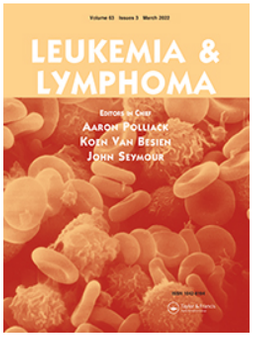

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REVIEW

Targeting mitochondrial metabolism in acute myeloid leukemia

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ABSTRACT

Cancer cells reprogram their metabolism to maintain sustained proliferation, which creates unique metabolic dependencies between malignant and healthy cells that can be exploited for therapy. In acute myeloid leukemia (AML), mitochondrial inhibitors that block tricarboxylic acid cycle enzymes or electron transport chain complexes have recently shown clinical promise. The isocitrate dehydrogenase 1 inhibitor ivosidenib, the isocitrate dehydrogenase 2 inhibitor enasidenib, and the BH3 mimetic venetoclax received FDA approval for treatment of AML in the last few years. Other mitochondrial inhibitors including CPI-613, CB-839, dihydroorotate dehydrogenase inhibitors, IACS-010759, and mubritinib, have shown encouraging preclinical efficacy and are currently being evaluated in clinical trials. In this review, we summarize recent metabolism-based therapies and their ability to target altered cancer metabolism in AML.

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Introduction

Cancer cells rewire their metabolism to meet new nutrient requirements and maintain proliferation. One of the earliest observations of altered metabolism in cancer cells was the Warburg Effect, which describes the tendency of cancer cells to take up more glucose than normal cells and rely on glycolysis as opposed to oxidative phosphorylation (OXPHOS) [1]. Since this discovery in the 1950s, many other energetic pathways altered in cancer have been characterized, including differences in the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC). In fact, contrary to Warburg's observation, some types of cancer rely less on glycolysis and are instead dependent on OXPHOS to produce energy and replicate [2].

AML is a disease that results from an outgrowth of myeloid precursor cells in the bone marrow and blood. It is the most common acute leukemia in adults, and typical treatment involves intensive induction and consolidation chemotherapy followed by allogeneic hematopoietic cell transplantation. Prognosis for elderly patients remains quite poor, with a median survival of only 5–10 months, prompting the urgent need for novel therapies [3].

One of the biggest challenges in treating AML is the persistence of leukemia stem cells (LSCs), which may evade chemotherapy treatment that eradicates bulk tumor cells and cause relapse of AML [4]. Recent work has highlighted important metabolic differences between bulk AML cells, LSCs, and normal hematopoietic stem cells (HSCs) [5]. Interestingly, studies have shown that when patient-derived models of AML are treated with standard chemotherapies, chemo-resistant cells show increased levels of OXPHOS, suggesting that inhibition of this pathway may augment chemotherapy [6]. While normal HSCs are able to rewire their metabolism and rely more on glycolysis to meet their energy requirements, thereby withstanding mitochondrial inhibition, LSCs do not retain this plasticity and are dependent on OXPHOS for survival. This difference may represent a therapeutic window that can be utilized to specifically eliminate LSCs [7]. To this end, mitochondrial inhibitors that disrupt the TCA cycle and ETC have demonstrated some success in preclinical and clinical studies, generating significant interest in exploring this promising therapeutic approach. In this review, we discuss these various mitochondrial inhibitors and their potential to serve as effective therapies for AML patients (Figure 1). Completed and ongoing clinical trials testing compounds targeting leukemia metabolism are summarized in Table 1.

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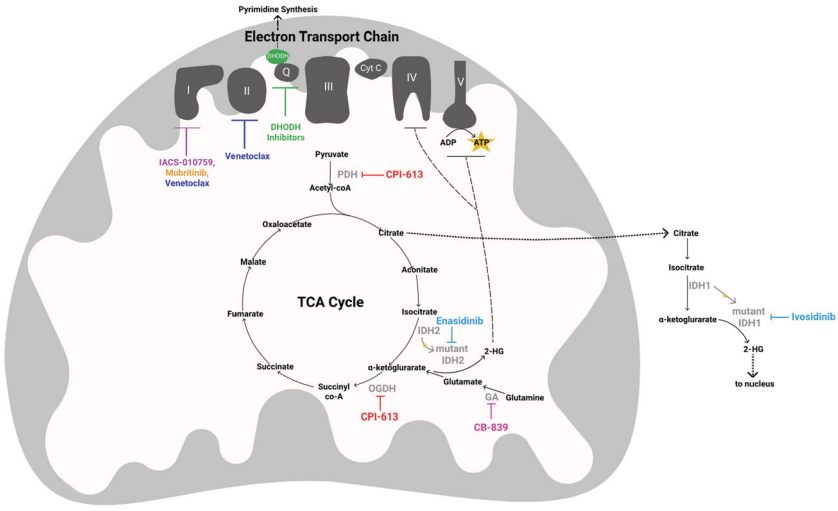

Figure 1. Summary of action of mitochondrial inhibitors. IACS-010759, Mubritinib, and venetoclax + azacitidine inhibit ETC complex I. Venetoclax also inhibits ETC complex II. DHODH inhibitors block the activity of DHODH, an enzyme in the mitochondrial membrane that catalyzes the first step in pyrimidine synthesis and reduces ubiquinone in the process. CPI-613 is a lipoic acid analog that inhibits the activity of TCA cycle enzymes that rely on lipoic acid, PDH and OGDH. CB-839 is a glutaminase inhibitor that prevents the conversion of glutamine to glutamate, therefore blocking entry of metabolites into the TCA cycle through α-ketoglutarate. Finally, ivosidenib and enasidenib are mutant IDH inhibitors that block the conversion of isocitrate to 2-HG, an oncometabolite that prevents differentiation of AML cells and blocks the activity of ETC complexes IV and V.

TCA cycle inhibitors

Mutant isocitrate dehydrogenase inhibitors

Isocitrate dehydrogenase (IDH) is an enzyme that converts isocitrate to α-ketoglutarate (αKG) within the TCA cycle. IDH has three isoforms: IDH1 converts isocitrate to αKG in the cytoplasm, IDH2 functions in the mitochondria, and IDH3 is localized to the mitochondrial matrix [8]. IDH1 or IDH2 mutations occur in 15%–30% of AMLs leading to the production of 2-hydroxyglutarate (2HG), a competitive inhibitor of αKG-dependent enzymes. Inhibition of histone demethylases by 2HG, for example, results in hypermethylation of the genome and impairs hematopoietic differentiation [9–11]. However, 2HG's role within the cell is complex, as it has been shown to inhibit the function of cytochrome *c* oxidase (COX) and ATP synthase, components of complexes IV and V in the ETC, respectively; this inhibition results in decreased ATP production and slowed cell growth [12,13]. This highlights the intricacies of 2HG as an oncometabolite, balancing pro- and anti- cancer effects [14].

Ivosidenib prevents the dimerization of R132 IDH1 mutants, inhibiting the catalytic function that produces 2HG [15]. In clinical trials, patients with IDH1-mutated relapsed or refractory AML treated with ivosidenib showed an overall response rate of 41.6%, with a complete remission or complete remission with partial hematological recovery rate of 30.6% [15]. Remissions proved to be durable, with a mean overall survival of 12.6 months after a follow up of 23.5 months [16]. Ivosidenib was FDA approved for front line treatment of IDH1 mutant AML patients in 2019.

The mutant IDH2 inhibitor enasidenib targets the IDH2 R140 and R172 mutants by allosterically binding to the enzyme and preventing catalysis [17]. Enasidenib achieved a response rate of 40.6% in a clinical trial in patients with relapsed or refractory AML with IDH2 mutations [18]. Enasidenib was well tolerated by the patients and reduced serum 2HG levels by 90%. Interestingly, patients who did not achieve a clinical response also showed decreased serum 2HG levels, but these patients had mutations in the RAS signaling pathway, suggesting a mechanism of enasidenib resistance [19]. Enasidenib received FDA approval for patients with relapsed or refractory AML in 2017.

CPI-613

CPI-613 is a rationally designed lipoic acid analogue that is currently under investigation in clinical trials for patients with pancreatic cancer and AML. Mechanistically, CPI-613 displaces lipoic acid, a cofactor for the TCA cycle enzymes pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (OGDH), preventing the activity of these enzymes and halting the TCA cycle [20,21].

PDH acts as the connection between glycolysis and the TCA cycle through the oxidative decarboxylation

Table 1. Summary of mitochondrial inhibitors for AML treatment.

Drug	Clinical Trial	Mechanism	Patient Population	Phase
Ivosidenib	NCT02074839	Prevents dimerization of isocitrate dehydrogenase 1 (IDH1) mutants, preventing formation of oncometabolite 2- hydroxyglutarate (2HG). 2HG is a competitive inhibitor of a-ketoglutarate (αKG) for many histone demethylases [9,10,15].	Newly diagnosed AML with IDH1 mutations Relapsed or refractory AML	FDA Approved in 2019
Enasidenib	NCT01915498	Allosterically binds to IDH2 mutants and prevents formation of 2HG [17].	Relapsed or refractory AML	FDA Approved in 2017
Venetoclax + azacitidine	NCT02203773 NCT02993523	Venetoclax inhibits pro-survival protein BCL-2, priming the cell to go through apoptosis [30]. Azacitidine is an inhibitor of DNA methylation, which induces differentiation in leukemia cells [36]. In combination, these drugs also suppress the activity of complexes I and II in the ETC and amino acid metabolism [32,33].	Adults 75 years or older who are considered unfit for intensive chemotherapy	FDA Approved in 2018
Venetoclax + low-dose cytarabine	NCT02287233	Cytarabine is a chemotherapeutic agent used in the standard treatment of AML. It is a cytidine analog and inhibits DNA replication in rapidly dividing cells [37].	Adults 75 years or older who are considered unfit for intensive chemotherapy	FDA approved in 2018
CPI-613 + high dose cytarabine mitoxantrone	NCT03504410	CPI-613 is a lipoic acid analog that inhibits pyruvate dehydrogenase and a-ketoglutarate dehydrogenase in the mitochondria [20,21].	Relapsed or refractory AML	Phase III
CB-839	NCT02071927	CB-839 is a glutaminase inhibitor that prevents glutaminolysis, decreases OXPHOS, and promotes apoptosis [28].	Relapsed or refractory AML or ALL	Phase I
IACS-010759	NCT02882321	IACS-010759 inhibits the ND1 subunit of ETC complex I, targeting cancer cells that are addicted to OXPHOS for survival [30].	Relapsed or refractory AML	Phase I
Brequinar	NCT03760666	Brequinar is an inhibitor of dihydroorotate dehydrogenase (DHODH), an enzyme that catalyzes the fourth step in the pyrimidine synthesis pathway and interacts closely with ubiquinone in the ETC [42].	Relapsed or refractory AML	Phase I
BAY2402234	NCT03404726	BAY 2402234 is a DHODH inhibitor [44].	Myeloid malignancies including AML, myelodysplastic syndrome (MDS), and chronic myelomonocytic leukemia (CMML)	Phase I
ASLAN003	NCT03451084	ASLAN003 is a DHODH inhibitor.	AML patients not eligible for standard treatment	Phase II

of pyruvate to acetyl-CoA. In lung cancer cells, CPI-613 increases the activity of PDH kinases (PDKs), which phosphorylate the E1α subunit of PDH and inhibits its function as measured by decreased carbon dioxide release [21]. Similarly, OGDH catalyzes the oxidative decarboxylation of α-KG to succinyl-CoA. CPI-613 has been shown to induce a burst of mitochondrial reactive oxygen species (ROS) production through the E3 subunit of OGDH. This ROS accumulation leads to increased glutathionylation of sulfhydryl groups exposed on the E2 subunit of OGDH, blocking its activity as indicated by decreased carbon dioxide release and reduced production of downstream TCA cycle intermediates [20].

In addition to inhibiting PDH and OGDH, CPI-613 can affect other areas of metabolism. A study in clear cell sarcoma (CCS) found that CPI-613 induces autophagosome formation. When CPI-613 is used in combination with chloroquine, which prevents autophagosome fusion with lysosomes and degradation of toxic products, cancer cells die and tumor burden is greatly reduced *in vivo* [22]. Similarly, fibroblasts treated with CPI-613 have a decreased membrane potential and increased number of autophagosome-lysosome fusions [23]. In pancreatic cancer, CPI-613 induces ROS accumulation, increasing autophagy and apoptosis. In these cells, CPI-613 also suppresses lipid metabolism through modulating 5′ AMP-activated protein kinase-acetyl-CoA carboxylase (AMPK-ACC) signaling, which promotes apoptosis. This study demonstrates that in addition to suppressing PDH and OGDH, CPI-613 plays a role in lipid metabolism [24].

CPI-613 in combination with high dose cytarabine and mitoxantrone chemotherapy is currently in phase III clinical trials for patients with relapsed or refractory AML (NCT03504410) after promising results and safety metrics from phase I and II clinical trials in older patients [25].

CB-839

Glutamine is a major source of fuel for the TCA cycle in AMLs. Glutamine is converted to glutamate by glutaminase, allowing glutamate to enter the TCA cycle and promoting OXPHOS downstream. CB-839 is a glutaminase inhibitor that blocks this reaction, thereby reducing anaplerosis of the TCA cycle by glutamine. Metabolic profiles of persistent AML cells revealed dependence on glutamine metabolism and pyrimidine synthesis, suggesting that therapies targeting these pathways may target chemo-resistant cells [26].

One study found that CB-839 treatment in AML cells decreased glutathione production, which caused ROS accumulation and promoted apoptosis. Additionally, when combined with other oxidative drugs, including arsenic trioxide and homoharringtonine, cell death was enhanced, suggesting that CB-839 can be used in combination with other agents [27]. In another study, CB-839 reduced OXPHOS and decreased proliferation in AML cells; these effects were abrogated by the addition of αKG, indicating the importance of glutaminase for AML cell survival [28]. Additionally, since CB-839 reduces the concentration of downstream TCA cycle metabolites, including αKG, AML cells harboring IDH mutations that convert αKG to 2HG were more sensitive to CB-839 treatment and showed increased differentiation [29].

CB-839 has undergone clinical trials for leukemia and myelodysplastic syndromes both alone and in combination with hypomethylating agent azacitidine (NCT02071927, NCT03047993).

ETC inhibitors

Venetoclax

Venetoclax is a small molecule inhibitor of the pro-survival protein B cell lymphoma 2 (BCL-2). The BCL-2 family is composed of pro- and anti-apoptotic proteins. BCL-2 promotes cell survival by binding pro-apoptotic proteins that contain BH3 domains, thereby suppressing their activity [30]. Venetoclax binds BCL-2 within its BH3 binding domain, which releases the pro-apoptotic factors and initiates cell death [31]. AML patients with IDH mutations respond particularly well to venetoclax because of an increased dependence on BCL-2 [32]. Along with the epigenetic changes described above, 2HG affects metabolism by inhibiting complex IV in the ETC, causing the leukemia cells to rely more heavily on BCL-2 to avoid apoptosis and making them more sensitive to venetoclax treatment [13].

In addition to the pro-apoptotic effects of venetoclax, this drug is also thought to impact cellular metabolism. The combination therapy venetoclax with the hypomethylating agents (HMA) azacitidine and decitabine, or low-dose cytarabine (LDAC) has been shown to target LSCs by suppressing mitochondrial OXPHOS, thereby decreasing ATP availability and leading to cell death. Specifically, the therapy decreases glutathionylation of succinate dehydrogenase in ETC complex II [32]. Additionally, the combination of venetoclax and azacitidine has been shown to inhibit ETC complex I, further decreasing ATP availability and contributing to cell death [33]. Interestingly, venetoclax was shown to inhibit OXPHOS through the integrated stress response protein activating transcription factor 4 (ATF4) independent of BCL-2 expression. This study also showed that venetoclax affects the TCA cycle, inhibiting its activity and causing reductive carboxylation [34]. In addition, it was shown that adding tedizolid, a ribosome inhibitor, to venetoclax/azacitidine can activate the integrated stress response, decrease respiration and ATP levels, and increase AML cell death [33].

Another avenue that venetoclax and azacitidine treatment uses to target OXPHOS is through amino acid metabolism. LSCs are specifically reliant on amino acid metabolism to convert amino acids to TCA cycle intermediates and perform OXPHOS. LSCs do not adjust to metabolize glucose for energy in the absence of amino acid metabolism, unlike AML blast cells. Venetoclax and azacitidine treatment blocks amino acid uptake and synthesis in LSCs, decreasing OXPHOS and promoting cell death [35].

The combination of venetoclax with HMA or LDAC was recently FDA approved as frontline therapy for AML patients who are either 75 years and older or are considered unfit to undergo intensive induction chemotherapy. The combination of venetoclax with HMA or LDAC has proven to be very effective in the treatment of older patients with AML. Phase III studies showed a median survival of 14.6 months in the venetoclax and azacitidine treatment group compared to 9.6 months for the azacitidine and placebo group, and another phase III trial achieved similar increases in survival using a combination of venetoclax and low dose cytarabine, with a median survival of 7.2 months

compared to 4.1 months in the LDAC and placebo group [36,37].

Venetoclax combination therapy has already revolutionized the therapeutic approach to AML. Further understanding of the multiple ways that venetoclax targets LSCs, including altering the balance of pro- and anti-apoptotic proteins, inhibiting different complexes in the ETC, and limiting amino acid availability, will inform the rational development of combined therapy regimens that increase the durability of the response to venetoclax.

Dihydroorotate dehydrogenase inhibitors

Dihydroorotate dehydrogenase (DHODH) is an enzyme located in the inner mitochondrial membrane that oxidizes dihydroorotate (DHO) to orotate in the fourth step of the pyrimidine synthesis pathway. DHODH transfers electrons from this reaction to ubiquinone, thereby linking its function to the ETC [38]. Depletion of DHODH in HeLa cells has been shown to partially inhibit ETC complex III, increase mitochondrial ROS, and decrease mitochondrial membrane potential [38]. Additionally, studies have shown that inhibition of ETC complex III suppressed the activity of DHODH by keeping ubiquinone in its reduced state, ubiquinol, making it unable to accept electrons from DHODH. This halted pyrimidine synthesis, which upregulated p53 and led to apoptosis in colon cancer cells [39,40]. In this way, DHODH is dependent on functional ETC complexes II and III to oxidize ubiquinone [41]. DHODH connects the pathways of respiration, pyrimidine synthesis, and tumorigenesis, as pyrimidine synthesis *via* DHODH is essential to tumor growth and depends on ubiquinone recycling through OXPHOS [41]. For these reasons, DHODH is an attractive target for cancer treatments.

In AML, leukemic myeloid blasts often contain a differentiation blockade. A compound screen showed that similar to IDH inhibitors, DHODH inhibitors could induce differentiation in myeloid cells. The specific DHODH inhibitor brequinar reduced tumor size, increased survival, and reduced the ability of cells to induce leukemia upon secondary transplant *in vivo* [42]. Phase I/II clinical trials for brequinar in the treatment of solid tumors took place in the 80 s and 90 s, but the drug was not very effective with the time course and tumor type investigated [43]. Renewed interest in brequinar has led to a new clinical trial for patients with AML (NCT03760666). BAY2402234 is another inhibitor of DHODH that has shown reduced proliferation and increased differentiation of AML blasts *in vivo* [44]. This drug is currently in Phase I clinical trials for AML patients (NCT03404726). ASLAN003, another DHODH inhibitor, is in phase II clinical trials for AML (NCT03451084).

IACS-010759

IACS-010759 is an inhibitor of ETC complex I, and as such, decreases the ability of cells to perform OXPHOS [45]. IACS-010759 shows potential as a treatment in multiple cancer types that rely on OXPHOS for survival, such as LSCs in AML. It also has fewer off-target effects than rotenone, another well characterized inhibitor of ETC complex I. This specificity improves the ability of IACS-010759 to act as a cancer treatment because it targets the cancer cells that are addicted to OXPHOS, while healthy cells are able to adjust their metabolism and survive. Brain cancer and AML cells treated with IACS-010759 showed ATP depletion and reduced aspartate synthesis, which affected other cellular processes downstream including nucleotide synthesis and DNA repair, ultimately leading to cell death [45]. It has also been found that IACS-010759 may have the potential to synergize with other compounds in AML samples; the combination of IACS-010759 and vinorelbine, a microtubule destabilizer, was effective in promoting cell death in both AML cell lines and primary samples [46].

IACS-010759 is currently in phase I clinical trials for patients with recurrent or refractory AML (NCT02882321). Interestingly, in chronic lymphocytic leukemia (CLL), IACS-010759 decreased OXPHOS but did not cause cell death unless glycolysis was also inhibited, suggesting that these cells can adapt and that IACS-010759 needs to be used in combination with another drug to be effective [47].

Mubritinib

Mubritinib is a selective inhibitor of human epidermal growth factor receptor 2 (HER2), which is upregulated in many urological and breast cancers. HER2 and related receptors are fundamental in controlling cell growth and development, and dysregulation of HER2 has been implicated in many cancer types, including bladder cancer, prostate cancer, and renal cell carcinoma. By targeting HER2, mubritinib slowed the growth of these urological cancers *in vitro* and *in vivo* [48].

Recently, mubritinib was identified as an effective treatment against AML cells in a chemical screen [49]. In mubritinib-sensitive AML samples, it was discovered that the drug was not acting on HER2 but was instead targeting ETC complex I in a ubiquinone-dependent

manner. Characterization of sensitive and resistant AML samples revealed that mubritinib decreased OXPHOS and was particularly effective in cells that depend on OXPHOS for survival. Mubritinib treatment was effective *in vitro* and *in vivo*, pointing to the potential therapeutic benefit for mubritinib in AML [49]. While the results of this screen are promising, more work is necessary to determine if mubritinib is safe and effective for AML treatment in patients.

Conclusion

The altered metabolism of leukemia cells represents a promising target for therapeutic intervention. Mitochondrial inhibitors block components of the TCA cycle or the ETC, impacting other areas of metabolism such as amino acid and nucleotide synthesis and eventually leading to cell death. In AML, recent work has led to FDA approval for mutant IDH inhibitors ivosidenib and enasidenib and the combination treatment targeting BCL-2 and the ETC, venetoclax and azacitidine. Additional therapies currently in clinical trial development include CPI-613, which inhibits PDH and OGDH as well as lipid metabolism, CB-839, which blocks glutaminase, DHODH inhibitors brequinar, BAY 2402234, and ASLAN003 which link the ETC to pyrimidine synthesis, IACS-010759, a specific inhibitor of ETC complex I, and mubritinib, a ubiquinone inhibitor that impacts ETC complex I. On the horizon, more therapies that target mitochondrial metabolism are under investigation, including ONC201 and ONC212, molecules that target the mitochondrial protease ClpP, and ME-344, which may inhibit ETC complexes I and III as well as microtubule polymerization. While promising, more work is required to determine the exact mechanism and effects of these drugs and move to clinical trials [50].

These drugs have shown promise in preclinical studies and provide exciting possibilities for the future of AML treatment, but there are still many questions for future investigation. Concerns regarding the therapeutic window of these therapies should be addressed, as the mitochondrial pathways targeted are critical in healthy cells as well as cancer cells. Additionally, how targeting specific metabolic pathways and enzymes induces differentiation in AML cells is an area of open investigation, which will uncover new insights into the relationship between metabolism and cell fate. Finally, it is unclear why LSCs are particularly dependent on OXPHOS. New technologies that allow for the *in vivo* analysis of metabolic flux and mitochondrial function will help answer this question and shed new light on regulation of metabolism as a whole.

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