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Mitochondrial metabolism as a target for acute myeloid leukemia treatment

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Abstract

Acute myeloid leukemias (AML) are a group of aggressive hematologic malignancies resulting from acquired genetic mutations in hematopoietic stem cells that affect patients of all ages. Despite decades of research, standard chemotherapy still remains ineffective for some AML subtypes and is often inappropriate for older patients or those with comorbidities. Recently, a number of studies have identified unique mitochondrial alterations that lead to metabolic vulnerabilities in AML cells that may present viable treatment targets. These include mtDNA, dependency on oxidative phosphorylation, mitochondrial metabolism, and pro-survival signaling, as well as reactive oxygen species generation and mitochondrial dynamics. Moreover, some mitochondria-targeting chemotherapeutics and their combinations with other compounds have been FDA-approved for AML treatment. Here, we review recent studies that illuminate the effects of drugs and synergistic drug combinations that target diverse biomolecules and metabolic pathways related to mitochondria and their promise in experimental studies, clinical trials, and existing chemotherapeutic regimens.

Keywords: Acute myeloid leukemia (AML), Mitochondria, Mitochondrial abnormalities/alterations, Mitochondrial metabolism, Mitocans, Leukemia stem cells, Synergy, Drug combinations

Background

Acute myeloid leukemias (AML) are a group of hematological cancers that involve clonal proliferation of immature myeloid progenitor cells in the bone marrow and peripheral blood. These myeloblasts tend to be intensely proliferative, even to the extent that they can compromise normal blood flow. Proliferation of the myeloblasts generates a bulk of largely non-functional cells, compromising hematopoiesis, leading to neutropenia and increasing vulnerability to infectious disease. AML is one of the most common leukemias to affect adults (~ 120,000 new cases per year worldwide) and is also one of the most lethal. Left untreated, most forms of AML are aggressive and patients can succumb to disease in weeks to a few months [1].

The most common chemotherapy treatment for AML is called induction and consolidation. The first stage, remission induction, is intended to reduce the bulk of the myeloblasts. Induction involves high doses of cytarabine, a nucleoside analog that compromises DNA replication, with an anthracycline antibiotic such as daunorubicin. The induction phase usually lasts for 7 days. After remission has been triggered, treatment moves into the consolidation stage. This step typically involves several 3-day courses of cytarabine, but can also involve hematopoietic stem cell transplantation [2]. Although the precise anti-cancer mechanism of the combination of cytarabine and anthracyclines is still poorly understood, they are believed to function by inflicting DNA damage, which leads to mitochondrial dysfunction and apoptosis [3]. The length of these courses has led to this treatment often being referred to as "7+3" induction and consolidation.

Although induction and consolidation is one of the most effective treatments currently available for AML, it is very hard on patients. This renders the treatment

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inappropriate for many older patients (65 years or older, who comprise more than half of all newly diagnosed patients), especially those with other contra-indicators, like secondary disease, adverse genotypes, or treatment-resistant cancers [4]. Although there are several options for these patients, including low-dose induction therapy or more targeted treatments, which will be discussed below, most of these treatments are associated with a reduced likelihood of remission (and shorter survival) compared with aggressive chemotherapy. For a large number of patients, only palliative care is available [4]. Problematically, the risk of relapse is high in AML; about one-third of patients who receive even intensive chemotherapy suffer relapse [4].

Despite limited treatment options, virtually no new treatments were approved for AML in the period between 1971 and 2017 [5]. New treatments have been released since, such as a liposomal combination of cytarabine and daunorubicin known as CPX-351, the isocitrate dehydrogenase inhibitor ivosidenib, the tyrosine kinase inhibitor gilteritinib, the sonic hedgehog inhibitor glasdegib, or the Bcl-2 inhibitor venetoclax [6, 7]. Many of these newer treatments target metabolic differences in tumor cells that will be discussed below.

In this review, we discuss studies that explore mitochondrial characteristics of AML myeloblasts and stem cells, in comparison with their normal counterparts, including alterations in metabolism and signaling, mitochondrial respiration, ROS generation and sensitivity, mitochondrial "priming", and mitophagy. Also, we describe various groups of mitocans—mitochondria-targeting chemotherapeutics—and their effects with regard to biology of AML cells. Finally, this review provides recent evidence on synergistic drug combinations based on mitocans targeting diverse metabolic pathways that have shown promising results by in vitro, in vivo studies, and clinical trials in AML patients.

Metabolic differences in LSCs

If curing AML was as simple as clearing the rapidly dividing, highly proliferative myeloblasts, treatment would be onerous, but straightforward. Unfortunately, it is not so simple as this. Most patients have a second population of leukemic cells known as leukemic stem cells (LSCs). LSCs share many characteristics with normal hematopoietic stem cells (HSCs), including being $CD38^+$ $CD34^-$, although LSCs often express other membrane markers that are absent from HSCs (however, the expression of these markers seems to vary among patients) [8]. Like HSCs (and unlike AML myeloblasts), LSCs divide slowly, making conventional anti-proliferative treatments less effective on them. LSCs also provide a reservoir for the re-emergence of the rapidly dividing myeloblasts and are the most common driving force for relapse and treatment resistance, which occurs in about half of all patients who can be treated with aggressive chemotherapy regimens and more than 80% of patients who cannot. Transfer of LSCs to a naïve host can recapitulate the onset of AML [9–12].

Many studies have reported a unique metabolic signature in AML cells [13]. Metabolic reprogramming in leukemic cells transcends the conventional Warburg effect [14], and includes increased glycolysis and elevated ROS levels possibly regulated by PI3K/AKT and mTOR pathways [15, 16]. Correspondingly, a higher level of anabolic pathway precursors, such as intermediates of the citric acid cycle (CAC) and the pentose phosphate pathway (PPP), have been found in AML [14]. High biosynthetic pathway activity is required for the production of the materials essential for cell growth and proliferation. Glutaminolysis is upregulated, and catabolism of this amino acid is a valuable source of both carbon and nitrogen [14]. Glutaminolysis also regulates OxPhos (oxidative phosphorylation) in AML through the production of NADH [14]. However, dysregulation of antioxidants has been found in AML, which potentially promotes leukemogenesis by increasing ROS level [17–19]. Altered lipid metabolism promotes the interaction of AML with bystanding cells, such as adipocytes, activates their lipolysis, and transfers lipids from adipocytes to myeloblasts [20]. Leukemic cells also tend to upregulate fatty acid oxidation via mitochondrial uncoupling [21]. Mutations in cytosolic and mitochondrial isocitrate dehydrogenases (IDH1 and IDH2), resulting in the production of the oncometabolite 2-hydroxyglutarate, are commonly seen in AML cells, and are frequently targeted for therapy, since they limit cellular differentiation and promote leukemogenesis [22, 23].

Part of the difficulty in treating AML is the profound metabolic differences in LSCs [24]. To a first approximation, LSCs retain much of the metabolic profile of healthy HSCs. In addition to dividing more slowly (making them more resistant to nucleoside analogs that disrupt DNA replication), LSCs rely upon oxidative phosphorylation (OxPhos) for ATP generation instead of glycolysis and lactic acid fermentation (the route most tumors use to obtain ATP). This does leave them vulnerable to the production of ROS, which can force cells out of quiescence and trigger programmed cell death pathways. Most ROS are generated in mitochondria via electron transport. LSCs respond to this threat by upregulating autophagy (which is critical for the maintenance of stemness and the elimination of damaged mitochondria that will produce excess ROS) and upregulate the expression of the hypoxic response transcription factor HIF-1α, even in normoxia, to further limit ROS production [25, 26]. Interestingly, LSCs tend to be metabolically

inflexible and rely heavily on fatty acid oxidation and glutaminolysis to maintain OxPhos [27, 28].

Glycolytic disruptions in AML blasts and LSCs

As noted above, myeloblasts have high glycolytic activity and its anabolic diversions, most importantly the pentose-phosphate pathway, to provide nucleotides, amino acids, and electron carriers, e.g., building blocks that are necessary for rapid proliferation of leukemia cells [29]. The first step of glycolysis, the conversion of glucose to glucose-6-phosphate, is catalyzed by hexokinases. Hexokinase II, the most common version of the enzyme in insulin-sensitive tissues, is a key player in controlling metabolic flux through this pathway. Unsurprisingly, it is also frequently upregulated in cancer cells (reviewed in [30, 31]). One potential method to target hexokinase is to use 3-bromopyruvic acid or 2-deoxy-D-glucose (2-DG), both of which inhibit glucose metabolism [32, 33]. Although targeting hexokinase with 2-DG alone is generally ineffective, it can sensitize AML cells to other drugs that affect mitochondria, including cytarabine, inhibitors of complex I of the ETC (such as rotenone), the mitochondrial uncoupler CCCP, and BH3-mimetic inhibitors of Bcl-2, like ABT-737 [13, 34, 35] (see Figs. 1 and 2 for an overview of druggable mitochondrial targets).

The next rate-limiting, and first committed, step in glycolysis is phosphorylation of 6-phosphofructose by phosphofructokinase-1 (PFK1) to produce fructose 1,6-bisphosphate. PFK1 is allosterically activated by the compound fructose 2,6-bisphosphate, which is overproduced in many cancer types by the overexpression of PFKFB3, a dual function 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase that is a therapeutic target itself [36]. Overexpression of PFKFB3, including in leukemia cells, drives increased activity of PFK1, enabling increased glycolytic flux. Computational analysis demonstrated that a novel tumor suppressor, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO), can competitively inhibit PFKFB3, and decreases intracellular concentrations of fructose 2,6-bisphosphate; this subsequently decreases glycolytic flux in various tumor models [37]. The same group synthesized 73 derivatives of 3PO, one of which (PFK15) was pre-clinically evaluated for targeting resistant hypoxic cancer cells [37]. 3PO was shown to effectively reduce lactate production and cell growth in a leukemia model [38].

A careful analysis of AML patients has revealed a variety of different genetic contributions to disease progression, including some that alter glycolytic activity. One commonly mutated gene is the FMS-like tyrosine kinase 3 gene (known as CD135 or FLT3). Although several amino acid substitutions have been found, the most common category of mutation identified is internal tandem duplication of one or more codons near the transmembrane domain (known as FLT3-ITD). This class of mutations is found in approximately one-third of AML patients and is associated with poor prognosis and increased risk of relapse [39–42]. Oncogenic mutations in FLT3 trigger overactivation of the tyrosine kinase, which promotes several pro-survival effects in cells, including AKT-mediated upregulation of hexokinase—increasing their glycolytic activity [43]. There has been an explosion in treatments available for patients with FLT3 mutations, including a number of tyrosine kinase inhibitors like midostaurin and lestaurtinib (derivatives of staurosporine that target multiple tyrosine kinases), sorafenib, quizartinib, crenolanib, and gilteritinib [44]. Of these, only midostaurin and gilteritinib have received approval from the US Federal Drug Agency, and the latter is the first drug identified to target both internal tandem duplications and tyrosine kinase domain mutations [45]. The metabolic shift caused by the mutation also sensitizes these cells to glycolytic inhibitors like 3-bromopyruvate, which potentiates treatment with tyrosine kinase inhibitors [34, 43].

Citric acid cycle disruptions in AML blasts and LSCs

Targeting enzymes involved in the flux of pyruvate into the mitochondrial metabolism or citric acid cycle (CAC) is another fruitful anti-leukemia strategy. In the transition between glycolysis and the CAC cycle, pyruvate needs to be decarboxylated and condensed with coenzyme A (CoA) to yield acetyl-CoA that can be combined with oxaloacetate to yield citrate. Acetyl-CoA production requires the pyruvate dehydrogenase complex (PDC), which is comprised of three different enzymes [46]. Interestingly, cancer tissues often exhibit increased expression of PDC kinases, which limit CAC activity, driving pyruvate toward conversion to lactate, with important implications for energy production and modification of the tumor microenvironment. High expression of PDKs in AML patients (particularly PDK3, which is the most active isoform) is a negative prognostic factor for survival [47].

Several synthetic inhibitors of PDKs have been identified, such as Nov3r, AZD7545, Pfz3, radicicol, and CPI-613 [46]. The addition of CPI-613 to conventional chemotherapy is a promising approach for older AML patients and those with poor-risk cytogenetics [48]. Unfortunately, most of these compounds have IC_{50} values in the low- to mid-millimolar range, suggesting that it would be very difficult to deliver appropriate concentrations of these compounds to tumor cells, particularly without unacceptable levels of off-target effects.

Mutations in the isocitrate dehydrogenase (*IDH*) genes of AML patients provided researchers with one of their

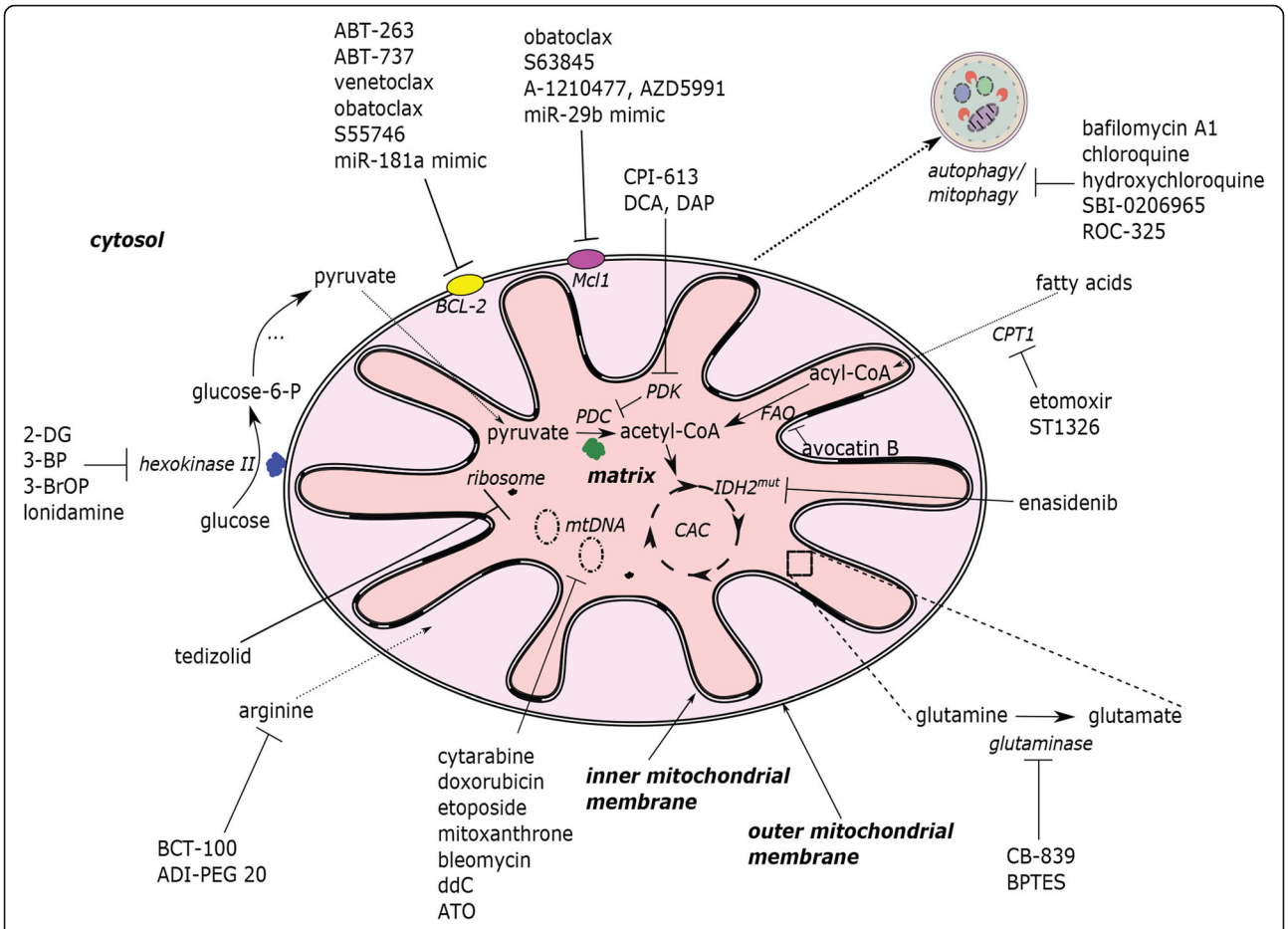

Fig. 1 Druggable mitochondrial targets in AML cell and selected pharmacological agents. A depiction of mitochondria, showing important biochemical targets (e.g., the citric acid cycle, mtDNA, mitophagy, etc.) and the drugs that are known to target each. The electron transport chain appears in Fig. 2. α-TOS: (+)alpha-tocopheryl succinate; ANT: adenine nucleotide translocator; ATO: arsenic trioxide; CCCP: carbonyl cyanide m-chlorophenyl hydrazone; CPT1: carnitine O-palmitoyltransferase 1; DAP: 2,2-dichloroacetophenone; DCA: dichloroacetate; ddC: 2′3′-dideoxycytidine; DHODH: dihydroorotate dehydrogenase; FAO: fatty acid oxidation; glucoso-6-P: glucose-6-phosphate; $IDH2^{mut}$: mutant isocitrate dehydrogenase 2; Mcl1: myeloid cell leukemia 1; miR: miRNA; mtDNA: mitochondrial DNA; PDC: pyruvate dehydrogenase complex; PDK: pyruvate dehydrogenase kinase; ROS: reactive oxygen species; SR4,9: dichlorophenyl urea compounds; CAC: citric acid cycle; UCP2: uncoupling protein 2; 2-DG: 2-deoxy-D-glucose; 3-BP: 3-bromopyruvate; 3-BrOP: 3-bromo-2-oxopropionate-1-propyl ester; I–V: Complexes of mitochondrial electron transport chain

first hints that mitochondrial metabolism was compromised in AML [30]. This occurs in 20% of AML cases and is associated with grim prognoses (median survival after diagnosis is approximately 6 months) [49]. Commonly, this results in neofunctionalization of IDH1 (cytoplasmic) and IDH2 (mitochondrial) enzymes, allowing them to convert α-ketoglutarate into 2-hydroxyglutarate. This onco-metabolite interferes with cellular metabolism and epigenetic regulation [50] and contributes to mitochondrial DNA instability [51]. It is believed that the ability of 2-hydroxyglutarate to interfere with processes that require α-ketoglutarate, such as histone and DNA demethylation, is also likely to interfere with the prolyl hydroxylases that regulate HIF-1α [52]. As noted above, HIF-1α is well known to play important roles in HSC and LSC maintenance [53]. Recently, ivosidenib and enasidenib, inhibitors of IDH1 and IDH2, have been approved by the US FDA for AML treatment [54]. Mutant IDH proteins can induce a reversible block of differentiation in leukemic cells by preventing IDH enzyme function [55].

Glutamine: key amino acid for cancer cell viability

Although cancer cells require a wide variety of materials for their survival and growth, at the most basic level this can be reduced to the demand for two nutrients: glucose (for anaerobic glycolysis) and glutamine [56]. Glutamine's uniquely important role in cancer arises from its ability to activate the key mTORC1 pathway (which integrates myriad inputs to regulate metabolic activity, autophagy, and apoptosis) [57, 58]. Glutamine can also be condensed with cysteine and glycine to form glutathione, which supports redox

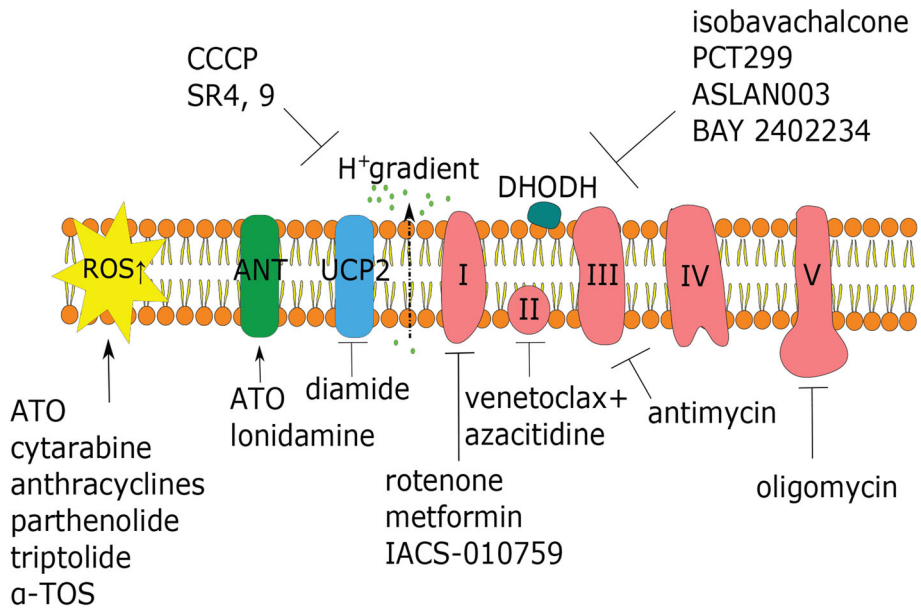

Fig. 2 Mitochondrial electron transport chain (ETC) as a therapeutic target in AML. A schematic representation of the ETC, showing the five complexes and potential therapeutic compounds that target each. Also shown is ROS, since the ETC is a major producer of the ROS in the cell by way of electron leak through complexes I and III. ATO: arsenic trioxide; α-TOS: (+)alpha-tocopheryl succinate; ANT: adenine nucleotide translocator; CCCP: carbonyl cyanide m-chlorophenyl hydrazone; DHODH: dihydroorotate dehydrogenase; ROS: reactive oxygen species; SR4,9: dichlorophenyl urea compounds; UCP2: uncoupling protein 2; I–V: complexes of mitochondrial electron transport chain

regulation and limits ROS damage; it also provides nitrogen for the synthesis of nucleotides for DNA replication [29, 59].

The key first step in the use of glutamine is carried out by glutaminase, which deaminates glutamine to yield glutamate. Inhibiting glutaminases has proven to be a popular anti-cancer strategy [60]. The most effective current candidate is Calithera's telaglenastat, also known as CB-839. As might be expected, given the functions of glutamine in cancer, telaglenastat increases susceptibility to redox-targeting therapies like arsenic trioxide and homoharrintonine and improves rates of AML apoptosis [61], while decreasing mTOR signaling [60].

Several AML mutations are known to generate idiosyncratic sensitivities to glutamine metabolism. For example, BPTES, from which CB-839 was derived, exhibits some specificity for *IDH*-mutated AML cells [62]. FLT3-ITD mutations are another example: aberrant FLT3 expression likely increases glutaminolysis. Inhibiting function with the tyrosine kinase inhibitor AC220 (also known as quizartinib) impairs glutamine uptake and glutathione production, hypersensitizing AML cells to oxidative stress [63]. Combination treatment of FLT3-ITD AML cells/primary samples with CB-839 and AC220 consistently resulted in reduced oxygen consumption, increased ROS production, and the activation of apoptosis [64].

Dependency on mitochondrial mass, mitochondrial respiration, and OxPhos

Both myeloblasts and LSCs have been shown to have increased mitochondrial mass compared with their healthy counterparts, although this difference is more pronounced in myeloblasts than in the $CD34^{+}CD38^{-}$ LSCs, further demonstrating the metabolic differences between these populations [65]. Intriguingly, this increase is not associated with a concomitant increase in respiratory function; instead, these cells exhibit a reduced spare reserve capacity, suggesting that their mitochondria are much less efficient [66]. Moreover, we have recently shown that AML cells have reduced coupling efficiency with underlying pre-existing proton leak and enhanced sensitivity to mitochondrial uncouplers compared with normal blood cells [67]. Interestingly, these phenotypes have led to the suggestion that AML progression requires increased mitochondrial biogenesis and OxPhos [67–71].

The importance of OxPhos is further highlighted by the fact that a cytarabine-resistant population of AML cells show enrichment not in LSCs *per se*, but in cells with up-regulated mitochondrial mass, membrane potential, and OxPhos. Importantly, inhibiting the latter improved sensitivity to cytarabine [68]. Quiescent LSCs with a low level of ROS are more reliant on oxidative phosphorylation, as they cannot efficiently utilize

glycolysis for energy homeostasis [72]. Consistent with this, the antimicrobial tigecycline, which inhibits mitochondrial translation, selectively kills LSCs (compared with HSCs) by compromising mitochondrial biogenesis in AML cells [65]. Unfortunately, a clinical trial studying the efficacy of intravenous infusion of tigecycline for refractory AML patients failed to show a clinical response, possibly due to the drug's short half-life [73]. Intriguingly, AML cells, including LSCs, are capable of taking up functional mitochondria from other cells in their environment, such as bone marrow cells, increasing their mitochondrial mass, and this phenomenon is thought to contribute to chemoresistance [74, 75]. This mitochondrial transfer increases during chemotherapeutic treatment and was proposed as an additional mechanism that provides AML cells with energy [75]. More specifically, bone marrow mesenchymal stem cells significantly protect leukemic cells from chemotherapy-induced ROS by increasing glutathione availability and utilization, mainly via the glutathione peroxidase system [75].

Mutations in mitochondrial genes that encode complexes I, III, and IV of the electron transport chain (ETC) have been linked to worsened outcomes in AML patients, suggesting that loss of proper function exacerbates disease [76]. However, there is substantial evidence that the complexes of the ETC are viable targets for therapeutic intervention, including in AML. For this reason, various strategies to disable mitochondrial ETC have been investigated in AML.

Among complex I inhibitors, the best known are the anti-diabetic biguanide metformin and the compound IACS-010759 (reviewed in [77, 78]). Metformin stimulates metabolic reprogramming, increasing glycolysis, pentose phosphate pathway, and fatty acid and anaplerotic metabolism and changing mitochondrial gene expression in leukemic cells [79]. Unfortunately, metformin is ineffective as an anti-AML agent on its own. Although it blocks mitochondrial respiration, it barely affects target cell proliferation or viability [77, 80].

In contrast, a more potent complex I inhibitor, IACS-010759, robustly inhibits proliferation and induces apoptosis, likely through a combination of energy depletion and impaired nucleotide biosynthesis due to reduced glutaminolysis [81]. Clinical trials with IACS-010759 for AML patients are still ongoing [81], but there have already been reports of it being used in combination with venetoclax, which showed strong promise at targeting LSCs and myeloblasts using a PDX model [82]. Similarly, we have recently determined that IACS-010759 can synergize with vinorelbine to improve efficacy and specificity, including in primary cells from AML patients [35].

In that same study, we also determined that rotenone, a well-known inhibitor of complex I, could synergize with the glycolytic inhibitor 2-DG. Rotenone has previously been investigated as a potential cancer therapeutic [83], although it was determined that its off-target toxicity and resultant hematopoietic suppression make it inappropriate for use at the dosages required to prevent proliferation [84]. By pairing it with other compounds, the dose required for efficacy can be significantly reduced, increasing the chance that the targeted effects would be more specific [35].

More recently, another drug called mubritinib (also known as TAK-165) was shown to have a strong effect in vivo against AML [85]. Mubritinib, canonically an inhibitor of ERBB2 (a receptor tyrosine kinase of the EGF receptor superfamily), was shown to inhibit the transfer of electrons through the ETC by blocking the function of complex I at ubiquinone [85]. This mechanism is similar to rotenoids and has similar efficacy.

Most attempts to target the ETC have focused on complex I, but some limited research has been performed on other ETC complexes. For example, a combination of venetoclax and azacytidine appears to have a synergistic effect that blocks glutathionylation of succinate dehydrogenase A (a component of complex II) and kills both myeloblasts and LSCs [86]. Targeting complex III may also be productive. For example, antimycin A more effectively limits oxidative phosphorylation and generates increased ROS production in primary AML cells [66]. As will be discussed in the next section, AML cells and LSCs are more sensitive to ROS than their healthy counterparts. Like rotenone, antimycin A is a well-known inhibitor of mitochondrial function; also like rotenone, it is unlikely to be successfully utilized on its own as a therapeutic due to off-target activity. However, it has been effectively combined with a third-generation glycolytic inhibitor, 3-bromo-2-oxopropionoate-1-propyl ester, which serves as a cell-permeable ester of 3-bromopyruvate [87]. This combination potentiated ATP depletion and promoted apoptosis in leukemic cells [87]. It has also shown potential in combination with rapamycin in leukemia and neuroblastoma [87, 88]. Finally, targeting the mitochondrial ATP-synthase (sometimes called complex V) with oligomycin A greatly sensitized leukemia cells to tyrosine kinase inhibitors in FLT3-dependent AML cells, both in vitro and in vivo [89].

Disruption of the ETC on a wider scale is also effective at reducing leukemia cell viability. By targeting the mitochondrial protease ClpP with a beta-lactone inhibitor called A2-32-01, Cole and colleagues demonstrated that this compound was effective at killing leukemia cells with high levels of ClpP expression [90]. Interestingly, this phenotype only appears in approximately half of the leukemic cell lines that were analyzed. Multiple publications have demonstrated that many of the targets of the ClpP protease are members of the ETC complexes [90,

91], perhaps to ensure that the components of the complexes remain in stoichiometric balance.

Modulation of mitochondrial ROS as AML treatment strategy

The formation of ROS is essential for normal cell physiology (Fig. 3); ROS are generated during mitochondrial oxidative metabolism as well as in response to exposure to xenobiotics, cytokines, and bacterial invaders [92]. But ROS have also long been acknowledged as having a role in cellular signaling [93, 94]. For instance, mitochondrial ROS stimulate signaling pathways promoting tumorigenesis such as JNK/ERK, HIF-1α, and mitochondrial biogenesis [94]. ROS have also been shown to regulate protein function (including kinases and phosphatases) via various oxidative post-translational modifications [93].

Superoxide anions (O_2^-) are produced as side products from the respiratory chain in mitochondria, by NADH oxidases 1–3 and 5 (NOX), and by other cellular enzymes. The electron transport chain, predominantly complexes I and III, is a major source of superoxide. During oxidative phosphorylation, 1–5% of electrons escape from ETC and produce O_2^- [93]. All NOX family members are transmembrane proteins that use intracellular NADPH to reduce extracellular oxygen to ROS [93]. Interestingly, NOX-derived ROS are linked to activating mutations in FLT3 and Ras: FLT3-ITD mutation in AML causes Akt activation and subsequent stabilization of $p22^{phox}$, a regulatory subunit for NOX1-4 [93, 95]. Moreover, in human AML, NOX2-derived superoxide stimulates bone marrow stromal cells to transfer their mitochondria to AML blasts [96]. Superoxide anions are converted to hydrogen peroxide (H_2O_2) by various superoxide dismutases, which are found in several subcellular compartments (the charged nature of superoxide limits its ability to move throughout the cell). Hydrogen peroxide is also produced by NOX4. Other reactive species, such as the short-lived hydroxyl radical ($OH^{\cdot}$), lipid hydroperoxides, peroxynitrite (NO_3^-), and hypochlorous acid (HClO), arise by metabolic reactions involving superoxide or H_2O_2 [95].

For normal HSCs, ROS present a significant threat, as they can trigger apoptosis, loss of quiescence, or induce differentiation [97]. As noted above, this is also true of LSCs. Metabolic adaptations to limit this sensitivity are likely to emerge and may include increased proton leak down the electrochemical gradient into the mitochondrial matrix [98], mitochondrial uncoupling (abrogation of ATP synthesis in response to $\Delta_{\Psi m}$) [99], and

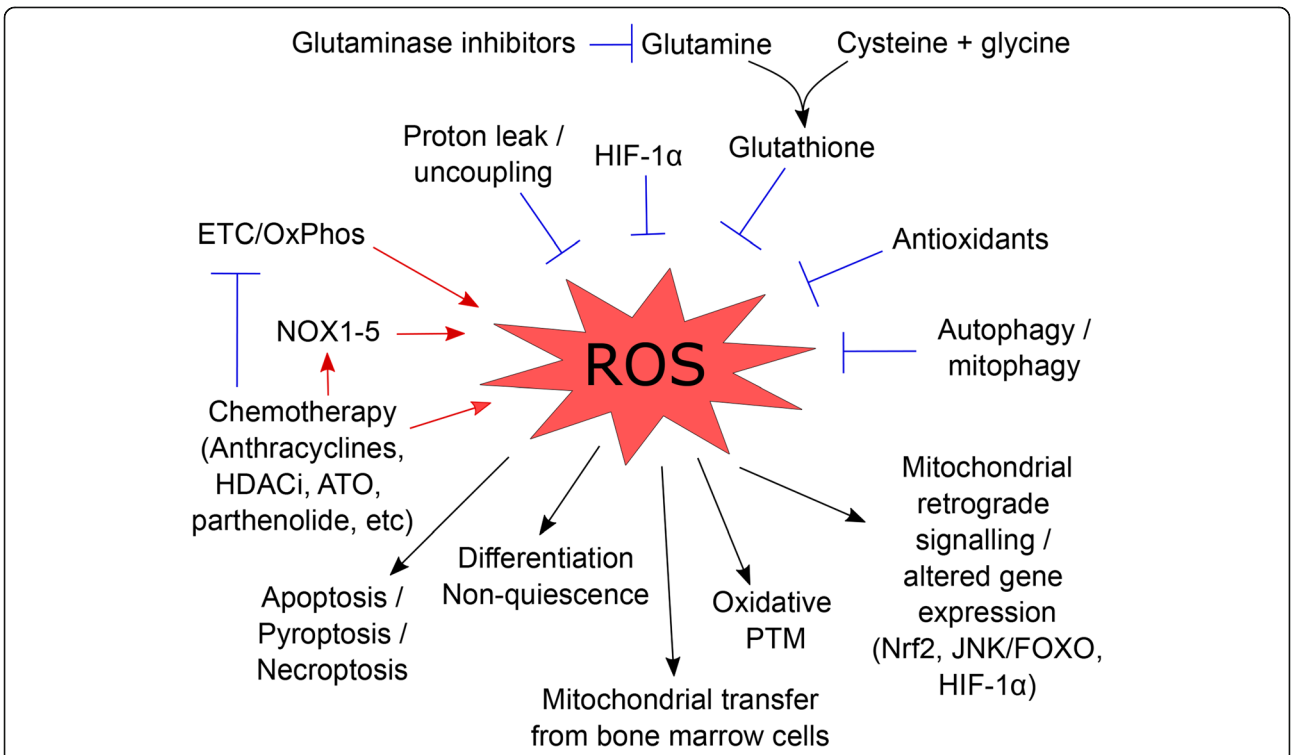

Fig. 3 Central role of reactive oxygen species (ROS) in AML biology and treatment. A representation of the wide variety of factors that produce and limit the production of ROS in AML, along with the outcomes of excess ROS production in these cells. ETC: electron transport chain; FOXO: forkhead box protein O; HDACi: histone deacetylases inhibitors; HIF-1α: hypoxia-inducible factor 1α; JNK: c-Jun N-terminal kinase; Nrf2: nuclear factor erythroid 2-related factor 2; NOX: NADH-oxidases; OxPhos: oxidative phosphorylation; PTM: post-translational modifications

increased autophagy. These events also promote the Warburg effect and cataplerotic reactions from the CAC and support the shift toward glutaminolysis-dependent fatty acid oxidation (FAO) [100]. This may be why disrupting these events is effective at killing cancer cells. The reduced spare respiratory capacity of AML myeloblasts also makes them unusually vulnerable to oxidative metabolic stress, indicating that increasing ROS may be a viable clinical strategy [66].

The potential for killing AML cells using ROS has been reviewed recently [93]. Redox-based treatments of hematological malignancies can be divided into two different approaches: 1) compounds that stimulate the overproduction of ROS; and 2) compounds that compromise the mitochondrial antioxidant system [101]. It is known that many AML treatments and novel compounds with anti-leukemic activities stimulate ROS production, including cytarabine and anthracyclines (the well-known components of induction and consolidation therapy), histone deacetylase inhibitors, such as vorinostat, and the proteasome inhibitor bortezomib [101, 102]. For example, the cytotoxic effects of the anthracycline doxorubicin are linked to the stimulation of the Fenton reaction that generates lethal hydroxyl radicals from superoxide [103]. The Fenton reaction requires the presence of heavy metals such as iron. One side effect of doxorubicin treatment is the preferential accumulation of iron inside of mitochondria [104]. Contrary to anthracyclines, the HDAC inhibitor vorinostat up-regulates ROS generation in leukemic cells by activating NADH oxidases [105]. Furthermore, the combination of vorinostat and PEITC (β-phenylethyl isothiocyanate), depleting antioxidant glutathione, acts synergistically in AML cells via modulating cellular redox status and H_2O_2 accumulation [105].

Arsenic trioxide (ATO) is another interesting example. ATO is a potent ROS inducer and is widely used in combination with all-*trans* retinoic acid (ATRA) to treat acute promyelocytic leukemia (APL), a subtype of AML [106, 107]. ATRA functions in this combination to stimulate differentiation of promyelocytic blast cells, which then spontaneously undergo apoptosis. ATRA also appears to trigger mitochondrial permeability transition and cell death [31]. ATO has replaced anthracycline antibiotics (e.g., daunorubicin, doxorubicin, etc.) as the choice companion drug to treat APL since it exhibits less severe side effects [108]. The cytotoxic effects of ATO on leukemic cells include oxidative stress induction, depolarization of the mitochondrial membrane, DNA damage, and induction of apoptosis [109]. More specifically, ATO increases superoxide generation in leukemia cells by inhibiting mitochondrial respiration upstream of complex IV [110]. Interestingly, in APL cell lines, increased catalase expression has been shown to correlate with ATO resistance [111]. Although ATO has been shown to work in concert with high-dose ascorbate, killing AML and APL blasts while leaving HSCs intact [112], ATO was not effective at treating non-APL forms of AML [113].

There are also several plant-derived compounds that exhibit anti-LSC properties, likely by targeting critical mechanisms of redox balance. These molecules include parthenolide, triptolide, cyclopamine, resveratrol, and avocatin B [114]. Mechanistically, parthenolide and its soluble analogue dimethylamino parthenolide stimulate superoxide anion generation by activating NADH oxidase, followed by activation of the kinase JNK and NK-κB [115]. Interestingly, a rationally designed regimen consisting of parthenolide, 2-deoxy-D-glucose, and temsirolimus has been shown to selectively target LSCs with little to no apparent effect on normal HSCs [116]. The anti-leukemic activity of this regimen is associated with its strong ability to induce oxidative stress without activating the compensatory responses in AML cells [116]. ROS-mediated dimerization of Bax, a pro-apoptotic member of the Bcl-2 protein family, and oxidation of cardiolipin trigger the release of cytochrome *c* into the cytosol, and has been proposed as oxidative stress-based mechanisms of apoptotic activation [117]. Another naturally occurring compound, cyclopamine, inhibits hedgehog signaling and induces apoptosis in AML $CD34^+$ blasts [114], and directly inhibits OxPhos in lung tumors [118]. Avocatin B induces ROS-dependent, mitochondria-mediated apoptosis in AML cells, as well as inhibits fatty acid oxidation. It also synergizes with cytarabine/doxorubicin to induce leukemia cell death [114].

Increasing ROS level beyond the capacity of antioxidant defense can cause several types of cell death in AML [101, 102, 119]. Apoptosis is the most common type of cell death resulting from increased ROS production [120]. ROS may activate both mitochondrial (intrinsic) and death receptor (extrinsic) pathways of apoptosis. Mitochondria-derived ROS are able to target mtDNA, disrupt respiratory chain function, lead to loss of mitochondrial membrane potential, impair ATP synthesis, and cause the release of cytochrome *c* due to mitochondrial outer membrane permeabilization [121, 122].

In addition to apoptosis, elevated ROS in AML may also induce ferroptosis [123]. Ferroptosis is an iron-dependent programmed cell death pathway caused by the failure of glutathione-dependent antioxidant defense and unregulated lipid peroxidation [124]. This has implications for AML therapy. For example, low doses of erastin (ferroptosis inducer) enhance the anti-cancer activity of cytarabine or doxorubicin in AML cells [123]. Lastly, necroptosis as a type of cell death is frequently associated with ROS generation in AML [120]. Death

receptor activators (TNFα, FasL) can induce mitochondrial and non-mitochondrial ROS generation, followed by activation of ASK1 (apoptosis signal–regulating kinase 1) and p38 MAPK (mitogen-activated protein kinase), which results in caspase-independent AML cell death [121, 125].

One limitation of this approach, at least in theory, is that the increased ROS will contribute to genomic instability that may increase the probability of treatment resistance, with the thought being that any cells that do not develop resistance will perish, leaving only the resistant cells to divide [126]. In addition, AML cells are not the only cells that are very sensitive to ROS; HSCs also exhibit strong sensitivity and it would be difficult to kill the AML cells without also doing considerable, perhaps irreparable, damage to the healthy HSCs.

Mitochondrial priming and Bcl-2 protein family

Another key requirement for the proliferation of AML LSCs and blasts is the release from apoptotic activation. Generally, in AML, this is achieved by the overexpression of pro-survival Bcl-2 family proteins, including Bcl-X_L, Mcl-1, and Bcl-2 itself [127]. The anti-apoptotic Bcl-2 proteins are members of a larger superfamily of proteins named after Bcl-2, the founding member. Proteins in the family typically share Bcl-2-like homology domains 1–4 (BH1-BH4), and include both pro- and anti-apoptotic members, although there is a third group, possessing only the BH3 domain, that are also pro-apoptotic [128, 129]. Members of this family trigger apoptosis by intercalating into the outer membrane, increasing its permeability, releasing pro-apoptotic factors, and activating the caspases responsible for a commitment to cell death [130]. Insertion into the membrane appears to, at least partially, depend on whether Bcl-2-family members have oligomerized via their BH3 domains. As reviewed elsewhere [128, 131], conventional cytotoxic chemotherapy often activates apoptosis via mitochondrial permeabilization using Bcl-2-family members.

For these reasons, it has become common to target the BH3 domain of the anti-apoptotic members of the Bcl-2 family with small molecule drugs [132]. The best known and most successful BH3-domain targeting drugs include obatoclax, ABT-737, and an orally available derivative called ABT-263 (also known as navitoclax), which target Bcl-2, Blc-X_L, and Bcl-W, and ABT-199 (also known as venetoclax), which targets Bcl-2 [86, 132–135]. Venetoclax has become the most clinically effective BH3-targeting drug approved by the FDA for leukemia treatment and has received FDA approval in several different contexts [136–138]. A comprehensive review of venetoclax's use and function has recently been published [139], so it will not be discussed in depth here.

Although venetoclax has demonstrated encouraging results in targeting Bcl-2, resistance can still develop. The most common cause of this is stabilization of Mcl-1 [140]. This, along with the fact that Mcl-1 is essential for the development and survival of AML cells, has led to the development of selective Mcl-1 inhibitors [141]. Sharon et al. used CRISPR knockout screen to determine that ribosome-targeting antibiotics such as tedizolid can overcome venetoclax resistance by suppressing mitochondrial translation and respiration, and activating the cellular stress response [142]. Moreover, the addition of tedizolid to azacitidine and venetoclax further enhanced the killing of resistant AML cells in vitro and in vivo [142].

Although mitochondrial permeabilization is sometimes considered to be an irreversible commitment, there is evidence that this may be an oversimplification. For example, it has been reported that not all mitochondria undergo permeabilization simultaneously [143, 144]. In addition, it is possible to measure the differences in mitochondrial permeabilization, which revealed that these differences, termed "priming", are associated with sensitivity to chemotherapy [145]. Interestingly, lower priming is also associated with resistance to chemotherapy [145]. Together, these phenomena suggest that targeting mitochondrial permeability may be an effective method of treating AML in general.

Mitophagy as a target for AML therapy

Even in healthy cells, the production of ROS is associated with damage to mitochondria. This damage reduces their effective function and can trigger apoptosis or macroautophagic mitochondrial recycling (also known as mitophagy). Under normal circumstances, mitochondria undergo frequent fission and fusion events that, by means yet unknown, sort intact and damaged components so that the former can be retained while the latter are recycled [146].

Although the sorting mechanisms remain unclear, the events coming after have begun to be illuminated. Currently, the best-known regulators of mitophagy are the PTEN-induced kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin, which are conserved at least as far back as the nematode *Caenorhabditis elegans*. While mitochondria are healthy, PINK1 is imported into mitochondria, where it is immediately cleaved by resident proteases [147]. Under stress conditions or loss of mitochondrial membrane potential (i.e., if mitochondrial import is blocked), PINK1 accumulates on the surface of mitochondria, phosphorylating itself and Parkin [148–150]. Once recruited, Parkin catalyzes the ubiquitination that

allows mitochondria to be recognized by autophagosomes [146].

Broadly speaking, the idea of autophagy-dependent cell death or, more specifically, mitophagy-dependent cell death, remains controversial [151]. On the one hand, the ability to remove defective mitochondria (mitigating ROS, preventing the activation of apoptosis, and providing building blocks for cell division) makes mitophagy an important tool for leukemic progression. Knockdown of autophagic genes involved in mitochondrial clearance, including BNIP3L/Nix and SQSTM1/p62 also sensitizes cells to mitochondria-targeted therapies [152, 153], arguing that these genes promote cancer cell survival. LSCs have also recently been argued to leverage mitophagy in an attempt to maintain stemness [154]. Mitophagy also promotes survival in the hypoxic conditions that exist in the bone marrow microenvironment [155]. Inhibiting autophagy in these conditions decreased in vivo tumor burden and enhanced apoptosis [155].

In contrast, there is some evidence that mitophagy can limit the growth of cancer cells. For example, inhibiting the activity of complex I in melanoma cells depolarizes the mitochondrial membrane, upregulating ROS, and causes mitophagy-dependent cell death activation [156]. Another report has demonstrated that a trihydroxyphenyl alkone also depolarizes the mitochondrial membrane and triggers autophagic death of melanoma cells [157]. Additionally, loss of autophagy in vivo is associated with a glycolytic shift and more aggressive growth of myelocytes [158]. Sodium selenite, a known activator of mitophagy, triggers programmed cell death in malignant glioma cells via an autophagy-dependent manner [159]. Disruption of autophagy genes is also associated with overproliferation in several solid tumors, further strengthening this connection [160, 161].

Critically, this included HSCs, where deletion of Atg7 or Atg5 resulted in myeloproliferation [158, 162]. Interestingly, these proliferated cells seemed to have lost their stemness and were not able to serve as LSCs, perhaps indicating another key difference between LSCs and myeloblasts. A statistical analysis has demonstrated that mutation of autophagy-related genes occurs more frequently in AML than would be expected by chance [158].

Perhaps most promisingly, there is at least one report that appears to directly target leukemia using activation of mitophagy [163]. The authors of this report demonstrated that FLT3-ITD AML cells were deficient in C_{18} ceramides, which have been associated with apoptosis-independent autophagic cell death [164]. The authors observed that the FLT3-ITD mutation reduced the function of the CerS1 gene (which is responsible for the biosynthesis of C_{18} ceramides) and that disrupting FLT3 improved C_{18} synthesis, which localized to mitochondria, recruited autophagic machinery, and triggered autophagy [163]. Normal markers of apoptosis and necrosis were not observed and pan-caspase and necroptotic inhibitors did not affect FLT3-ITD-targeted rescue. In contrast, bafilomycin A1, which prevents acidification of the autophagolysosome, prevented the cytotoxicity that was triggered by the kinase inhibitors sorafenib, crenolanib, or quizartinib [163]. The report also included evidence that a synthetic ceramide analog could potentiate mitophagy and kill tumor cells by overcoming their resistance to kinase inhibitors. Importantly, this effect was specific to leukemia cells and was observed in a murine PDX AML model, supporting both the potential of this approach and of this particular therapy.

Ultimately, the utility of mitophagy as a tool in the arsenal of anti-cancer treatments may be limited to certain genetic causes of AML or to certain populations of cells, such as myeloblasts or LSCs, but further study of this possibility will be essential to make this determination.

Conclusions and future perspectives

Over the last three decades, it has become clear that AML cells gain considerable metabolic plasticity during their escape from bone marrow niches and their transitions to proliferating cancer cells. Mitochondria are a central hub for many of these pathways, and the dependency of these cells on mitochondrial function and health is quickly becoming a hallmark of AML, and potentially their Achilles' heel. It is not surprising that many agents targeting mitochondria and mitochondrial function are currently being investigated in clinical trials or have already been approved by the US FDA for treatment of patients (summarized in Tables 1 and 2, Fig. 1).

One of the most promising future directions in AML therapy is the search for drug combinations with synergistic activity. The utility of this approach has been borne out with the classic example of cytarabine and daunorubicin [210, 211]. These AML-targeted combinations may be comprised of drugs from the same class, such as the pairing of various anthracyclines with cytarabine, or from drugs with different mechanisms of action, such as quizartinib and azacitidine, which inhibit FTL3 and DNA methyltransferase activities, respectively [288, 289]. Since monotherapies are known to result in the development of compensatory mechanisms and/or resistance, the rational design of drug regimens is of great importance. A carefully considered approach can also be more effective and comprehensive than traditional high-throughput searches [116, 290]. For example, the sesquiterpene lactone parthenolide was found to target the redox balance in AML cells, but also led to compensatory activity from the Nrf2 and pentose phosphate pathways [116]. However, by combining parthenolide with

Table 1 Mitochondria-targeted chemotherapeutics (mitocans) as monotherapy against AML

N	Drugs	Targets/inhibition related to mitochondria	AML subgroup if applicable	Level 1: preclinical (in vitro, PDX)	Level 2: clinical trials/ studies in AML patients
1. DNA-targeted agents/cytotoxic chemotherapy					
1.1.1	Cytarabine	DNA polymerase, topoisomerase II, incorporation into DNA/RNA	AML	[165]	[166]
1.1.2	Doxorubicin/idarubicin/ daunorubicin				[167]
1.1.3	Mitoxanthrone			[168]	[169]
1.1.4	Etoposide			[170]	Phase II [171]
1.2	ddC/alovudine	Mitochondrial DNA polymerase γ, OxPhos	AML	[172, 173]	–
1.3	Bleomycin	mtDNA, OxPhos	AML	[174]	–
2. Bcl-2 family inhibitors					
2.1.1	Navitoclax	Bcl-2	AML	[72]	–
2.1.2	Obatoclax			[175]	–
2.1.3	Venetoclax		R/R AML/unfit for intensive therapy	[176, 177]	Phase II [138]
2.2	Obatoclax	Pan Bcl-2	de novo AML	[178]	Phase I/II [179]
			R/R AML		Phase I [180]
2.3.1	S63845/S64315	Mcl1	AML	[181]	Phase I (NCT02979366)
2.3.2	A-1210477			[182]	–
2.3.3	AZD5991		R/R AML	[183]	Phase I/II (NCT03218683)
2.4	α-TOS	Bid cleavage, complex I, ROS production	APL	[184, 185]	–
3. Agents targeting mitochondrial metabolism					
3.1.1	2-DG	Hexokinase II	AML, FLT3-ITD AML	[34, 43]	–
3.1.2	3-BP	Hexokinase II, OxPhos, ROS production		[186, 187]	–
3.1.3	3-BrOP	Hexokinase II		[43]	–
3.2	3-PO	6-Phosphofructo-1-kinase	AML	[37]	–
3.3.1	CPI-613	PDK, OxPhos	AML	[188]	Phase I [188]
3.3.2	DAP			[189]	–
3.4	Enasidenib	$IDH2^{mut}$	$IDH2^{mut}$ R/R AML	[190]	Phase I/II [191] FDA-approved
3.5.1	Telaglenastat	Glutaminase	AML	[192]	Phase I (NCT02071927)
3.5.2	BPTES		AML with IDH1/2 mutations	[62]	–
3.6.1	ADI-PEG 20	Arginine depletion	R/R or poor-risk AML	[193]	Phase II (NCT01910012)
3.6.2	BCT-100		Pediatric R/R AML	[194]	Phase I/II (NCT03455140)

Table 1 Mitochondria-targeted chemotherapeutics (mitocans) as monotherapy against AML *(Continued)*

N	Drugs	Targets/inhibition related to mitochondria	AML subgroup if applicable	Level 1: preclinical (in vitro, PDX)	Level 2: clinical trials/ studies in AML patients
3.7	L-asparaginase	Asparagine depletion, glutamine uptake inhibition	AML	[195]	Phase I (NCT02283190)
3.8.1	Etomoxir	FAO (CPT1)	AML	[21]	–
3.8.2	Ranolazine	FAO (3-ketoacyl CoA thiolase)			
3.8.3	ST1326	FAO (CPT1)		[196]	
3.8.4	Avocatin B	FAO, ROS production, cytochrome c release		[197]	
4. Agents targeting OxPhos and/or mitochondrial biogenesis/respiration					
4.1	Tigecycline	Mitochondrial translation, mitochondrial biogenesis	AML	[65]	Phase I [73]
4.2.1	Metformin	Complex I, mitochondrial oxygen consumption	AML	[79]	–
4.2.2	IACS-010759		R/R AML	[81]	Phase I (NCT02882321)
4.2.3	Rotenone		AML	[35]	–
4.3	A2-32-01	Mitochondrial protease ClpP, Complex II	AML	[90]	–
4.4	Cysteinase	Complex II	AML	[198]	–
4.5	Antimycin	Complex III	AML	[66]	–
4.6.1	Isobavachalcone	Pyrimidine biosynthesis (DHODH)	AML	[199]	–
4.6.2	PTC299		R/R AML/AML patients unfit for standard therapy	[200]	Phase I (NCT03761069)
4.6.3	ASLAN003			[201]	Phase II (NCT03451084)
4.6.4	BAY 2402234		AML	[202]	Phase I (NCT03404726)
5. Agents inducing ROS production/targeting MPTP					
5.1	Arsenic trioxide	ANT, ROS production, MMP, DNA damage	De novo AML, secondary AML, R/R AML	[109]	Phase II [203]
			APL		Phase I/II (NCT00008697)
5.2	Lonidamine	ANT, OxPhos (complex II)	AML	[67, 204, 205]	–
5.3	Parthenolide	ROS production, NF-kB inhibition	AML	[206]	–
5.4	Triptolide (minnelide as a soluble prodrug)	ROS production, Mcl1, MMP	AML	[207]	Phase I/Ib (NCT03760523)
5.5	Resveratrol	NF-kB, apoptosis induction	AML	[208]	–
6. Mitochondrial uncouplers					
6.1	CCCP	MMP	AML	[67]	–
6.2	Dichlorophenyl urea (SR4, SR9)	MMP	AML	[209]	–

the anti-glycolytic 2-deoxy-D-glucose and the mTOR inhibitor temsirolimus, effective AML eradication was achieved [116]. Similarly, classic chemotherapeutics can be paired with novel classes of treatments like autophagic inhibitors or miRNA mimics/antisense to achieve a synergistic therapeutic effect [291, 292].

Where AML was once one of the most lethal and most rapidly developing cancers, the identification and

Table 2 Mitochondria-targeted chemotherapeutics (mitocans) in synergistic combinations against AML

N	Drug combination	Targets/inhibition related to mitochondria	AML subgroup if applicable	Level 1: preclinical (in vitro, PDX)	Level 2: clinical trials/studies in AML patients
1. DNA-targeted combinations/cytotoxic chemotherapy					
1.1	CPX-351, vyxeos (cytarabine + daunorubicin in liposomal encapsulation at 5:1 synergistic ratio)	mtDNA	AML with myelodysplasia-related changes; therapy-related AML. Can be used to treat elderly patients	[210]	Phase III [211] FDA-approved
1.2	Etoposide + cytarabine + azacitidine	mtDNA	Elderly de novo AML patients	[212]	[213]
1.3	Cytarabine/daunorubicin/idarubicin + HDACi (vorinostat, parabinostat, etc)	mtDNA	R/R AML	[3, 214]	–
			Pediatric AML		Phase I (NCT02676323)
			de novo AML		Phase II [215]
1.4	Etoposide + mitoxanthrone	mtDNA	R/R AML		Phase II [216] [217];
1.5.1	MEC (mitoxanthrone, etoposide, and cytarabine) + sirolimus	mtDNA, mTOR	R/R AML or secondary AML	[218, 219]	Phase I [220]
1.5.2	Cytarabine (consolidation therapy) + everolimus		AML		[221]
1.5.3	Low-dose cytarabine + everolimus		Elderly AML		Phase Ib [222]
1.5.4	Cytarabine + daunorubicin + everolimus		Relapsed AML		Phase I (NCT00544999)
1.6	Cytarabine + ibrutinib	mtDNA, NF-kB	AML	[223]	Phase IIa [224]
1.7	Cytarabine + 2-DG	mtDNA, hexokinase II	AML	[13, 34]	–
2. Combinations based on apoptosis induction (Bcl-2, Mcl1 inhibition)					
2.1	Venetoclax + hypometylating agents (e.g., decitabine, azacitidine)	Bcl-2,OxPhos (complex II),amino acid uptake, Nrf2 pathway	De novo/relapsed AML	[86, 225, 226]	Phase Ib [227] FDA-approved
2.2.1	Venetoclax/obatoclax + FAO inhibitors (etomoxir, ranolazine)	Bcl-2, FAO (CPT1a), MPTP	AML	[21]	–
2.2.2	Venetoclax + azacitidine + FAO inhibitors			[28]	
2.3.1	Venetoclax + low-dose cytarabine	Bcl-2, mtDNA	AML patients > 60 y.o. ineligible for induction chemotherapy	[228]	Phase Ib/II [229]; phase III (NCT03069352) FDA-approved
2.3.2	Venetoclax + cytarabine +/- idarubicin		Pediatric R/R AML		Phase I [230]
2.3.3	Venetoclax + cytarabine + daunorubicin; liposome-encapsulated		R/R AML; de novo AML		Phase II (NCT03629171)
2.4	Venetoclax + FLT3-ITD inhibitor (quizartinib)	Bcl-2	AML with FL3-ITD mutation	[231]	Phase Ib/II (NCT03735875)
2.5	Venetoclax + IDH2 mutant inhibitor (enasidenib)	Bcl-2, citric acid cycle	AML with IDH2 mutation R/R AML	[232]	Phase Ib/II (NCT04092179)
2.6.1	Venetoclax + tedizolid	Bcl-2, mitochondrial protein synthesis, OxPhos	AML	[142]	–
2.6.2	Venetoclax + azacitidine + tedizolide				
2.7	Obatoclax + 2-DG	Bcl-2, hexokinase II	AML	[34]	–
2.8	S63845 + S55746	Mcl1, Bcl-2	AML	[233]	–
2.9.1	S63845 + daunorubicin	Mcl1, mtDNA	MLL-AF9 AML	[234]	–
2.9.2	S63845 + venetoclax	Mcl1, Bcl-2			

Table 2 Mitochondria-targeted chemotherapeutics (mitocans) in synergistic combinations against AML *(Continued)*

N	Drug combination	Targets/inhibition related to mitochondria	AML subgroup if applicable	Level 1: preclinical (in vitro, PDX)	Level 2: clinical trials/studies in AML patients
2.10.1	A-1210477 + venetoclax	Mcl1, Bcl-2	AML	[140]	–
2.10.2	UNBS1450 + venetoclax			[235]	
2.11	AZD5991 + venetoclax	Mcl1, Bcl-2	AML	[183]	Phase I/II (NCT03218683)
2.12	Obatoclax + HDACi	Bcl-2,autophagy induction	AML	[236]	–
3. Combinations targeting mitochondrial metabolism					
3.1	CPI-613 + mitoxanthrone + high-dose cytarabine	PDK, mtDNA	R/R AML	[48]	Phase I [48]
3.2	Telaglenastat + venetoclax	Glutaminase, Bcl-2	AML	[59]	–
3.3.1	Telaglenastat + arsenic trioxide	Glutaminase, ROS production, MMP	AML	[61]	–
3.3.2	Telaglenastat + homoharringtonine				
3.4	Telaglenastat + azacitidine	Glutaminase	AML	[237]	Phase I (NCT02071927)
3.5	Telaglenastat + AC220 (FLT3 inhibitor)	Glutaminase, ROS production	FLT3-mutated AML	[238]	–
3.6.1	ADI-PEG 20 (pegylated arginase) + cytarabine	Arginine depletion, mtDNA	AML	[193]	Phase I (NCT02875093)
3.6.2	BCT-100 (pegylated arginase) + cytarabine			[194]	–
3.7.1	Asparaginase + low/high-dose cytarabine	Asparagine depletion, mtDNA	R/R AML/Elderly AML patients > 65 y.o.		Phase II (NCT01810705) [239];
3.7.2	Asparaginase + high-dose cytarabine + mitoxanthrone				[240]
3.8	Etomoxir (FAO inhibitor) + cytarabine	CPT1a, MPTP, mtDNA	AML	[21, 68]	–
3.9.1	Etomoxir + arsenic trioxide	CPT1a, MPTP, ROS production	AML, APL	[241]	–
3.9.2	Etomoxir + arsenic trioxide + 2-DG/lonidamine	CPT1a, MPTP, ROS production, Hexokinase II			
3.10	Avocatin B + cytarabine	FAO, ROS production, mtDNA	AML	[242]	–
4. Combinations targeting OxPhos					
4.1.1	Metformin + 2-DG	Complex I, hexokinase II	AML	[79]	–
4.1.2	IACS-010759 + 2-DG			[35]	–
4.1.3	Rotenone + 2-DG				
4.2	Metformin + sorafenib	Complex I, mTOR	FLT3-mutated AML	[243]	–
4.3	Metformin + 6-BT	Complex I, STAT5, glycolysis	FLT3-mutated AML	[244]	–
4.4	Metformin + cytarabine	Complex I, mTOR, mtDNA	R/R AML	[245]	Phase I (NCT01849276)
4.5	Metformin + NSAIDs (diflunisal + diclofenac)	Complex I	AML	[80]	–
4.6	CCCP + 2-DG	MMP, hexokinase II	AML	[35, 67]	–
4.7	IACS-010759 + vinorelbine	Complex I, OxPhos	AML	[35]	–

Table 2 Mitochondria-targeted chemotherapeutics (mitocans) in synergistic combinations against AML *(Continued)*

N	Drug combination	Targets/inhibition related to mitochondria	AML subgroup if applicable	Level 1: preclinical (in vitro, PDX)	Level 2: clinical trials/studies in AML patients
4.8	IACS-010759 + doxorubicin + cytarabine	Complex I, mtDNA	AML	[246]	–
4.9	Antimycin + 3-BrOP	Complex III, glycolysis, ATP depletion	AML	[87]	–
4.10	Oligomycin + tyrosine kinase inhibitors	Complex V, ROS production	FLT3-mutated AML	[89]	–
4.11	Isobavachalcone + doxorubicin	DHODH, mtDNA	AML	[199]	–
4.12	ASLAN003 + azacitidine	DHODH	AML patients > 60 y.o.		Phase II (NCT03451084)
5. Combinations inducing ROS generation/targeting mitochondrial membrane complexes					
5.1	Diamide + doxorubicin	UCP2, mtDNA	AML	[247]	–
5.2	Arsenic trioxide + high-dose ascorbate	ANT, MMP,ROS production	APL (more promising results than in AML)	[112]	Phase II (NCT00184054) [113, 248];
5.3.1	Arsenic trioxide + decitabine/ azacitidine	ANT, MMP,ROS production	AML	[249]	Phase II (NCT02190695)
5.3.2	Arsenic trioxide + decitabine/ azacitidine + ascorbate				Phase I [250]
5.4.1	Arsenic trioxide + low-dose cytarabine	ANT, MMP, ROS production, mtDNA	AML patients > 60 y.o.		Phase I/II [251]; phase III (NCT00513305) [252];
5.4.2	Arsenic trioxide + high-dose cytarabine + idarubicin		AML patients < 60 y.o.		Phase I [253]
5.5	Arsenic trioxide + mTOR inhibitors (rapamycin)	ANT, MMP, ROS production, mTOR	AML lacking t(15;17) translocation (non-APL)	[254]	–
5.6	Arsenic trioxide + proteasome inhibitor bortezomib	ANT, MMP, ROS production, NF-kB, UPR activation	AML, APL/relapsed APL	[255, 256]	Phase II [257]
5.7.1	Arsenic trioxide + lonidamine	ANT, MMP, ROS production, mTOR, glycolysis	AML	[258]	–
5.7.2	Arsenic trioxide + 3-BP	ANT, MMP, ROS production, glycolysis	AML	[186]	–
5.8	Arsenic trioxide + DCA	ANT, MMP, ROS production, PDK, Mcl1	AML, including FLT3-ITD, R/R AML	[259]	[259]
5.9	Arsenic trioxide + ATRA	ANT, MMP, ROS production	APL	[260]	Phase III [261]
5.10	Parthenolide + 2-DG+ temsirolimus	ROS production, Nrf2, PPP, mTOR, hexokinase II	AML	[116]	–
5.11.1	Parthenolide + ibrutinib	ROS production, NF-kB, mtDNA	AML	[223, 262]	–
5.11.2	Daunorubicin + ibrutinib				
5.12	Triptolide + idarubicin	ROS production, Nrf2, HIF1α	AML	[263]	–
5.13	Resveratrol + HDACi	ROS production, DNA damage	AML	[264]	–
5.14	Cytarabine + PK11195 (PBR ligand)	mtDNA, MPTP	AML	[265]	–
6. Combinations targeting autophagy/mitophagy					

Table 2 Mitochondria-targeted chemotherapeutics (mitocans) in synergistic combinations against AML *(Continued)*

N	Drug combination	Targets/inhibition related to mitochondria	AML subgroup if applicable	Level 1: preclinical (in vitro, PDX)	Level 2: clinical trials/studies in AML patients
6.1.1	Bafilomycin A1 + cytarabine	Autophagy, ROS production, MMP, mtDNA	AML	[266]	–
6.1.2	Chloroquine + cytarabine				
6.1.3	Hydroxychloroquine + cytarabine			[267, 268]	
6.2	Hydroxychloroquine + mitoxanthrone + etoposide	Autophagy, mtDNA	R/R AML		Phase I (NCT02631252)
6.3	Chloroquine + arginase	Autophagy, arginine depletion	AML	[269]	–
6.4	Chloroquine + HDACi (valproic acid/ vorinostat)	Autophagy, accumulation of ubiquitinated proteins	t(8;21)-mutated AML	[270]	–
6.5	ROC-325 + azacitidine	Autophagy	AML	[271]	–
6.6.1	SBI-0206965 + cytarabine	ULK1 (autophagy), ROS production, DNA damage, mtDNA/Bcl-2	AML	[272, 273]	–
6.6.2	SBI-0206965 + venetoclax				
6.6.3	SBI-0206965 + daunorubicin			[274]	
6.7.1	JQ1 + daunorubicin	BET-bromodomain proteins (S100A8/9, BRD4), mtDNA	AML	[275]	–
6.7.2	JQ1 + cytarabine			[276]	
6.8	Birabresib + venetoclax	BET-bromodomain proteins, Bcl-2	AML	[277]	–
6.9	LCL-461 + FLT3-inhibitor crenolanib	Activation of ceramide-dependent mitophagy	AML with FL3-ITD mutation	[163]	–
6.10	TAK-165 + FLT3-inhibitor AC220	Autophagy	AML with FL3-ITD mutation	[278]	–
6.11	Petromurin C + FLT3-inhibitor gilteritinib	Induction of early autophagy and apoptosis, Mcl1	AML with FL3-ITD mutation	[279]	–
7. Combinations targeting mitochondria-related miRNAs					
7.1	miR-181a/b mimics + doxorubicin/ daunorubicin/cytarabine	Mcl1, Bcl-2, mtDNA	AML	[280–282]	–
7.2	miR-15a/16-1 mimic + arsenic trioxide	UCP2, MMP, cytochrome c release, ROS production	AML	[283]	–
7.3	miR-9 mimic + daunorubicin	EIF5A2, Mcl1, mtDNA	AML	[284]	–
7.4.1	miR-29b mimic + cytarabine	Mcl1, mtDNA	AML	[285]	–
7.4.2	miR-29b mimic + decitabine			[286]	
7.5	Antisense miR-32 + cytarabine	Bim upregulation, mtDNA	AML	[287]	–

development of effective treatments have made remission a common occurrence. These new approaches, like conventional chemotherapy, can be very effective at inducing remission, even complete remission. Also like conventional treatments, however, they must take into account the metabolic differences between AML myeloblasts and LSCs (such as the differences in energy production, mitochondrial turnover, and sensitivity to ROS) discussed above. As LSCs commonly persist after therapy and are a reservoir for relapse and resistance, it is crucial to continue to investigate these differences and identify new treatments that can specifically target LSCs without causing inappropriate damage to normal HSCs at the same time. Much of our understanding of LSC metabolism has only begun to appear within the last decade, making this an active and developing area of research that promises to lead to even greater improvements in the treatment of AML. When this knowledge is leveraged and these treatment gaps are filled, long-term remission will become commonplace and the promise of effective AML treatments will finally be fulfilled.

Abbreviations

AKT: Protein kinase B (Akt); α-TOS: (+)Alpha-tocopheryl succinate; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AMPK: AMP-activated protein kinase; ANT: Adenine nucleotide translocator; APL: Acute promyelocytic leukemia; Ara-C: Cytarabine; ATO: Arsenic trioxide; ATRA: All-*trans*-retinoic acid; Bak1: Bcl-2-antagonist/killer 1; Bcl-2: B cell lymphoma 2; BET: Bromodomain and extra-terminal domain; BH(1/2/3/4): Bcl-2 homology domain 1/2/3/4; BRD4: Bromodomain-containing protein 4; CAC: Citric acid cycle; CCCP: Carbonyl cyanide m-chlorophenyl hydrazone; CerS1: Ceramide synthase 1; CPT1: Carnitine O-palmitoyltransferase 1; DAP: 2,2-Dichloroacetophenone; DCA: Dichloroacetate; ddC: 2′3′-Dideoxycytidine; DHODH: Dihydroorotate dehydrogenase; EIF5A2: Eukaryotic translation initiation factor 5A-2; ETC: Electron transport chain; FAO: Fatty acid oxidation; FIS1: Mitochondrial fission 1 protein; FLT3: FMS-like tyrosine kinase 3; GSH: Reduced glutathione; HDACi: Histone deacetylases inhibitors; HIF-1α: Hypoxia-inducible factor 1α; HSC: Hematopoietic stem cells; IDH: Isocytrate dehydrogenase; ITD: Internal tandem duplication; JNK: c-Jun N-terminal kinase; KRAS: K-Ras protein; LSC: Leukemia stem cells; MAPK: Mitogen-activated protein kinase; Mcl1: Myeloid cell leukemia 1; miRNA: MicroRNA; MDR: Multidrug resistance; MMP: Mitochondrial membrane potential; MOMP: Mitochondrial outer membrane permeabilization; MPTP: Mitochondrial permeability transition pore; mtDNA: Mitochondrial DNA; mTORC1: Mammalian target of rapamycin complex 1; NF-kB: Nuclear factor kappa B; NOX: NADH-oxidase; NSAIDs: Nonsteroidal anti-inflammatory drugs; NRAS: Neuroblastoma RAS protein; Nrf2: Nuclear factor erythroid 2-related factor 2; OxPhos: Oxidative phosphorylation; PBMC: Peripheral blood mononuclear cells; PBR: Peripheral benzodiazepine receptor; PDC: Pyruvate dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; PDX: Patient-derived xenografts; PFK1: Phosphofructokinase-1; PFKFB: Phosphofructokinase-2/fructose bisphosphatase; PINK1: PTEN-induced kinase 1; PPP: Penthose phosphate pathway; ROS: Reactive oxygen species; R/R: Relapsed/refractory AML; TCGA: The Cancer Genome Atlas; UCP: Uncoupling protein; ULK1: Unc-51-like autophagy activating kinase 1; VDAC: Voltage-dependent anion-selective channel; 2-DG: 2-Deoxy-D-glucose; 2-HG: 2-hydroxyglutarate; 3-BP: 3-bromopyruvate; 3-BrOP: 3-bromo-2-oxopropionate-1-propyl ester; 3-MA: 3-methyladenine; 3-PO: 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; 4HNE: 4-hydroxy-3-nonenal

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Authors' contributions

SBP wrote the first draft with the help of JP. NVK revised the manuscript and wrote the final version. SBP, JP, and NVK contributed to and edited the final version of the manuscript. The author(s) read and approved the final manuscript.

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