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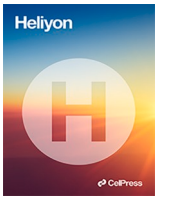

Review article

Glycolysis and chemoresistance in acute myeloid leukemia

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ABSTRACT

While traditional high-dose chemotherapy can effectively prolong the overall survival of acute myeloid leukemia (AML) patients and contribute to better prognostic outcomes, the advent of chemoresistance is a persistent challenge to effective AML management in the clinic. The therapeutic resistance is thought to emerge owing to the heterogeneous and adaptable nature of tumor cells when exposed to exogenous stimuli. Recent studies have focused on exploring metabolic changes that may afford novel opportunities to treat AML, with a particular focus on glycolytic metabolism. The Warburg effect, a hallmark of cancer, refers to metabolism of glucose through glycolysis under normoxic conditions, which contributes to the development of chemoresistance. Despite the key significance of this metabolic process in the context of malignant transformation, the underlying molecular mechanisms linking glycolysis to chemoresistance in AML remain incompletely understood. This review offers an overview of the current status of research focused on the relationship between glycolytic metabolism and AML resistance to chemotherapy, with a particular focus on the contributions of glucose transporters, key glycolytic enzymes, signaling pathways, non-coding RNAs, and the tumor microenvironment to this relationship. Together, this article will provide a foundation for the selection of novel therapeutic targets and the formulation of new approaches to treating AML.

1. Introduction

Tumor metabolism is characterized by high levels of glucose dependence and enhanced glycolytic metabolic activity [1]. Even under normoxic conditions, the glycolytic machinery remains active within the cytosol of tumor cells, converting glucose into lactate and ATP through a form of abnormal aerobic glycolysis, referred to as the “Warburg effect” [2]. Relative to healthy cells，malignant cancer cells exhibit markedly enhanced potential for aerobic glycolysis, providing high levels of energy that can help support tumor cell survival [3]. Higher levels of glucose uptake and aerobic glycolytic activity are key tumor-associated phenotypes, and they also

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play important functional roles as mediators of therapeutic resistance and tumor recurrence [4].

Acute myeloid leukemia (AML) is a hematologic malignancy originated from hematopoietic stem cells and progenitor cells, which is characterized by abnormally elevated levels of myeloid precursor and immature cell proliferation leading to symptoms including anemia, infections, hemorrhage, and extramedullary organ infiltration [5]. AML is the most frequently diagnosed form of acute leukemia among adults, and while curative outcomes can generally be achieved in 35%–40 % of AML cases under 60 years of age, long-term remission is generally only achieved in 15 % of AML patients over the age of 60 [6]. AML cases comprise 15–20 % of all pediatric leukemias, and the overall survival rate of children with AML is no more than 82 %, with a 5-year event-free survival rate of 46–69 % [7]. Treatment approaches for AML patients generally entail initial induction therapy, post-remission therapy, hematopoietic stem cell transplantation, and immunotherapy [8]. While clinical advances have conferred marked improvements to AML patient complete remission and 5-year survival rates, an estimated 60–80 % of those patients who achieve complete remission, ultimately relapse at some point, with chemoresistance being a key contributing factor to such relapse incidence [9–11]. Many interacting factors contribute to the emergence of drug resistance, including the inhibition of apoptotic cell death, the abnormal activation of intracellular survival signaling pathways, the altered expression of miRNAs related to drug resistance, metabolic abnormalities, and changes in multi-drug resistance enzyme dynamics [12,13]. The close relationship between glucose metabolism and chemoresistance has been a focus of growing interest in the leukemia research space [14]. The inhibition of glycolysis may represent an effective means of improving chemoresistance [15,16]. This review provides an overview of the contributions of glucose transporters and key glycolytic enzymes (Fig. 1), as well as signaling pathways, non-coding RNAs (ncRNAs), and the tumor microenvironment to drug resistance in AML with the goal of providing a foundation for new approaches to studying and overcoming AML-associated chemoresistance.

2. Glucose transporters and chemoresistance in AML

Glycolysis is the core oxidative catabolic process that all organisms employ when processing glucose [17]. When sufficient oxygen is available, pyruvate generally enters into the mitochondria wherein it is processed through the tricarboxylic acid cycle (TCA), producing CO2 and H2O; when oxygen is unavailable, pyruvate is instead processed by the glycolytic machinery leading to the generation of lactate through the effects of lactate dehydrogenase [18]. Glucose transporters (GLUTs) are a family of proteins that control the influx and efflux dynamics of glucose in particular organs and tissues, with the transport of glucose into the cytosol via plasma membrane GLUTs, serving as the first rate-limiting step in the process of glucose metabolism [19]. GLUTs are transmembrane mediators of facilitated sugar diffusion encoded by *SLC2* gene family members [20]. Many tumor cells, including those in leukemia, present with GLUT upregulation [21,22]. A GLUT1, GLUT3, GLUT4 , GLUT5 upregulation has been linked to chemoresistance in leukemia, and the inhibition of these transporters can confer greater leukemia cells sensitivity to chemotherapeutic agents [23,24] (Table 1).

Glucose transporter 1 (GLUT1), also known as solute carrier family 2 member 1 (SLC2A1), is among the most important GLUT transporters in tumor cells [25]. Consisting of a single intracellular domain and 12 transmembrane helices , GLUT1 is responsible for

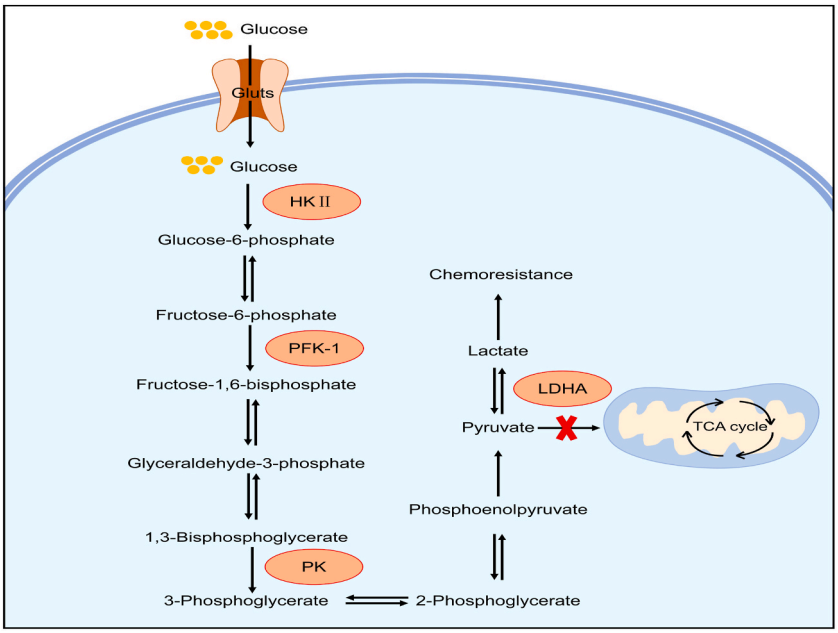

Fig. 1. Overview of glucose transporters and key glycolytic enzymes in AML resistance. Under normoxic conditions, glucose is converted to lactate and ATP with the assistance of GLUTs and glycolytic enzymes instead of entering the TCA cycle. GLUTs：Glucose transporters; HKII：Hexokinase II; PFK-1：Phosphofructokinase-1; PK：Pyruvate kinase; LDHA：Lactate dehydrogenase A; TCA：tricarboxylic acid cycle.

Table 1
GLUTs and their characteristics in AML chemoresistance.

GLUTs	Characteristics	Reference
GLUT1	High expression of GLUT1 increases resistance to Adriamycin; GLUT1 overexpression increases the resistance of AML cells to cytarabine (Ara-C).	[14,28,29]
GLUT3	GLUT3 silencing increased the sensitivity of AML cells to Vincristine (VCR).	[32]
GLUT4	GLUT4 is highly expressed in drug-resistant leukemia cells, and the decreased expression of GLUT4 can enhance the sensitivity of drug-resistant leukemia cells to Adriamycin; The decreased expression of GLUT4 can increase the sensitivity of AML cells to Ara-C;	[28,35]
GLUT5	High expression of GLUT5 is associated with poor prognosis in AML patients, and inhibition of GLUT5 to block the utilization of fructose can enhance the cytotoxicity of Ara-C.	[38]

facilitating basal cell glucose uptake in many different tissue types, in addition to catalyzing glucose diffusion into erythrocytes [25]. As the most important member of the GLUTs family, GLUT1 is majorly responsible for limiting the metabolic processing of glucose within tumor cells, and it is frequently upregulated in tumor cells, thereby driving enhanced glucose uptake [26,27]. Song et al. determined that AML patients who did not achieve remission and AML-resistant cell lines presented with increased GLUT1 expression and concomitant enhancement of glycolytic activity. Downregulating the expression level of GLUT1 or the use of the glycolytic inhibitor 3brpa or 2-DG combined with Adriamycin (ADR) to inhibit GLUT1 activity was sufficient to reduce glucose consumption and ADR resistance, underscoring the importance of altered glucose metabolism as a regulator of chemoresistance in AML and highlighting the promise of GLUT1 as target for tumor chemosensitization [14,28]. Abacka et al. also found that PGL compounds (putative GLUT1 inhibitors) are capable of enhancing GLUT1-overexpressing AML cell sensitivity to cytarabine, providing an opportunity to overcome cytarabine resistance [29].

GLUT3 ， encoded by the *SLC2A3* facilitates energy-independent glucose transport across the hydrophobic cell membrane to regulate intracellular concentrations [30]. GLUT3 is present within intracellular vesicles, regulates early embryonic development, is important for the development of the hematopoietic system, is upregulated in the majority of leukemia cells, and is closely associated with leukemia onset, progression, and drug resistance [31]. Zhuang et al. determined that silencing GLUT3, in combination with vincristine, can inhibit proliferative activity and induce the apoptotic death of AML cell lines, increasing their vincristine sensitivity. This activity may be related to the fact that the inhibition of GLUT3 can result in the downregulation of the breakpoint cluster region-Abelson (BCR::ABL1)fusion gene, leading to higher levels of expression of apoptotic factors including phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and caspase-3, while limiting the efflux of vincristine efflux [32].

GLUT4 is a key glucose transporter expressed in skeletal muscle cells ，adipocytes, and cardiomyocytes that is involved in insulin regulation and glucose transmembrane transport [33]. GLUT4 is expressed at high levels in tumor cells, increasing the uptake of glucose and facilitating the malignant progression of tumors [34]. Zhang et al. determined that GLUT4 was expressed at high levels in drug-resistant leukemia cell lines, with the combination of the hexokinase inhibitor 2-DG and Adriamycin (ADR) reducing GLUT4 expression levels in drug-resistant leukemia cell lines, reducing glucose uptake of leukemia cells, inhibiting glycolytic function, suppressing cellular proliferation, and enhancing ADR sensitivity [35]. Cheng et al. found that combined treatment with cytarabine (Ara-C) and Brusatol (a main tetracyclic triterpenoid component extracted from Bruceajavanica) was sufficient to reduce GLUT4 expression in AML cells, decreasing the consumption of glucose and the production of lactate to while increasing Ara-C sensitivity [28].

The fructose transporter GLUT5, encoded by SLC2A5 is primarily expressed by cells of the intestinal epithelium [36]. High GLUT5 expression levels have been reported in pediatric leukemia and linked to poor prognostic outcomes, potentially owing to the fructose-mediated protection of tumor cells against nutritional deficiencies or drug-induced cell death [37]. Chen et al. demonstrated that AML cells exhibit increased GLUT5 expression together with a higher rate of fructose uptake that is correlated with poor prognostic outcomes in AML patients; when glucose levels are low, AML cell lines are more likely to rely on GLUT5 for fructose uptake as a compensatory mechanism. The blockade of fructose utilization with the fructose analogue (2,5-AM) provides a means of inhibiting leukemia incidence and enhancing Ara-C cytotoxicity [38].

3. Glycolytic enzymes and chemoresistance in AML

3.1. HKII (Hexokinase II)

Hexokinase II (HKII), a member of the HKs family, is the first rate-limiting enzyme in the glycolytic pathway, which functions by phosphorylating glucose using ATP to generate G6P [39]. HKII expression is rarely observed in normal adult cells, but it is commonly upregulated in tumors, playing a key role in aerobic glycolytic activity in a range of malignancies including B cell lymphoma, prostate cancer, breast cancer, and glioblastoma multiforme, being linked to poor prognostic outcomes in cancer patients [40–43]. Song et al. determined that glycolysis-related GLUT1, HKII, and hypoxia-inducible factor 1α (HIF-1α) expression levels are elevated in imatinib (IM) resistant cell line, and that combining 2-DG or 3BrPA with imatinib was sufficient to decrease the glucose consumption activity of K562 cell lines, resulting in the insufficient synthesis of ATP and thereby chemosensitizing these cells [44]. Zhang et al. demonstrated that HK activity and glycolytic capacity are enhanced in leukemia cells exhibiting drug resistance, and as an HK inhibitor, 2-DG can suppress glycolytic activity, glucose consumption, lactate production and ATP biogenesis in drug-resistant leukemia cells, inhibiting cellular proliferation and overcoming ADR resistance in drug-resistant leukemia cells was reversed [35]. Yuan Zhang et al. assessed urothelial carcinoma-associated 1 (UCA1) expression in samples of bone marrow from patients with pediatric AML, and found it to be

abnormally upregulated in ADR-treated patients, with corresponding upregulation in ADR-resistant HL-60 cells. These authors also determined that UCA1 can serve as a miR-125a molecular sponge, negatively regulating HK2, with UCA1 knockdown leading to the downregulation of HK2 and the inhibition of glycolytic activity via targeting miR-125a in HL-60 and HL-60/ADR cells, thereby potentially contributing to greater chemosensitivity in pediatric AML [45]. Song et al. observed that AML patients not in remission (NR) exhibited higher levels of HK2 expression as compared to AML patients in complete remission (CR) with the same also being true in HL-60/ADR cells, along with concomitant increases in glycolytic, while inhibiting glycolysis was sufficient to decrease the consumption of glucose, reversing ADR resistance [14]. Cheng et al. determined that combined Ara-C/Brusatol treatment significantly suppressed HK2, GLUT1, and GLUT4 expression reducing the consumption of glucose and the production of lactate, inhibiting cellular proliferation, promoting apoptotic death, and improving AML cell Ara-C sensitivity [28] (Table 2).

3.2. PFK-1 (Phosphofructokinase-1)

As the second rate-limiting glycolytic enzyme, Phosphofructokinase-1 (PFK-1) is responsible for catalyzing of fructose-6-phosphate (F-6-P) phosphorylation to generate fructose-1, 6-diphosphate (F-1,6-P) [46]. The tetrameric PFK-1 is characterized by three different isoforms (PFKP, PFKM, and PFKL) [47], with PFKL being the predominant isoform in renal and hepatic tissues, whereas the PFKM and PFKP are isoforms are respectively most abundant in muscle tissue and platelets [48]. PFK-1 activity is impacted by a range of allosteric effectors in the cytosol, including ATP, ADP, F-6-P, and F-2,6-BP, with fructose-2, 6-diphosphate (F-2,6-BP) serving as the most potent positive allosteric effector of PFK-1 [47,49]. A close link between PFK-2/fructose-2, 6-bisphosphatase (FBPase-2), PFK-2/PFKFB is a bifunctional enzyme exhibiting a phosphatase domain encoded by four different genes (PfKfb1-4) that is capable of consuming F-2, 6-BP and is responsible for synthesizing and degrading this compound [50,51]. PFKFB3 is closely associated with glycolytic activity, growth, and metastatic progression in cancers. Li Chen et al. determined that knocking down the HOX antisense intergenic RNA myeloid 1 (HOTAIRM1) lncRNA was sufficient to reduce PFKP expression levels within AML cells, reducing the consumption of glucose and the production of lactate while inhibiting overall glycolytic activity and enhancing Ara-Cinduced cytotoxicity [52].

3.3. PK (Pyruvate kinase)

Pyruvate kinase (PK) is the final rate-limiting enzyme involved in the glycolytic pathway, catalyzing phosphoenolpyruvate conversion into pyruvate and ADP conversion into ATP [53]. The four PK isoforms include PKL, PKR, PKM1, and PKM2 [54]. The PKLR gene encodes PKR and PKL, the former of which is only expressed in erythrocytes, whereas the latter is expressed in cells including those in the kidneys, liver, pancreas, and intestines [55]. The PKM gene is alternatively spliced to generate muscular PKM (PKM1, PKM2) [56]. PKM2 overexpression is observed in many forms of leukemia and promoting proliferation, differentiation, and chemoresistance through its effects on transcriptional, autophagic, and apoptotic activity [57–60]. High levels of PKM2 expression have been observed in AML patients harboring *NPM1* mutations, and these levels have been linked to poor prognostic outcomes [61]. Sun et al. observed high levels of PKM2 expression in resistant APL cells and determined that such upregulation was related to the mechanisms underlying therapeutic resistance. Specifically, PKM2 expression was found to promote APL cell resistance to retinoic acid (RA), with the inhibition of PKM2 weakening the glycolytic pathway and promoting drug-resistant APL cell differentiation [57]. Chen et al. observed that resistant AML cells presented with higher levels of PKM2 expression, glycolytic activity, glucose consumption, and lactate biogenesis relative to sensitive cells, with the 2-DG-mediated inhibition of glycolysis inhibiting viability and inducing ADR-resistant AML cell apoptosis, contributing to increased ADR-resistant leukemia cell sensitivity to chemotherapeutic drug treatment [62].

3.4. LDH (Lactate dehydrogenase)

Lactate dehydrogenase (LDH) is an enzyme that plays a role in the last step of glycolytic pathway, functioning by catalyzing pyruvate conversion into lactate [63]. Active LDH consists of a tetramer composed of the LDHA (LDH-M) and/or LDHB (LDH-H) subunits,

Table 2
The overview of current clinical trial drugs in AML.

clinical trial drugs	Target	Finding	Reference
3BrPA	GLUT1	3BrPA or 2-DG combined with Adriamycin (ADR) to inhibit GLUT1 activity was sufficient to reduce glucose consumption and ADR resistance.	[14,28]
2-DG	GLUT1 GLUT4	3brpa or 2-DG combined with Adriamycin (ADR) to inhibit GLUT1 activity was sufficient to reduce glucose consumption and ADR resistance. 2-DG combined with ADR reducing GLUT4 expression levels in drug-resistant leukemia cell lines, reducing glucose uptake of leukemia cells, inhibiting glycolytic function, and enhancing ADR sensitivity.	[14,28,35]
PGL compounds	GLUT1	PGL compounds can enhance GLUT1-overexpressing AML cell sensitivity to cytarabine.	[29]
Brusatol	HK2 GLUT1 GLUT4	Ara-C combined with Brusatol can reduce HK2, GLUT1, and GLUT4 expression in AML cells, decreasing the consumption of glucose and the production of lactate to increase Ara-C sensitivity.	[28]
2,5-AM	GLUT5	Blockading fructose utilization with the fructose analogue (2,5-AM) provides a means of inhibiting leukemia incidence and enhancing Ara-C cytotoxicity.	[39]

which are respectively more abundant in muscle and heart tissue [64]. High levels of LDHA expression are observed in various cancers, and it can contribute to chemoresistance such that inhibiting LDHA can restore chemotherapeutic drug sensitivity [65–67]. High expression levels and increased LDHA activity can contribute to paclitaxel resistance in breast cancer and oral squamous cell carcinoma, while knocking down LDHA can reverse these effects, leading to paclitaxel sensitivity [65,68]. Song et al. determined that in patients with AML, significantly higher LDH levels were evident in patients not in remission as compared to those who achieved complete or partial remission. Mpakou et al. determined that 5-aza-resistant (5-AZA-R) MDS/AML patients express higher LDHA mRNA levels [69]. This suggests an association between LDHA and chemoresistance in AML (Table 3).

4. The relationship between glycolytic signaling pathways and chemoresistance in AML

4.1. Wnt/β-catenin signaling pathway

First reported in 1982 by Nusse and Varmus, the *Wnt* gene was named based on a combination of the *Drosophila* wingless gene and the int gene from homologous mouse breast cancer cells [70]. The cysteine-rich secreted Wnt glycoprotein is important in the context of proliferation, cellular differentiation, and apoptosis [71,72]. The Wnt signal pathways include the classical β-catenin pathway and the nonclassical β-catenin-independent pathway, with the Wnt/β-catenin axis being important to hematological disease incidence and progression [73]. Wnt/β-catenin signaling is activated by Wnt ligand binding to the seven transmembrane protein FZD receptor. In the absence of cytosolic β-catenin accumulation, target gene transcription is suppressed by the combination of the T cell factor (TCF) transcription factor and the Groucho protein. When Wnt ligands are present, Wnt can bind to the core receptor complex to activate downstream Wnt signaling through the recruitment of the cytosolicDvl protein and the disruption of blockade of Axin/GSK3/APC complex formation, ultimately suppressing β-catenin degradation and facilitating the cytosolic accumulation of β-catenin [74]. After accumulating within the cytoplasm, β-catenin can undergo nuclear translocation, while UBR5 ubiquitination inactivates the Groucho/TLF represser. The binding of β-catenin to TCF converts it into a transcriptional activator, resulting in downstream target gene upregulation [75]. The Wnt/β-catenin signaling pathway has been shown to play a role in the regulation of glycolytic metabolism within tumor cells. Abnormal Wnt/β-catenin pathway activation can shape tumorigenesis and tumor resistance to drug treatment [76–78]. Vallee et al. found that Wnt/β-catenin pathway activation results in enhanced glycolytic enzyme activity, contributing to a greater aerobic glycolytic capacity [79]. Wang et al. further found that increases in Ca^{2+} -permeable transient receptor potential channel 5 (TrpC5) and GLUT1 expression were evident in the 5-fluorouracil (5-FU) -resistant human HCT-8/5-Fu CRC line; with TrpC5 inhibition suppressing GLUT1 expression through the blockage of Wnt/β-catenin pathway activation and the modulation of CRC cell chemoresistance [80]. Kang et al. determined that lncRNA CRNDE (colorectal neoplasia differentially expressed) upregulation was positively correlated with MDR1 expression in AML patients, while CRNDE downregulation was able to suppress AML proliferation, induce apoptotic death, and suppress P-gp-mediated ADR resistance through the inhibition of Wnt/β-catenin signaling , conferring greater chemoresistance in AML [81]. Chen et al. found that knocking down the lncRNA HOTAIRM1 was able to block Wnt/β-catenin activation, inhibiting glucose consumption, lactate production, and PFKP expression in AML cells to increase overall cytarabine sensitivity [52].

4.2. PTEN/AKT signaling pathway

Phosphatase and tensin homolog (PTEN) is an important tumor suppressor gene closely related to tumorigenesis and is named for the phosphatase and tensin homolog deleted on chromosome 10 [82]. It functions as a protein and lipid phosphatase that can dephosphorylate phosphatidylinositol 3,4,5-triphosphate (PIP3) to suppress PI3K-mediated growth signaling, thereby modulating the growth, differentiation, migration, and survival of cells [83]. PTEN can suppress tumor growth through its ability to reduce insulin sensitivity, with PTEN loss activating downstream AKT and increasing insulin sensitivity in the skeletal muscle and adipose tissue, initiating the uptake of glucose [84]. Activated AKT can prevent the mitochondrial transport of pyruvate for TCA cycle-mediated processing, shifting the metabolic activity of tumor cells away from oxidative phosphorylation and towards aerobic glycolysis

Table 3
Key enzymes and their characteristics in AML chemoresistance.

Glycolytic enzymes	Characteristics	Reference
HK2	Low expression of UCA1 can down-regulate the expression of HK2 by targeting miR-125a in AML-resistant cells, inhibit cell glycolysis, and improve the sensitivity of pediatric AML to ADR. HK2 is highly expressed in AML patients without remission and AML-resistant cells, which leads to enhanced glycolysis. Inhibition of glycolysis can reverse the resistance of AML-resistant cells to ADR. Ara-C combined with Brusatol can inhibit the expression of HK2, reduce the glucose consumption and lactate production of AML cells, inhibit cell proliferation and promote cell apoptosis, thereby improving the sensitivity of AML cells to Ara-C.	[14,28,45]
PFK-1	HOTAIRM1 knockdown can inhibit PFKP expression in AML cells, reduce glucose consumption and lactate production, and inhibit glycolysis, thereby enhancing the cytotoxicity of Ara-C.	[52]
PK	PKM2 is highly expressed in AML-resistant cells, which increases glycolysis. Inhibition of glycolysis by 2-DG can increase the sensitivity of AML cells to Adriamycin.	[62]
LDH	LDH was highly expressed in non-remission AML patients and 5-AZA-R AML patients.	[14,69]

through its ability to trigger the expression of GLUT1, together with the stimulation of phosphofructokinase activity, the phosphorylation of HK2, and the inhibition of PKM2 activity [85]. PI3K/AKT signaling increases the available supply of energy through this regulation of aerobic glycolytic activity, enhancing the ability of cells to excrete antitumor drugs through the use of ABC transporters, culminating in multi-drug resistance (MDR) [86]. Members of the ATP-binding cassette (ABC) transporter family are key targets for efforts to overcome chemoresistance in AML, with the overexpression of these transporters protecting against sufficient chemotherapeutic drug accumulation within cells [87]. The activity of these ABC transporters is dependent on ATP, which is primarily derived from enhanced glycolytic activity. Glycolytic inhibition leads to the inhibition of ABC transporter activity such that chemotherapeutic drugs are retained within cells, thereby leading to the restoration of the cytotoxic effects of these drugs on AML cells [88]. PTEN can inhibit protein kinase B (Akt) activity via its antagonistic effects on PI3K, inhibiting downstream signaling and controlling the proliferative, migratory, and invasive activity of cells [89,90]. Deletion and mutation of the *PTEN* gene led to abnormal activation of the PI3K/Akt pathway, and increased AKT phosphorylation and activity, contributing to enhanced tumor cell growth, proliferation, invasivity, and metastatic progression [91]. Ryu et al. found that GLUT1 and HKII expression was enhanced in drug-resistant AML cells, together with PTEN depletion, enhanced AKT phosphorylation, and higher levels of lactate production, AKT can promote the proliferation of resistant AML cells, contributing to more robust aerobic glycolytic activity, while inhibiting AKT can sensitizing AML cells to chemotherapeutic treatment. These findings suggest that the PTEN/AKT pathway can mediate chemoresistance in patients with refractory AML through the enhancement of glycolytic activity [92].

4.3. mTOR signaling pathway

mTOR (rapamycin) is a serine/threonine protein kinase, belonging to the phosphoinositide-3-kinase (PI3K) - related kinase family, which exhibits a high degree of evolutionary conservation, with the two mTOR complexes (mTORC1 and mTORC2) playing key roles in a various processes including metabolism, autophagy, and apoptosis [93]. mTOR signaling is associated with leukemogenesis, and mTOR pathway inhibition through rapamycin treatment can help combat leukemia [94–96]. The activated mTORC1 is capable of regulating diverse metabolic pathways including glycolysis, promoting a metabolic shift from oxidative phosphorylation to glycolysis, while increasing glycolytic enzyme expression and increasing pentose phosphate pathway flux, thereby facilitating proliferative activity and growth [97,98]. mTORC1 can additionally stimulate the uptake of glucose, promote glycolysis and increase the production of lactate [97]. mTORC2 is involved in the phosphorylation and activation of AKT, promoting cellular survival, proliferation, and migratory activity while also regulating glycolysis and other forms of metabolic activity [99,100]. The knockdown of rictor (a component of mTORC2) can impair glycolytic activity in adipocytes and skeletal muscle, with mTORC2 regulating metabolism through the phosphorylation of AKT and downstream activation of FoxO3a [101]. Poulain et al. found that mTORC1 primarily regulates the expression of glycolysis and PPP-related gene expression, controlling overall glycolytic activity within AML cells to promote glycolytic activity and glucose dependence. The mTORC1 activity level drives overall AML cell sensitivity to glycolysis or G6PD inhibition, with higher mTORC1 activity levels conferring greater sensitivity to G6PD inhibition. The 6-AN-mediated inhibition of G6PD activity has cytotoxic effects on AML cells, synergistically sensitizing leukemia cells to chemotherapeutic treatment [102]. Liu et al. determined that inhibitors of mTOR signaling can suppress the uptake of glucose and the production of lactate within AML cells, increasing their sensitivity to Aurora kinase inhibitors [103]. Braun et al. demonstrated that contact with substrate significantly increased the phosphorylation of mTOR in primary AML cells and AML cell lines, while rapamycin-mediated inhibition of mTOR activity was sufficient to inhibit glucose transporter upregulation, glucose uptake, and the production of lactate, limiting basal glycolysis and the glycolytic capacity of AML cell lines and primary AML cells, while synergistically inducing cytotoxicity [104] (Tables 4–5 , Fig. 2).

5. ncRNA promote chemoresistance through glycolysis

Long non-coding RNA (lncRNA) over 200 nucleotides long generally lacking substantial coding potential [105,106]. However, they can control target gene expression at the epigenetic, transcriptional, and post-transcriptional levels [107]. In addition to regulating protein-coding gene expression within solid tumors, lncRNAs are also important in the context of AML and other hematological

Table 4
Signaling pathway and their characteristics in AML chemoresistance.

Glycolysis signaling pathway	Characteristics	Reference
Wnt/β-catenin	lncRNA HOTAIRM1 knockout increases the drug sensitivity of AML cells to Ara-C by blocking the activation of Wnt/β-catenin pathway, inhibiting glucose consumption and lactate production, as well as the expression of glycolytic enzyme PFKP in AML cells.	[52]
PTEN/AKT	PTEN/AKT signaling pathway mediates chemotherapy resistance in refractory acute myeloid leukemia by enhancing glycolysis.	[92]
mTOR	mTOR inhibitors can reduce glucose uptake and lactate production in AML cells, resensitizing AML cells to Aurora kinase inhibitors. Blockade of mTOR activity by rapamycin effectively inhibited the upregulation of glucose transporters, glucose uptake, and lactate production, reduced basal glycolysis and glycolytic capacity in AML cell lines and primary AML cells, while producing synergistic cytotoxicity.	[103, 104]

Table 5
The overview of clinically applied drugs in AML.

clinically applied drugs	Finding	Reference	Target
Rapamycin	Inhibiting mTOR activity by rapamycin was sufficient to inhibit glucose transporter upregulation, increased glucose uptake, and the production of lactate, inducing cytotoxicity.	[101]	mTOR
Dasatinib	Dasatinib could overcome FLT3 inhibition resistance through the suppression of the activation of STAT5 together with the inhibition of glycolysis.	[126]	STAT5

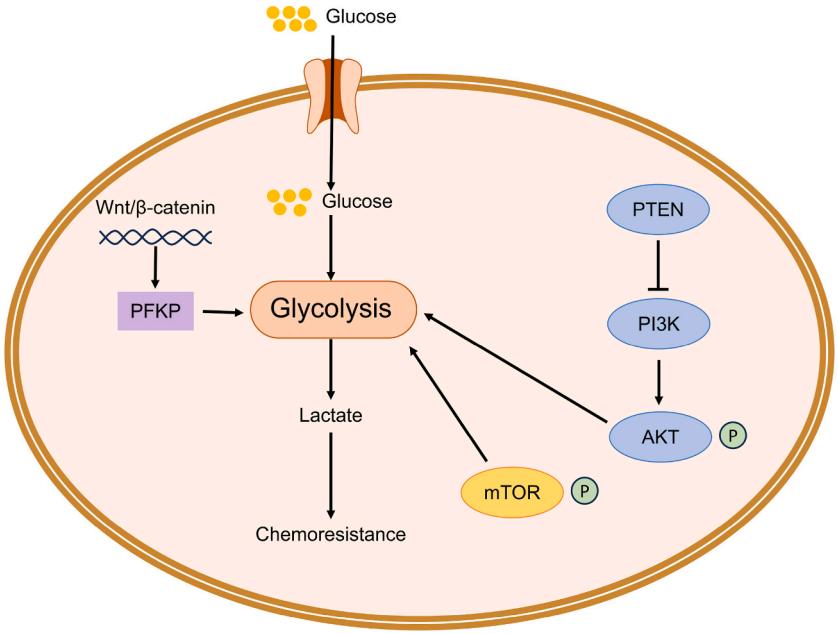

Fig. 2. AML resistance pathways associated with glycolysis. Activation of the Wnt/β-catenin pathway induces high expression of PFKP, leading to enhanced glycolysis and increased lactate production. Consequently, this metabolic alteration contributes to drug resistance in AML cells. Conversely, the deletion of the PTEN gene results in abnormal activation of the PI3K/Akt pathway, leading to increased Akt phosphorylation and elevated levels of lactate production. This metabolic shift further promotes drug resistance in AML cells. Additionally, activation of the mTOR signaling pathway augments glycolysis and fosters drug resistance in AML cells.

malignancies, shaping processes such as proliferation, apoptosis, migration, and chemoresistance such that they contribute to poor leukemia patient outcomes [81,108,109]. The competitive endogenous RNAs (ceRNA) hypothesis states that some RNAs, as ceRNAs, can suppress microRNA (miRNAs) expression, ultimately leading to the derepression of miRNA targets. LncRNA can act as "miRNA-sponges" to inhibit the miRNA target genes expression by competitively binding to intracellular miRNA, thereby regulating chemotherapeutic drug resistance in AML [110,111] (Table 6,Fig. 3).

LncRNA taurine-upregulated gene 1 (TUG1) is a 7.1 kb lncRNA encoded on chromosome 22q12, which was first characterized in a study of the development of murine retinal cells [112]. TUG1 reportedly functions in an oncogenic manner in several cancers, including AML [113]. Mechanistically, it can modulate the expression of the glycolytic enzymes HK2 and PKM2 to control apoptotic induction and therapeutic resistance [114,115]. Chen et al. reported the upregulation of TUG1 in resistant AML cells, and found that

Table 6
lncRNA and their characteristics in AML chemoresistance.

lncRNA	Characteristics	Chemoresistance status	Reference
TUG1	LncRNA TUG1 was highly expressed in HL60/ADR cells. TUG1 knockout can inhibit glycolysis by reducing the expression of glycolytic enzymes HK2 and PKM2, thereby increasing the sensitivity of HL60/ADR cells to Adriamycin.	Chemoresistance to ADR	[62]
UCA1	UCA1 knockdown inhibited HIF-1α-dependent glycolysis in ADR-resistant AML cells and reduced the chemoresistance of pediatric AML mediated by miR-125a/HK2.	Chemoresistance to ADR	[45]
HOTAIRM1	Knockout of HOTAIRM1 inhibited glucose consumption and lactate production, as well as the expression of glycolytic enzyme PFKP in AML cells, and enhanced the cytotoxicity of Ara-C by regulating the Wnt/β-catenin/PFKP signaling pathway.	Chemoresistance to Ara-C	[52]

knocking down lncRNA TUG1 was sufficient to suppress glycolytic activity through reductions in PKM2/HK2 expression, with a corresponding increase in AML cell sensitivity to doxorubicin [62].

The 1.4 kb UCA1 lncRNA encoded on chromosome 19p13.12 is reportedly expressed at high levels in bladder transitional cell carcinoma [116]. In several reports, a role for UCA1 has been reported in the control of tumor chemoresistance, with UCA1 silencing inhibiting gastric tumor cell malignant proliferation and ADR resistance [117]. Overexpression of UCA1 can promote increases in multi-drug resistance gene (MDR1) expression, in addition to competitively binding to miR-16 to promote imatinib resistance in CML [118]. Yao et al. observed high levels of UCA1 expression in AML and found that the overexpression of this lncRNA reduced the daunorubicin sensitivity of AML cells through its ability to sequester miR-613 and to modulate PI3K/AKT signaling [119]. Zhang et al. determined that UCA1 was upregulated following ADR chemotherapy, with UCA1 deficiency increasing the cytotoxic effects of ADR treatment in AML cells, thereby overcoming resistance to ADR; further study found that knocking down UCA1 was sufficient to not only inhibit chemoresistance in AML through the blockade of HIF-1α-dependent glycolysis, but also to serve as a sponge for miR-125a, leading to the downregulation of HK2 and the suppression of aerobic glycolysis within AML cells , contributing to reduced chemoresistance in childhood AML cases [45].

LncRNA HOTAIRM1 is a 5415bp lncRNA encoded on human chromosome 7p15.2 between HOXA1 and HOXA2 genes, and it was first described by Zhang et al. in the bone marrow cell system [120]. HOTAIRM1 plays an important role in regulating chemoresistance in various cancers including glioma and colorectal cancer. It can suppress 5-Fu-resistant colorectal cancer cell progression via the miR-17-5p/B cell translocation gene 3 (BTG3) axis [121]. HOTAIRM1 is also capable of spongifying hsa-miR-17-5p to facilitate the growth and therapeutic resistance of glioma cells, in addition to mediating reductions in intracellular ROS production [122]. HOTAIRM1 can promote drug resistance in AML cells through its control of glycolytic activity, with high HOTAIRM1 expression having been observed in AML patients while its knockdown suppressed the expression of the rate-limiting PFKP enzyme, reducing glucose consumption, lactate production, and aerobic glycolysis glycolytic activity to enhance overall Ara-C cytotoxicity [52,123]. On the other hand, HOTAIRM1 knockdown could alleviate the effects of HOTAIRM1 knockdown on AML cell glycolysis and Ara-C cytotoxicity by inhibiting the activation of Wnt/β-catenin pathway, suggesting that reductions in HOTAIRM1 levels enhanced the in vitro cytotoxicity of Ara-C on AML cells through the modulation the Wnt/β-catenin/PFKP axis [52].

Circular RNAs (circRNAs) are back-splicing-derived ncRNAs with a closed-loop structure that can serve as ceRNAs and are important mediators of AML progression [124]. Shang et al. determined that circPAN3, for example, can mediate autophagy via the AMPK/mTOR axis to contribute to enhanced drug resistance in AML [125]. Yi et al. further identified a role for circ-PTK2 as a driver of malignant AML phenotypes through its ability to sequester miR-330-5p, promoting increases in FOXM1 expression [126]. Elevated levels of circ-SFMBT2 and ZBTB20, together with lower levels of miR-582-3p, have been reported in patients with AML and in AML cells. The knockdown of circ-SFMBT2/ZBTB20 was sufficient to impair AML cell proliferative, migratory, invasive, and glycolytic activity while inducing apoptotic death. In addition, circ-SFMBT2 has been found to facilitate progression in patients with AML through its ability to serve as a sponge for miR-582-3p, which targets ZBTB20 to hamper AML development [127].

MicroRNAs (miRNAs) are a subset of ncRNAs (18–25 nt in length), which are important regulators of proliferation, apoptotic induction, differentiation, and chemoresistance in AML [128,129]. Wang et al. founds microRNA-155 (miR-155) is upregulated in

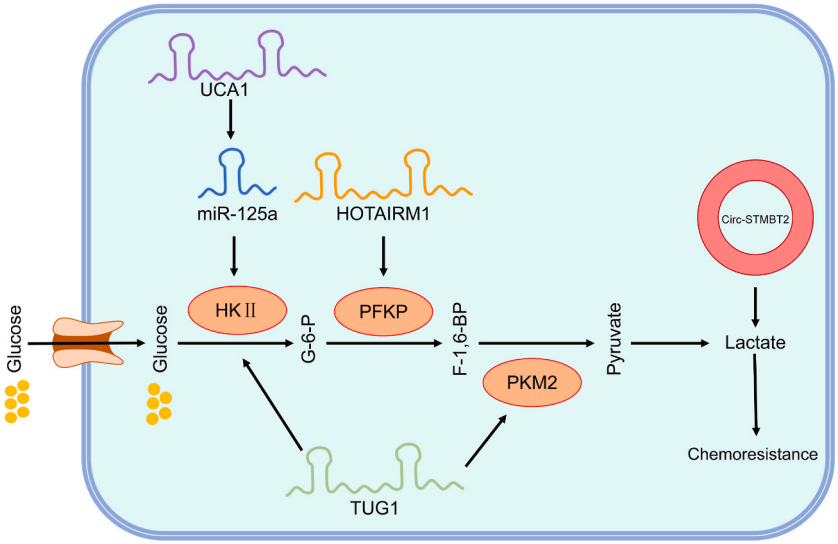

Fig. 3. ncRNAs regulate glucose metabolism in AML chemoresistance. UCA1 facilitates the upregulation of HK2 in AML cells by promoting the expression of miR-125a. This, in turn, promotes aerobic glycolysis and leads to chemotherapy resistance. Similarly, HOTAIRM1 in AML cells enhances aerobic glycolysis by upregulating the expression of the PFKP enzyme, resulting in cellular resistance. Additionally, circ-SFMBT2 contributes to AML resistance by promoting lactic acid production in AML cells. Moreover, TUG1 plays a role in enhancing glycolytic activity and promoting treatment resistance by increasing the expression of glycolytic enzymes HK2 and PKM2.

FLT3-ITD + AML and in the FLT3-ITD + AML cell lines. FLT3 tyrosine kinase inhibitors (TKIs), as the first form of targeted treatment for newly diagnosed FLT3-mutant AML. This miRNA-155 has been demonstrated to control metabolic activity and to promote STAT3 activation and consequent HK2 upregulation [130]. MiR-155 thus serves as a key mediator of aerobic and chemoresistance, with cells in which this miRNA has been knocked out presenting with reductions in HKI, PKM, PKM1/2, and PFKP expression [130]. Lower levels of miR-155 expression have been linked to decreased glucose utilization and the production of lower levels of lactate, consistent with the overall downregulation of glycolytic activity. Decreases in miR-155 expression can thus increase therapeutic sensitivity to both chemotherapy and FLT3 inhibitors in FLT3-ITD + AML cells [130].

6. Bone marrow stromal cells induce AML chemoresistance through glycolysis

The bone marrow niche is a microenvironment that was first proposed to serve as a form of "sanctuary" capable of enabling AML cells to evade chemotherapeutic treatment and targeted killing in 1978 [131,132]. Bone marrow stromal cells (MSCs) are a class of stromal cells that help ensure the maintenance of normal bone marrow hematopoietic function while also promoting leukemia stem cells (LSC) survival, leading to an increase in the ability of leukemia cells to resist drug treatment [133,134]. The bone marrow stroma can shield malignant AML cells from apoptotic death through their interactions and the associated induction of malignant cell proliferation and drug resistance [135]. Co-culturing of AML cells with the HS-5 BMSC cell line can prevent their apoptotic death and protect against drug-induced cell death, leading to enhanced therapeutic resistance [13]. Following contact with the bone marrow stroma, AML cell lines exhibit increased GLUT1-4 surface density, together with significant increases in glucose uptake and a concomitant rise in glycolytic capacity. AML cells treated with the glycolysis-targeting 2-DG and diclofenac agents exhibit greater drug sensitivity following BMSC contact [104]. Study have reported an enhancement in glycolysis within FLT3-ITD AML cells, which can be partially suppressed by FLT3 TKI treatment [136]. Researches indicate that soluble factors released within the bone marrow microenvironment can directly enhance glycolysis in FLT3-ITD + leukemia cells, limiting the effects of FLT3 TKI on glycolytic activity and thus resulting in chemoresistance [136,137]. Recent research has found that the culture of FLT3-ITD AML cells in human HS-5 BM stromal cell medium or through cell co-culture has the remarkable ability to reinstate glycolysis in FLT3-ITD AML cells, and which ultimately leads to the development of resistance to TKI treatment in FLT3-ITD AML cells. Patel et al. determined that dasatinib could overcome stroma-based resistance to FLT3 inhibition through the inhibition of glycolysis, thereby resensitizing FLT3-ITD + leukemia cells quizartinib-mediate inhibition of FLT3 [137].

7. Exosomes induce AML chemoresistance through glycolysis

Exosome is a kind of double-layer vesicular structure formed by membrane fusion with a diameter of 30–150 nm, which contains biological macromolecules such as nucleic acids (mRNA, tRNA, lncRNA, microRNA, etc.), proteins, and lipids, and it was first discovered in the maturation process of sheep reticulocyte [138–140]. Exosomes are present in all biofluids, including serum, plasma, urine, lacrimal secretions, and cerebrospinal fluid. They are produced by virtually all cell types including tumor cells, with secreted exosomes facilitating intercellular communication by transferring mRNA, miRNA and protein, regulating the indirect connection between leukemia cells and the surrounding microenvironment [141–143]. These tumor-derived exosomes (TDE) can facilitate malignant cancer onset, progression, invasion, metastasis, and chemoresistance [144,145]. Chemotherapy can elevate exosomal secretions in AML cells, resulting in the transfer of chemoresistance-related miRNA and mRNA to the adjacent cancer cells to induce susceptibility to chemotherapy [146–148]. Wu et al. demonstrated that AML-BMSCs released exosomes that delivered miR-10a to leukemia cells and downregulated RPRD1A, which activated Wnt/b-catenin that subsequently conferred protection of leukemia cells from chemotherapy [146]. Lyu et al. found that BM-MSC-exos increased the metastatic potential, maintained the stemness and contributed to the chemoresistance of leukemia cells. Mechanistically, BM-MSC-exos promoted the proliferation, invasion and chemoresistance of leukemia cells via upregulation of S100A4 [147]. In colorectal cancer, exosomes from oxaliplatin-resistant cells can deliver circRNA-122 into sensitive cells, thereby promoting glycolysis and drug resistance through miR-122 sponge and PKM2 upregulation [149]. Bone marrow stromal cells (BMSCs) -derived exosomes can modulate c-Jun, p53, p38, and AKT expression within multiple myeloma (MM) cells, inducing the survival and proliferation of these cells while inhibiting their apoptotic death in response to drug treatment and bolstering their resistance to the proteasome inhibitor bortezomib [150]. Nathalie et al. found that bone marrow stromal cell-derived fibroblast growth factor 2 (FGF2) is secreted in exosomes, and that that stromal cell lines and primary AML -associated stroma samples exhibit increases in FGF2 and receptor FGFR1 expression, with FGFR knockdown or silencing) significantly reducing the secretion of FGF2-containing exosomes, leading to weaker interstitial leukemia cell protecting and overcoming the resistance of these cells to TKIs [151]. Wang et al. found that exosomes derived from AML cells containing VEGF/VEGFR were able to induce glycolytic activity in HUVECs, resulting in vascular remodeling and the onset of chemoresistance [152].

8. Discussion and perspective

The Warburg effect continues to be a pivotal characteristic of cancer, granting tumor cells the capacity to proliferate, flourish, and spread, all the while fostering resistance to immune-mediated clearance and chemotherapy. Aerobic glycolysis encompasses a multifaceted regulation of glycolytic enzymes, signaling pathways, ncRNAs, and the overall microenvironment of the bone marrow. The chemoresistance of AML can be overcome by using glycolytic inhibitors, either alone or in combination with conventional cytotoxic therapies.

As previously mentioned, glycolysis-associated molecules including GLUTs, HK2, PFK-1, PK, and LDH can affect glycolysis of AML

cells, modulating their proliferation and chemosensitivity. Additional research has demonstrated that the glycolytic enzyme GAPDH is prominently expressed in cancer cells and can enhance drug resistance by elevating glycolytic activity [153]. In solid tumors, studies have shown that monocarboxylate transporters (MCTs) play a crucial role in transporting lactate generated by glycolysis to the extracellular environment. These transporters are often overexpressed in cancer cells and can contribute to drug resistance by facilitating the removal of lactate from cancer cells [154]. Apart from the aforementioned enzymes and channels, glycolysis also encompasses a diverse array of other enzymes and channels. However, there is a paucity of reports on AML resistance related to these components. Further investigations into these glycolytic enzymes and channels will be beneficial in comprehensively understanding the mechanism of glycolytic involvement in AML resistance.

Previous studies pointed out that blocking the Wnt/β-catenin, PTEN/AKT, and mTOR signaling pathways has been shown to reduce the expression of glycolysis-related molecules, resulting in decreased glycolytic activity and increased chemosensitivity in AML cells. Additionally, molecules such as p38α-MAPK, FBN1/VEGFR2/STAT2, and PI3K/AKT/GSK 3β are also critical in regulating chemotherapy resistance in solid tumor glycolysis metabolism [155–157]. Further research is necessary to uncover the mechanisms through which glycolysis-related signaling pathways regulate glycolysis, ultimately influencing chemotherapy resistance and paving the way for novel AML treatment strategies.

It is reported that ncRNAs are abundantly expressed in chemoresistant AML, where they can act as sponges for specific miRNAs, leading to changes in glycolytic enzymes, transporters, and signaling pathways that contribute to chemoresistance. However, existing research predominantly concentrates on lncRNAs, with limited studies on miRNAs and circRNAs. Further exploration is essential to identify new targets and facilitate the development of innovative treatment approaches. In addition, studies found that the interactions between AML cells and the bone marrow stroma can create an environment that supports therapeutic resistance and escape. The involvement of immune cells, enzymes, and cytokines in the tumor microenvironment in AML resistance is not yet fully understood. Immunotherapy has shown promise in cancer treatment, including AML. Therefore, further research on the role of the tumor microenvironment in AML resistance is essential to unravel the mechanisms underlying resistance and to explore the potential of immunotherapy as a treatment option.

Additionally, certain regulators of glucose metabolism, such as 3-BrPA and 2-DG, have demonstrated potential in reversing drug resistance in AML. However, the clinical use of these drugs has been limited due to adverse reactions [158]. Moreover, TCM has been recognized for its high efficiency, low toxicity, and strong specificity in inhibiting leukemia cell growth by regulating aerobic glycolysis. Gao et al. have found that Dihydroartemisinin (DHA) can impede the proliferation of chronic myelogenous leukemia (CML) K562 cells by modulating glycolysis through the suppression of PKM2 and GLUT1 expression [159]. Liang et al. discovered that Imperatorin (IMP) has the capability to decrease the glucose consumption and lactate production of K562/DOX cells. Additionally, IMP was found to enhance the antitumor effect of doxorubicin (DOX) in K562/DOX xenograft tumors in NOD/SCID mice [160]. The research on TCM offers a novel approach and strategy for the development of targeted therapy drugs that focus on glycolysis. However, it is important to note that researches on targeting glycolysis to overcome drug resistance in AML are still lacking, there is a significant potential for further exploration in this area. Conducting more in-depth research in this field holds promise for enhancing our understanding of AML resistance mechanisms and developing novel therapeutic strategies to combat this challenging disease.

9. Conclusions

In this review, we offer a comprehensive summary of the current research status concerning the relationship between glycolytic metabolism and AML resistance to chemotherapy, mainly focusing on the contributions of glucose transporters, key glycolytic enzymes, signaling pathways, ncRNAs, and the tumor microenvironment. We also suggest potential research directions to obtain insights into the mechanisms of glycolysis in AML resistance, in hopes of improving therapies in the future.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Yan Yang: Methodology. **Jianlin Pu:** Methodology. **You Yang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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