}$ hematopoietic stem and progenitor cells, and its absence results in elevated ROS production and accumulated DNA damage in AML [30].

2.1.2 PFK-1

PFK-1 catalyzes the conversion of fructose-6-phosphate (F-6-P) to fructose-1,6-bisphosphate (F-1,6-BP) using ATP, serving as another critical enzyme in glycolysis. In human tissues, PFK-1 has three isoforms: PFKP (platelets), PFKM (muscle), and PFKL (liver) [12]. PFKP holds a more pivotal role than PFKL and PFKM [31]. Elevated PFKP expression is frequently associated with disease. For instance, AML patients exhibit higher PFKP expression, particularly in subtypes with poorer cytogenetic risk [32]. Although PFK-1 inhibitors cannot specifically inhibit PFKP, studies have shown that R-2-hydroxyglutarate (R-2HG) can inhibit the activity of fat-mass- and obesity-associated (FTO) protein, a key oncogenic factor in AML, thereby inhibiting the glycolysis process of sensitive leukemic cells, and further reducing the expression of glycolytic enzymes PFKP and LDHB, ultimately demonstrating antitumor activity [33].

2.1.3 PKM2

PKM2 is overexpressed in a variety of cancers and is regarded as a potential therapeutic target [34]. Notably, the expression level of PKM2 in the peripheral blood of AML patients is markedly increased [35]. The drug deoxyshikonin suppresses PKM2 expression through the inactivation of the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, thereby reducing glycolysis and suppressing cell viability in AML cells [36].

Besides its role as a metabolic regulator, PKM2 also functions as a protein kinase involved in cellular activities. In AML cells with NPM1 mutation, autophagic activity is elevated, and metabolic enzymes are involved in autophagy regulation. Highly expressed PKM2 enhances the phosphorylation of Beclin-1, a key autophagy protein, and has the potential function of promoting cell survival by maintaining autophagy in AML with NPM1 mutation [37]. Studies have shown that PKM2 plays a critical role in the proliferation and differentiation of AML cells. The inhibition of PKM2 expression leads to cell cycle arrest at the G1 phase, induces apoptosis, and suppresses AML cell proliferation *in vitro* [38]. Disruption of the interaction between PKM2 and RUNX1 blocks myeloid differentiation *in vitro* and in xenograft models [37, 39]. JOSD2, a member of the Machado–Joseph deubiquitinase (MJD) family expressed at a low level in AML, inhibits the acetylation of K433 of PKM2 and regulates the nuclear localization of PKM2 rather than its protein level, thereby inhibiting the progression of AML [40].

2.2 The metabolite Lactate is involved in the immunosuppression of AML

2.2.1 The role of glycolytic enzymes in immunosuppression and evasion

Increased expression of HK2 promotes the development of an immunosuppressive and tumor-promoting environment by regulating the ratio of $CD8^{+}$ T cells to regulatory T (Treg) cells. Higher HK2 expression represents a higher rate of tumor glycolysis and is associated with an immunosuppressive microenvironment, which is usually related to poor prognosis in patients [41]. HK2 promotes the expression of programmed cell death ligand-1 (PD-L1) in breast cancer cells, establishing a connection between aerobic glycolysis and immune escape in tumor cells [42]. In hepatocellular carcinoma (HCC), epidermal growth factor (EGF) promotes the upregulation of PD-L1. Inhibiting PKM2 can block EGF-induced PD-L1 expression, thereby reducing the inhibition of T cell proliferation and function [43]. High level of PKM2 is associated with poor prognosis [35], and in lung cancer, PKM2 expression is negatively correlated with immune cell infiltration [44]. In addition to regulating tumor cell metabolism, PKM2 also plays a role in regulating immune cell metabolism. PKM2 translocates to the nucleus and interacts with signal transducer and activator of transcription 3 (STAT3), enhancing the activation of STAT3 and thereby promoting the differentiation of Th-17 cells [45]. Inducing the tetramerization of PKM2 in T cells and preventing its nuclear translocation can inhibit glycolysis by suppressing signaling pathways and reducing T cell activation, proliferation, and cytokine production [46]. PKM2 expressed in macrophages in TME contributes to tumor cell migration and invasion and promotes disease progression. In cancer immunity, PKM2 plays a sequential role in tumor cell killing and immune escape, regulates the expression of PD-L1 in M2 macrophages, and reduces the number and activity of $CD8^{+}$ T cells [47, 48].

2.2.2 The role of lactate in the AML tumor microenvironment

TME is a complex environment where tumor cells, immune cells and stromal cells coexist and interact. The metabolic reprogramming of tumor cells transforms the TME into a tumor-promoting environment, greatly affecting tumor growth and progression. Tumor cells undergo rapid glycolysis, leading to reduced glucose and increased lactate levels in adjacent cells (including immune cells) [49]. As a result of extensive glycolysis, the accumulation of lactate in the TME suppresses anti-tumor immune responses. Lactate is a substrate for histone lactylation. Histone lactylation is a post-translational modification that regulates gene expression by

covalently attaching lactate groups to lysine residues on proteins. Lactylation plays a role in various physiological and pathological processes [50]. AML cells use lactate as a metabolic bypass to enhance mitochondrial respiration and maintain cell viability, which contributes to drug resistance in AML [51]. Elevated tumor glycolysis levels lead to an immunosuppressive tumor microenvironment by reducing the function of effector T cells [49]. Lactate promotes the accumulation of PD-1-positive regulatory T cells (Treg cells), which are key immunosuppressive components in the tumor microenvironment of AML patients [52]. Lactic acid upregulates the thymocyte selection-associated high mobility group box (TOX), leading to the exhaustion of $CD8^+$ T cells in AML [53]. In leukemia cells, the histone lactylation on the PD-L1 promoter promotes the expression of PD-L1, which further inhibits the activation of $CD8^+$ T cells [54].

2.3 Clinical application value of glycolysis inhibitors

Clinically, AML is mainly diagnosed by evaluating whether the proportion of blast cells in bone marrow or peripheral blood exceeds 20%, analyzing immunophenotype, or detecting specific chromosomal translocations.

More than 97% of AML cases have gene mutations. These molecular changes are related to the development of AML and provide key insights for the diagnosis and treatment of AML [55]. These mutations drive the heterogeneity of AML phenotypes and clinical outcomes [56]. Common mutated genes include *FLT3-ITD* [57], *NPM1* [58], and *CEBPA* [59]. Understanding the relationship between AML gene mutations and glycolysis is essential for developing metabolic pathway interventions targeting these mutations.

In patients with cytogenetically normal AML (CN-AML), the level of glycolytic metabolites is negatively correlated with patient prognosis. In NPM1-mutated AML, glycolytic enzymes promote autophagy and tumor proliferation [37, 60]. The combination of cytarabine and the glycolysis inhibitor 2-DG results in increased tumor cell death, indicating that glycolysis inhibitors can enhance the sensitivity of tumor cells to chemotherapy. *In vivo* experiments have shown that inhibiting the expression of PKM2 and LDHA not only reduces the glycolytic metabolism of leukemia cells but also impairs the proliferative capacity of hematopoietic cells [61]. FLT3-ITD mutations increase glycolysis levels through AKT-mediated upregulation of HK2, making FLT3-ITD mutant leukemia cells highly dependent on glycolysis. Therefore, glycolysis inhibition leads to severe ATP depletion and extensive cell death in FLT3-ITD leukemia cells. Glycolysis inhibitors significantly enhance the cytotoxic effects induced by sorafenib inhibitors [62].

3 Research developments on aging in AML

3.1 Immunosenescence

3.1.1 Characteristics of immunosenescence

Immunosenescence refers to age-related disturbances in the immune system, including thymic involution, reduced naive T cell populations, impaired functionality of memory T cells, and decreased diversity in T cell antigen recognition, resulting in a reduction of immune cell subsets and an overall decline in immune function [63, 64]. Many diseases are associated with immunosenescence, which affects both innate and adaptive immunity. T cell senescence is a complex process involving various phenomena and characteristics. The accumulation of dysfunctional and terminally differentiated T cells is a hallmark of T cell aging [64]. The terminally differentiated $CD8^+$ effector memory $CD45RA^+$ T_{EMRA} cells accumulate during chronic viral infections and exhibit certain features of cellular senescence; however, their cell cycle arrest is reversible, distinguishing them from truly senescent cells [65]. The proliferation capacity and effector functions of aged T cells are diminished, making them less effective at recognizing and killing tumor cells. T cell senescence impairs the body's immune surveillance capabilities, weakening the ability to recognize and respond to pathogens, which hinders the timely clearance of infections. Furthermore, changes in the cytokine profile secreted by aged T cells may also influence TME, promoting tumor growth and metastasis [66]. Aging leads to the redistribution of NK cell subsets, indicating that the NK cell population undergoes a remodeling process. Telomere shortening may result in dynamic changes in NK cells, leading to reduced proliferation and production rates. Aging alters the expression and function of NK cell receptors, impacting their interactions with other cells and diminishing their ability to initiate adaptive immune responses [67]. The aging process results in changes in the distribution of mature B cell subsets, leading to impaired activation upon stimulation [68].

3.1.2 Molecular mechanisms

In immunosenescence, metabolic and epigenetic mechanisms play crucial roles in determining the fate of T cell subsets. T cells gradually enter a state of dysfunction, undergoing metabolic reprogramming and epigenetic remodeling until they reach senescence or even apoptosis [69]. Continuous antigen-induced genomic or epigenomic damage leads to the activation of p38, ultimately triggering a DNA damage response, cell proliferation arrest, and autophagy inhibition, which in turn induces T cell senescence [70]. MicroRNAs (miRNAs) mediate chromatin remodeling and release inflammatory mediators in immunosenescence [71], and interfere with the development and differentiation of T cells [72], and B cells [73].

3.2 The role of senescent cells in the AML microenvironment

AML is a hematological malignancy caused by clonal proliferation due to genetic mutations, which is more common in elderly patients [74]. The health status of AML patients varies with age. Compared to younger patients, older patients are more likely to experience comorbidities, adverse cytogenetics, higher expression of multidrug resistance, and poorer responses to chemotherapy [13]. Irreversible cell cycle arrest, while maintaining viability and metabolic activity, is a hallmark of cellular senescence [75]. The persistent presence of senescent cells in tissues and organs promotes tumorigenesis [76]. Hematopoietic stem cells (HSCs) provide a lifelong supply of various mature blood cells in peripheral blood and tissues. Over time, aging leads to somatic mutations within individual HSC clones, conferring a proliferative advantage to specific clones. This age-related clonal hematopoiesis is common but carries a risk of transformation

into hematological malignancies [77].

3.2.1 Senescence of MSC and the role of SASP in AML

Bone marrow aging is closely associated with various cellular dysfunctions, including hematopoietic disorders, susceptibility to hematological malignancies, and the progression of leukemia [78]. Mesenchymal stem cells (MSCs) play a crucial role as core components of the supportive microenvironment in hematopoiesis. Although different types of leukemia have specific genetic defects, alterations in the bone marrow microenvironment may produce similar effects [79]. The increased incidence of hematological malignancies with aging is influenced by changes in the microenvironment [80]. Bone marrow mesenchymal stromal cells (BM-MSCs) are key regulators of hematopoietic stem cell maintenance and fate determination [81]. The accumulation of aged BM-MSCs may promote the progression of precursor hematological disorders to overt malignancies. In patients with myelodysplastic syndromes (MDS) and AML, BM-MSCs exhibit elevated levels of senescence-associated secretory phenotype (SASP) factors, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [82]. The increased expression of SASP factors in the bone marrow and plasma of MDS patients can predict OS and actively promote the progression from MDS to AML. Previous reports have indicated that IL-6 can promote the growth of the AML cell line HL-60. Aged BM-MSCs exhibit enhanced survival of leukemia cells while providing reduced support for normal hematopoiesis [83]. Aged BM-MSCs in MDS may create a tolerant, SASP-rich microenvironment for leukemia cells, promoting the reprogramming of adjacent cells and the progression from MDS to AML [84]. SASP mediated by senescent cells promotes the occurrence and progression of AML by creating a pro-inflammatory environment in the bone marrow microenvironment, SASP may influence the prognosis of AML patients by reshaping the TME [85]. Senescent T cells induced by tumor cells and Tregs possess a unique SASP that can secrete large amounts of cytokines, such as IL-6, IL-8, and TNF, through autocrine or paracrine mechanisms, creating an immunosuppressive microenvironment that induces more senescent T cells while also affecting immune and tumor cells [86]. SASP promotes the expansion of $FOXP3^+$ Tregs and $CD11b^+Ly6G^{Hi}$ cell populations, leading to immune evasion and suppression of tumor immune responses [87].

3.2.2 Immune senescence in AML

Cellular senescence plays a crucial role in regulating the immune environment of AML and influencing treatment outcomes [88]. Senescent cells can be effectively recognized and cleared by immune cells, being replaced by healthy cells [89]. Due to age-related immune system decline, the clearance of these cells is impaired, leading to immune cell recruitment and subsequent functional impairment. The immune system gradually loses its ability to effectively respond to pathogens and cancer cells, increasing susceptibility to various pathogens and the risk of certain cancers [64, 90]. Detecting immune senescence is crucial for disease detection and clinical guidance. The proportion of most age-related immune cells begins to decline after the age of 35, with significant changes observed in $CD4^+$ T cells, $CD8^+$ T cells, and γδ T cells, which are often associated with cancer development and various immune deficiency diseases [91]. Dysfunction of T cells and NK cells, such as the aging and exhaustion of $CD8^+$ and $CD4^+$ T cells, as well as impaired function of NK and γδ T cells, is critical in AML. These immune abnormalities are closely related to treatment responses, patient prognosis, and survival rates in AML [92]. An increased number of senescent T cells has been detected in AML, which is associated with a reduced likelihood of achieving chemotherapy response. AML progenitor cells actively induce $CD8^+$ T cell senescence. Senescent-like bone marrow $CD8^+$ T cells exhibit impaired cytotoxicity against autologous AML progenitor cells, and their proportion is negatively correlated with OS [93]. Reversing immune dysfunction is an attractive approach for AML treatment. Senescent cells release danger signals, activate interferon signaling, enhance MHC class I mechanisms, and present senescence-associated antigens, effectively activating $CD8^+$ T cells. Inducing senescence in human primary cancer cells can enhance the ability of anti-tumor $CD8^+$ T lymphocytes. These findings suggest that leveraging senescent cells could generate an effective, protective $CD8^+$ T cell-dependent anti-tumor immune response [94].

3.2.3 Accumulation of senescent cells in AML and its impact on treatment

AML progenitor cells promote the survival and proliferation of leukemia cells by inducing a senescent phenotype in stromal cells within the bone marrow microenvironment, primarily through p16INK4a-driven SASP. Targeting NOX2 to reduce stromal cell senescence may improve the prognosis of AML patients [95]. Studies have found that ginsenoside Rg1 can significantly inhibit the proliferation of $CD34^+CD38^-$ leukemia stem cells derived from KG1a AML cells, inducing cellular senescence by activating the SIRT1/TSC2 signaling pathway [96]. Gefitinib affects glutamine metabolism in leukemia cells via the glutamine transporter SNAT1 (SLC38A1), regulating metabolic pathways such as the tricarboxylic acid cycle and 2-hydroxyglutarate, resulting in reduced ATP production, decreased glutathione synthesis, and increased reactive oxygen species levels, thereby promoting cellular senescence [97]. 753B is a novel BCL-XL/BCL-2 protein hydrolysis-targeting chimera (PROTAC) that targets BCL-XL in senescent cells to enhance chemotherapy efficacy and exhibits significant monotherapy activity across different AML subtypes [98]. Chemotherapy can induce reversible senescence in myeloid leukemia cells, allowing them to resist drug treatment and resume proliferation after drug removal, although they retain senescence-associated phenotypes. During the therapy-induced senescence process, the lysosomal pathway is upregulated, promoting the survival of DA3/EPOR cells. Inhibiting lysosomal function and eliminating therapy-induced senescent cells may reduce the adverse effects of SASP and lower the frequency of AML relapse [99] (Fig. 2)

3.3 The role of senescence-related genes in the prognosis of AML

In intermediate-risk AML (IRC-AML), characterized by a lack

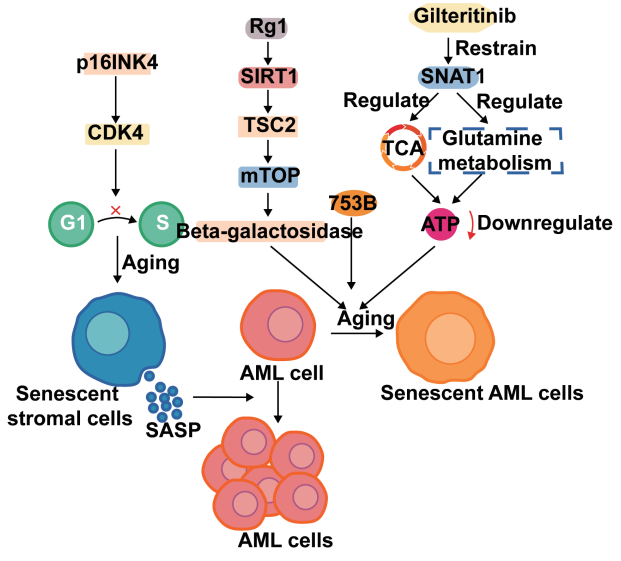

Figure 2 The progression of AML with the participation of senescence. Stromal cells expressing p16INK4a facilitate the survival and proliferation of leukemia cells via the senescence-associated secretory phenotype (SASP). The drug Ginsenoside Rg1 propels cells into a senescent state by activating the SIRT1/TSC2 signaling pathway; 753B is capable of boosting the efficacy of chemotherapy for AML by targeting senescent cells; Gilteritinib induces leukemia cells to enter a senescent state by acting on the glutamine transporter SNAT1 and associated metabolic pathways.

of specific genomic abnormalities, short telomere length (TL) is an independent adverse prognostic factor, potentially reflecting the link between genomic instability and disease progression [100]. Most senescence-associated genes (SAGs) are involved in mitochondrial dysfunction and immune senescence. Among the seven SAG characteristics, PTPN1, DGAT1, SOD1, GSTP1, and NUDT1 are risk factors, while EMD and STK11 are protective factors. The 7-SAG signature effectively predicts OS in AML and serves as an independent prognostic factor for AML outcomes [101]. Among the cellular senescence-related genes (SRGs), six highly upregulated and two significantly downregulated differentially expressed genes were identified. The SRG signature can classify AML patients with differing OS outcomes. AML patients with higher SRG scores exhibit an immunosuppressive tumor microenvironment, which may hinder the immune system's ability to eliminate tumor cells. This score correlates positively with the infiltration levels of M2 macrophages, B cells, monocytes, and myeloid dendritic cells. Furthermore, the high-scoring group exhibits increased levels of inflammatory regulatory factors and growth factors, along with markedly elevated levels of T cell exhaustion markers (including PD-1, CTLA-4, and LAG3), confirming that T cell function may significantly decline as senescence progresses [88].

4 Conclusion

The five-year survival rate of AML patients is lower than 30%, and 60% of these patients will relapse and eventually die of the disease [4]. Various treatment strategies have been proposed to improve the clinical prognosis of AML patients, but combination chemotherapy remains the cornerstone of AML treatment [102].

The crucial role of the Warburg effect in tumors has driven the exploration of new therapeutic strategies. The high expression of glycolytic enzymes and excessive products during glycolysis may also promote tumor progression. In this review, we discuss the important roles of glycolytic enzymes and their products in regulating AML proliferation, death, drug sensitivity, and altering the TME. The elevated levels of pyruvate and lactate in the serum of AML patients are associated with poorer survival and can aid in prognostic assessment [103]. Targeting glycolytic enzymes can inhibit AML progression, thereby improving prognosis and prolonging the survival time of patients. Inhibiting glycolysis by suppressing glycolytic enzymes results in significant energy loss and leukemia cell death [104]. Inhibiting HK2 with 2-DG enhances the cytotoxicity of cytarabine against AML cells [103], and AML cells with genetic mutations are more susceptible to 2-DG treatment than normal hematopoietic cells [105]. Therefore, glycolytic enzymes play a crucial role in the diagnosis and treatment of AML, and the application of glycolytic enzyme inhibitors is a promising therapeutic method.

Aging is a continuous challenge for humans and affects health on multiple levels. In terms of immunity, the function of senescent immune cells is impaired, leading to a decrease in the ability to clear pathogens and an acceleration of tumor progression. The cytokines secreted by senescent cells can be used as markers for diagnosis and prognosis. Targeting senescent cells may effectively alleviate diseases. The treatment of elderly AML patients is challenging. Studying the changes in immune responses related to physiological age is crucial for developing targeted therapies for elderly AML patients. The characteristics of immunosenescence affect innate and adaptive immunity. The aging of T cells affects immune surveillance and TME. In AML, the dysfunction of T cells and NK cells is related to treatment response and so on. The aging of hematopoietic stem cells and bone marrow mesenchymal stem cells can promote disease progression. Senescent cells can also produce anti-tumor immune responses. Some drugs can resist leukemia. Chemotherapy can induce reversible aging of leukemia cells. Eliminating senescent cells may improve treatment results. Certain genetic characteristics can predict the prognosis and tumor microenvironment of AML and provide guidance for treatment.

Author contributions

T. C, X. A. C. and C. Y. had developed the concept, synthesized the literature, drafted and finalized the manuscript. Y. L. and L. L. collected and synthesized the literature, drafted the manuscript. J. F. and Z. Y. J. developed the concept and finalized the manuscript.

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Conflict of Interests

The author declared no conflict of interests in relation to this research or its publication

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