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Investigating the Metabolic Landscape of AML: Myeloblasts, Leukemic Stem Cells, and Haematopoietic Stem Cells

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ABSTRACT: Up to 60% of persons with acute myeloid leukaemia (AML) may relapse and ultimately pass away from their illness despite aggressive treatment regimens. Recent research suggests that leukaemic stem cells (LSCs) trigger AML recurrence by altering their metabolic profile while staying in the bone marrow niche. New hallmarks of leukemogenesis include metabolic adaptability and LSC plasticity, which offer crucial biological mechanisms necessary for tumour initiation, development, and treatment responses. These results underline how crucial it is to focus on metabolic pathways in leukaemia biology, which may be the Achilles' heel in the fight against AML recurrence. The metabolic distinctions between healthy haematopoietic cells, bulk AML cells, and LSCs are highlighted in this paper. We concentrate on four significant metabolic pathways that are dysregulated in AML; glycolysis, mitochondrial metabolism, amino acid metabolism, lipid metabolism, and metabolic process of carbohydrates. We next go through current and upcoming pharmacological therapies that use the metabolic needs of leukemic cells to treat AML. AML cells' metabolic profile changes under many biological circumstances, including treatment and quiescence. Therefore, focusing on these cells' metabolic weaknesses may enable their selective elimination and increase the overall survival of AML patients.

KEYWORDS: leukemic stem cells, cancer metabolism, metabolic targeting, and acute myeloid leukaemia.

I. INTRODUCTION

The most prevalent acute leukaemia in adults is acute myeloid leukaemia (AML) (1, 2). Leukaemic blasts, an aberrant proliferation of undifferentiated hemopoietic cells, are its defining feature (3). Around 23% of adult leukemias are caused by AML, which occurs at varying rates depending on age (1). Allogeneic stem cell transplantation, monoclonal antibodies, and small-molecule inhibitors that target major leukemogenic drivers are a few of the therapy approaches that have been suggested to enhance clinical outcomes in AML patients. However, combined chemotherapy is still the go-to method for treating diseases (4). In the past, the stages of AML therapy have been called induction and consolidation. The "7+3" regimen, which combines anthracyclines such as daunorubicin, doxorubicin, or idarubicin for 3 days every 7 days after cytarabine (Ara-C) for 7 days, forms the basis of induction treatment (4, 5). Despite aggressive treatment plans, the median survival rate for adults remains depressingly low, and the majority of patients will eventually pass either from side effects of medication or a recurrence of their illness. Although younger patients have substantially better treatment outcomes, with a full remission rate of around 80%, there is still a 5-year overall survival rate of only about 40% due to recurrence and refractory illness (4). As a result, it is difficult to treat AML and calls for a thorough understanding of the cellular and molecular processes that underlie the illness. Energy may be produced through a number of dynamic processes known as metabolism in response to cellular needs. Therefore, the proliferation, differentiation, and quiescence of a cell all affect metabolism (6). For example, normal cells use an organised network of metabolic processes and a balanced supply-demand turnover (6). In order to preserve their existence and generate multipotent progenitors in the bone marrow (BM) niche, normal haematopoietic stem cells (HSCs) often modify their metabolic profiles at a low demand condition (7, 8). Contrarily, the majority of AML patients have rapidly reproducing cells that need extra energy sources to thrive and survive (9). Nevertheless, these myeloid stem/progenitor cells can occasionally develop genetic abnormalities, become malignant leukaemic stem cells



(LSCs), and create an excess of immature CD34+/CD38+ blast cells that do not differentiate (3, 11). HSCs, LSCs, and AML blasts exhibit different genetic and phenotypic characteristics, as well as metabolic variations (12), and each cell group is highly heterogeneous (13, 14). According to groundbreaking research, LSCs are a rare subgroup of the immature CD34+/CD38- population that can cause leukaemia in immunodeficient mice (11, 15). However, under the same circumstances, highly developed CD34+/CD38+ AML blasts failed to spread the illness (15). However, further research has been done to identify specific membrane markers for LSCs, including CD32, CD44, CD47, CD123, TIM3, CD45RA, and CD96, given that LSCs and normal HSCs have a similar CD34+/CD38-surface immunophenotype (14, 16, 17). Additionally common within sub-populations of particular haematopoietic cell types is genome and metabolome heterogeneity. For instance, recent research showed that additional elements, such as reactive oxygen species concentration, are able to distinguish whether cells are functioning LSCs within specific immunophenotypic fractions, such as CD34+/CD38- (18, 19). Additionally, analyses of leukaemogenesis using mathematical modelling have shown that mature myeloid cells frequently have the same genotype as leukaemic blasts, demonstrating that differentiation of leukaemic blasts is not entirely prevented in the illness (20). According to a thorough single-cell sequencing investigation by Bernstein et al., malignant AML cells exhibit intra-tumor heterogeneity, and certain unknown phenotypic markers may be expressed by both cancerous and healthy cells (21). This supports the idea that identifying immunophenotypes would not be effective in detecting the beginning of leukaemogenesis and that determining disease-initiating populations in AML might benefit from additional research into other molecular markers such metabolites and metabolic pathways (22). LSCs, like typical HSCs, are found in the BM niche of AML patients (23), where they get assistance for survival and defence from chemotherapeutic drug therapy (24–26). Additionally, the presence of hypoxic conditions in the bone marrow microenvironment (BMME) leads to lower reactive oxygen species (ROS) content, which not only distinguishes LSCs from AML blasts but also maintains stemness, encourages anaerobic metabolism, and distinguishes LSCs from AML blasts (27, 28). All of these factors shield LSCs from chemotherapy (29, 30). Circulating AML blasts, as opposed to dormant LSCs, have greater ROS levels (18, 31) and upregulate a number of metabolic pathways to provide the necessary energy for proliferation (19) The metabolic profile of AML and the justification for focusing on dysregulated metabolic pathways in leukemic blasts have been widely studied in the past (9, 32–35). But further research is needed to clarify the metabolic landscape of various haematopoietic cells. The discrepancies in the metabolic profiles of healthy haematopoietic and AML cells will thus be the main focus of this review. The attention will next shift to the metabolic variations between healthy HSCs, LSCs, and AML blasts in order to logically design innovative therapeutic strategies to eradicate AML-causing cells.

HSC, LSC, AND LEUKAEMIC BLASTS HAVE DIFFERENT METABOLIC COMPONENTS.

According to earlier studies, normal HSCs, LSCs, and AML blasts all have distinctive metabolic characteristics. Leukaemic blasts require more ATP generation to maintain their accelerated cellular division compared to normal HSCs' modest energy requirements (36). (37). The building components of macromolecules, including amino acids, nucleotides, fatty acids (FAs), and electron carriers, are produced by leukaemic blasts by upregulating metabolic pathways such as glycolysis (37) and the pentose-phosphate pathway (38) in order to sustain the leukemic state (33, 39). LSCs, on the other hand, rely more on mitochondrial metabolism to maintain their dormancy and capacity for self-renewal (18, 40).

GLUCOSE METABOLISM

Dr. Otto Warburg found over a century ago that tumour cells prefer to ferment glucose to turn pyruvate into lactate rather than allowing it to join the tri-carboxylic acid (TCA) cycle. This is true even when there is oxygen present. As a result, cancer cells may produce ATP at a high rate to support fast cell proliferation (41). In addition to its function in bioenergetics, the metabolism of glucose involves a number of other pathways, such as the pentose-phosphate pathway, which produces pentose phosphate for the synthesis of ribonucleic acids, serine biosynthesis, which produces amino acids, and one-carbon metabolism, which produces NADPH as the universal electron carrier (42). As a result, glycolysis not only produces energy but also provides a platform for the production of cancer-related molecular building blocks (42) AML cells need specialised membrane transporters termed GLUTs, which are expressed by the solute carrier family 2A gene, to take in glucose and begin glycolysis. Higher glucose levels in AML cell lines and blasts generated from patient samples were associated with GLUT1 and lactate dehydrogenase overexpression, which promoted treatment resistance and tumour cell survival (43). Similarly, at diagnosis, AML patients' blood levels of pyruvate and lactate were found to be greater than those of healthy controls, and these findings were linked to poor survival (37). Pyruvate and lactate, which are formed in the last glycolytic processes catalysed by PKM2 and LDHA, respectively, are two essential glycolytic molecules. Fascinatingly, LDHA deletion significantly inhibited the activity of both HSCs and progenitors during haematopoiesis while deleterious mutations of PKM2 affected progenitor cell



function without affecting HSCs, highlighting a crucial metabolic difference between various haematopoietic cells (44). A network of signalling molecules, including AMPK and PI3K/Akt/mTOR, regulates glycolysis (45, 46). All other metabolic processes, including OXPHOS, the pentose phosphate pathway, and nucleotide biosynthesis, which are required for healthy haematopoiesis, are connected to this network. Many pathways are dysregulated in AML, which causes blast cells to multiply more quickly and fuel leukaemia. For instance, it has been demonstrated that leukemogenesis was inhibited by AMPK loss-of-function mutations by disrupting the glucose flow via downregulating the GLUT1 transporter (47). Similarly, leukemogenesis was demonstrated to be suppressed by mTORC1 inhibition because LSCs express mTORC1 more than HSCs do (38). In several processes, mTORC1 is essential. activities carried out by cells, such as glycolysis and the pentose phosphate pathway. Additionally, the inhibition of mTORC1 compels AML cells to produce their ATP through OXPHOS rather of glycolysis, which ultimately results in oxidative stress and DNA damage (38). Leukaemic blasts can therefore rewire their metabolic profile and depend on OXPHOS to resist chemotherapy even if they prefer glycolytic metabolism to survive and grow. The PI3K/Akt pathway, which is constitutively active in 50–80% of AML patients and is linked to decreased overall survival, induces mTORC1 (48). A thorough protein array profiling revealed that elevated PI3K/Akt phosphorylation and activity are present in more than 60% of initial AML cells (48). The PI3K/Akt axis also controls glucose absorption and glycolytic flux, which is crucial for proper haematopoiesis and leukemogenesis (49, 50). Normal HSCs require the PI3K/Akt pathway to operate, and in mice models with constitutive PI3K/Akt activation, this system's dysregulation reduced the number of normal HSC cells and caused myeloproliferative illness and AML (49). Another work by Xu et al. showed that primary AML blasts have a constitutively active PI3K/Akt/mTOR pathway that is necessary for their survival, while normal HSCs do not depend on mTOR for either long- or short-term survival (51). In the same study, rapamycin, which inhibits the PI3K/Akt/mTOR pathway, re-sensitized LSCs to the topoisomerase II inhibitor etoposide without having an adverse effect on healthy HSCs, highlighting the significance of this route in the maintenance of the LSC population (51). Additionally, glycolysis is linked to the pentose phosphate pathway in AML cells that have the Fms-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD), a frequent leukaemic mutation that imparts a bad prognosis for AML patients (52). A different research revealed that glucose-6-phosphate dehydrogenase is a key regulator of the pentose phosphate system, and that its overexpression is associated with a poor prognosis (38). Lestaurtinib's pharmacological inhibition of FLT3 and suppression of glucose-6-phosphate dehydrogenase were found to have a strong anti-leukemic impact in AML cells with FLT3-ITD, suggesting a viable treatment approach (53). Further in vivo and in vitro research in these cells are required since, unlike AML blasts, the involvement of the pentose-phosphate pathway in normal HSCs and malignant LSCs has not been well studied. The BMME is a crucial regulator of glycolysis and glucose uptake. Both HSCs and LSCs with low ROS levels rely on the BMME to survive. While ROS-low LSCs achieve energy metabolism through mitochondrial respiration, HSCs primarily obtain their energy through glycolysis (19, 54). Leukaemic blasts, on the other hand, may absorb glucose and fructose from the peripheral circulation at significantly faster rates. In accordance with this, it has been discovered that restricted fructose absorption lowers leukemogenesis and increases Ara-cytotoxicity C's in the BMME's rapidly proliferating cells. This shows that Ara-C resistance is conferred by rapidly growing AML cells in the BMME via means of carbohydrate metabolism (55). Normal HSCs and quickly reproducing AML blasts have increased glucose content and glycolytic activity as a group compared to LSCs, which emphasises the importance of glucose metabolism in leukemogenesis.

II. MOTOR METABOLISM IN MITOCHONDRIAL

The TCA cycle is formed when many metabolic pathways that feed on carbohydrates, amino acids, and fatty acids converge in the mitochondria, which are traditionally thought of as the powerhouse of cancer cells. The mitochondrial environment supports and regulates key metabolic processes, including as the TCA cycle, glutaminolysis, OXPHOS, and fatty acid oxidation (FAO), in addition to bioenergetic activities (58). Some of these mitochondrial pathways, which are essential for AML cell survival and function, are drastically changed in AML cells. High-energy electron carriers from glycolysis, such NADH and FADH₂, are gathered by the TCA cycle and transported to the mitochondria's electron transport chain (ETC) through this major metabolic hub (59). Pyruvate, a product of the glycolysis end-stage, initiates the TCA cycle in normal HSCs due to their well-organized metabolic profile. By driving cells to convert pyruvate to lactate, AML blasts with a dysregulated metabolic profile, on the other hand, dissociate glycolysis from the TCA cycle. This decoupling makes it possible for AML cells to use alternative carbon sources, such glutamate, to meet their energy needs. Consequently, inhibiting glutamine metabolism may be an effective AML treatment (60). To replenish TCA intermediates, glutamate dehydrogenase in cancer cells converts glutamate to α-ketoglutarate (α-KG) (61). According to this theory, glutamine transporters (SLC1A5, SLC38A1, and SLC382) and glutaminase (GLS), which provide α-KG for the TCA cycle and have been found to shield cells against the anti-proliferative effects of the



BCL-2 inhibitor ABT-199 (venetoclax), are enriched in AML cell lines (62). These findings support the conventional wisdom that carbon from glutamine is diverted by cancer cells into citrate, which may subsequently be supplied into the TCA cycle (63). In LSCs with low ROS levels, but not in ROS-high AML blasts, TCA cycle activity is also elevated. Significant ¹³C₁₆ palmitate absorption was seen in ROS-low LSCs, and this palmitate was integrated into the TCA cycle intermediates citrate and malate (18). Contrary to LSCs and quickly proliferating AML cells, metabolomic profiling of metabolites controlled by HIF-1 α , a transcription factor responding to cellular hypoxia, includes 2-oxoglutarate, acetyl-CoA, and succinyl-CoA. The dependency on glycolysis in HSCs with HIF-1 α loss-of-function mutations was reduced, and they had poor quiescence (64). Isocitrate dehydrogenase is responsible for catalysing the production of α -KG from isocitrate in the TCA cycle (IDH). But it has been demonstrated that somatic mutations in the IDH1/2 active site in AML cells cause an excess of the oncometabolite 2-D-hydroxyglutarate, which prevents differentiation and speeds up the disease's development (65). Additionally, in vivo IDH2R140Q mutations promote abnormal self-renewal activity and prevent differentiation in healthy HSCs. Additionally, IDH2R140Q and FLT3-ITD co-mutant in vivo animals caused early leukaemia and were crucial for the continuation of leukaemia (66). IDH1/2 mutations have been demonstrated to increase self-renewal and restrict differentiation of healthy HSCs, resulting in the clonal growth of pre-LSCs, a kind of stem/progenitor cell (67). These mutations remained in the pre-LSC population in AML patients who had undergone induction treatment and experienced long-term full remission (68). IDH1 mutations have also been demonstrated to be conserved throughout the evolution of illness. IDH1 mutations in diagnostic and relapse samples of AML patients were similar, proving that IDH1 mutations are conserved in LSCs that cause disease recurrence (69). AML patients with IDH1/2 mutations were evaluated for the presence of a pre-leukemic cell population in a similar research by Shlush et al., and they found that 2 out of 6 samples had IDH2 mutations in certain progenitor and mature populations (70).

Since cancer cells primarily rely on glycolysis for life, it was first thought that cancer cells had defective mitochondrial respiration (41). But it is now known that tumour cells use oxygen in the OXPHOS process to produce large amounts of ATP by moving electrons to TCA Cycle. In addition to supplying energy, OXPHOS controls the permeabilization of the mitochondrial membrane, regulating the equilibrium between apoptosis and proliferation, and playing a significant role in redox biology (71). Normal HSCs rely on glycolysis and lower their rate of mitochondrial respiration to stay in a dormant condition (72). In agreement with this, "krti" et al. have demonstrated that AML blasts had greater baseline oxygen consumption and mitochondrial biogenesis than normal HSCs (73) But it has also been demonstrated that quiescent HSCs, unlike AML blasts, may maximise their energy production with increased glycolytic activity and electron flow, or the "spare reserve capacity," while enduring oxidative stress (46, 72). This suggests that whereas AML blasts are prone to mitochondrial oxidative stress, normal HSCs may offset energy loss by increasing glycolysis. LSCs, like quiescent HSCs, have typical low oxygen consumption and OXPHOS levels, yet they nonetheless depend on this metabolic system for life (19). According to a recent research by Cole et al., the CD34+ CD38 LSC population of initial AML samples overexpresses the mitochondrial ATP-dependent Clp protease (ClpP) (74). As a result, enhanced OXPHOS in AML patients may be biomarked by increased ClpP expression. Accordingly, Jones et al. investigations of metabolomics and gene expression revealed that LSC-enriched subsets are metabolically inactive populations and, unlike HSCs, prefer to rely on amino acid metabolism for OXPHOS-related energy generation. In LSCs and, under some circumstances, AML blasts, ATP molecules are produced via the TCA cycle, OXPHOS, and mitochondrial metabolism. Thus, re-sensitizing LSCs and AML blasts to conventional chemotherapeutic drugs and improving AML patient outcomes may be achieved by targeting OXPHOS alone or in conjunction with other metabolic pathways.

III. METABOLISM OF AMINO ACID

The creation of proteins, nucleotides, lipids, and glutathione (GSH), among other various cellular activities essential for tumour cell growth, all depend on the 20 standard amino acids (75). Aside from their function in metabolism, amino acids are essential for regulating post-transcriptional modification and epigenetic control (75). Glutamate is the most crucial amino acid for the survival and growth of AML. Together with glucose, glutamine is essential for the growth of tumours because it not only serves as α -KG for the TCA cycle but also facilitates the import of leucine into AML cells, which activates mTORC1-mediated protein synthesis (60). The SLC1A5 transporter brings glutamine into the AML cells, where it undergoes a process known as glutaminolysis in which it is transformed into glutamate and α -KG (76). Leukemic blasts import a disproportionately higher amount of glutamine for survival and expansion compared to normal HSCs. Normal HSCs from healthy donors shown resistance to apoptotic induction in an in vivo investigation after glutamine elimination. In contrast, glutamine depletion by SLC1A5 shRNA knockdown caused apoptosis in eight primary AML samples (77), demonstrating that leukemic blasts rely more on glutamine metabolism than normal HSCs.



Additionally, compared to high-glutamine cells, low-glutamine cells had a much lower rate of oxygen consumption, indicating that glutamine deprivation is what causes OXPHOS suppression (60, 78). At the time of diagnosis, ROS-low LSCs produced from AML patients mostly rely on amino acid metabolism to power OXPHOS (18). LSCs from recurrent AML, however, were able to prevent amino acid loss by improving FA metabolism, mostly via increasing palmitate absorption. Palmitate may be broken down to produce NADH and FADH₂ for OXPHOS and TCA cycle intermediates (18). Therefore, it is required to block auxiliary pathways that produce oxidative-related energy, such as the suppression of fatty acid metabolism in the mitochondria, in order to target and eradicate ROS-low LSCs originating from patients with recurrent AML (79). Similar to this, a thorough proteomic investigation of leukemic cells found that the CD34+CD38- LSC population had higher levels of branched-chain amino acid transaminase 1 (BCAT1) than the non-LSC AML population did. BCAT1 is a negative regulator of α -KG, a significant TCA cycle intermediate. In addition to its function in the TCA cycle, α -KG serves as a co-factor for DNA demethylases such the hypoxia-inducible factor 1 (HIF-1) and ten-eleven translocation family of the Egl-9 family. Therefore, the CD34+CD38- LSC population with elevated BCAT1 levels has a hyper-methylated phenotype comparable to instances of mutant IDH1/2, in which DNA demethylases are prevented from working by the oncometabolite D-2-hydroxyglutarate (80). Key tumour suppressor genes are inhibited by this hypermethylation, which promotes the growth of LSC. As a result, leukaemia cells with suppression of BCAT1 accumulated α KG, which led to the degradation of demethylases protein and eliminated leukaemia-initiating capacity (80). Other amino acids, such arginine, are necessary for the survival of AML cells in addition to glutamine metabolism. Aspartate and arginine are essential for producing amine groups and nucleotides, respectively. AML cells with arginosuccinate synthetase-1 mutations cannot produce arginine from citrulline and aspartate like normal HSCs and must import extracellular arginine instead (81). Measuring plasma arginine might be a crucial component of the immunotherapy for people with AML since arginine catabolism is a major factor in inhibiting the immune response to antigens on AML blasts (82). Overall, compared to AML blasts, LSCs have a higher concentration of amino acids and a more significant amino acid metabolism, providing a chance to target the LSC population specifically (18, 19, 83).

IV. A LIPID METABOLISM

Lipids are the third source of energy for the multiplication and survival of cancer cells, following glucose and glutamine (84). Lipids are extremely complex biomolecules that serve as both an energy source and a source of the building blocks for functional fatty acids needed for the synthesis of cell membranes and the control of signalling pathways (85). When compared to normal haematopoietic cells, AML blasts frequently have dysregulated lipid metabolism suggesting the possibility of targeting lipid production for therapeutic benefit in AML patients (86, 87). Comprehensive lipidomic profiling of plasma from AML patients at diagnosis and healthy blood donors revealed a decrease in total fatty acids and cholesterol and a rise in certain free fatty acids, such as arachidonic acid, which was likely caused by increased FAO (86). FAO itself feeds the TCA cycle with acetyl-CoA intermediate, which results in citrate increase and serves as the precursor to the creation of new fatty acids (88). A multi-enzyme protein called FA synthase (FASN) catalyses the production of FA. It was discovered that it is low in healthy donor-derived normal HSCs and greatly overexpressed in AML patients. It is necessary for the proliferation of AML cells. Acute promyelocytic leukaemia cells that had FASN inhibition by RNAi or epigallocatechin-3-gallate had rapid granulocytic development and became once again sensitive to ATRA therapy (89). It was proposed that autophagy and lysosomal biogenesis might facilitate this process (89). Another route that is dysregulated in AML is fatty acid oxidation (FAO), which is crucial for leukemic cell survival and quiescence (90). FAs are oxidised by FAO, which is the opposite of FA synthesis, to produce acetyl-CoA. Glycolysis and amino acid catabolism, in addition to FAO, also create additional acetyl-CoA molecules, which are subsequently fed into the TCA cycle to make ATP (91). As a result, learning the molecular workings of one pathway would reveal others that may be used therapeutically. When compared to healthy HSCs, AML cells have higher levels of certain FAO-related enzymes and transporters, such as carnitine palmitoyltransferase 1A and carnitine transporter CT2 (32, 92, 93). FAO rates are kept at a baseline level by quiescent HSCs to maintain their dormancy (94). Whether or not HSCs divide symmetrically or asymmetrically after emerging from quiescence determines their destiny (95). Two daughter cells are produced by the asymmetric division; one will develop the capacity for self-renewal and stay dormant, and the other will differentiate and join the circulatory system. The symmetric division, however, will only result in two daughter cells that can undergo cell proliferation and differentiation (95). FAO metabolism encourages asymmetric division, which maintains HSCs' capacity for self-renewal (94). FAO is crucial for LSC maintenance and plays a significant part in venetoclax resistance, similar to HSCs (79). The expression of FAO was enriched in resistant ROS-low LSCs with RAS pathways mutations, whereas CD36 expression was elevated (79). In the CD36+ LSC population, CD36 is a crucial fatty acid transporter that aids in lipid

absorption. In the gonadal adipose tissues of the BM, these CD36+CD34+ cells are substantially more abundant, protecting them from the damaging effects of venetoclax and enabling them to use FAO necessary for their preservation (87). It has been demonstrated that AML blasts and BM adipocyte cells interact to cause lipolysis, release FAs from adipocytes to AML, and boost AML cell survival and proliferation in vivo (96). Sphingolipids play a significant role in leukemogenesis in addition to FAs and associated metabolic pathways by controlling the equilibrium between cell proliferation and cell death (97, 98). Sphingosine kinases and acid ceramidases, two carcinogenic proteins, are necessary for the synthesis and operation of sphingolipids in AML cells. Sphingosine kinase 1 produces the bioactive lipid sphingosine-1-phosphate, which controls the life and demise of AML cells in a constitutively active way (99). According to a recent study, S1PR3, a sphingosine-1-phosphate receptor, is increased in AML blasts and CD34+CD38- LSCs as opposed to regular HSCs. In AML blasts and CD34+CD38- LSCs, S1PR3 modulates myeloid development and stimulates inflammatory pathways. In early AML samples, S1PR3 activation encouraged LSC differentiation, which resulted in the eradication of these cells (100). Based on these findings, it can be concluded that the energy generation mechanisms used by HSCs, LSCs, and AML blasts are all different. In order to target certain cellular populations in AML, addressing metabolic pathways with selective inhibitors may be a feasible method.

V. DRUG RESISTANCE IS PROMOTED BY THE METABOLIC PROFILE OF LSCs.

Normal HSCs or multipotent progenitors with genetic abnormalities that cause dysregulated self-renewal capability develop into AML, a clonal disease of hemopoiesis (13, 101). These cells are referred to as "pre-leukaemic HSCs," and they serve as the leukemia's evolutionary forebears (101). HSCs eventually develop into mature blood cells during normal haematopoiesis, but certain genetic abnormalities prevent this process from happening, leaving LSCs with acquired clonogenic and leukaemia-initiating potential (3, 13, 101, 102) The LSC population is produced by evolutionary processes before to the start of treatment and represents a modest portion of the illness that is resistant to chemotherapy (103, 104) (104). Relapse of the illness is caused by this drug-resistant CD34+CD38- LSC fraction, which has infinite self-renewal potential, after therapy and subsequent remission in patients (102). Due to the LSC population's homing in the BMME, which promotes their quiescence and ability to self-renew, current treatment regimens are less successful in eliminating the population of rapidly dividing bulk AML cells (105, 106). The BMME is essential for the preservation and retention of dormant LSCs and for facilitating communication between stromal cells and LSCs, which has a major impact on the onset, progression, and therapeutic response to leukaemia (106). Additionally, BMME cellular architecture has a significant impact on the gene expression profiles of HSCs and LSCs, and these cells show a dynamic and heterogeneous molecular landscape in comparison to leukemic blasts (23). Six main processes, including altered epigenetic pathways, cellular plasticity, the tumour microenvironment, integrated stress responses, cellular signalling, and metabolic dysregulation, were thoroughly categorised in a recent research by van Gils et al (107). Among these pathways, metabolic dysregulation's beneficial influence on LSCs' chemotherapy resistance (24, 108). As a well-known illustration, the overexpression of ABC transporters in LSCs enables these cells to expel harmful medicines and small molecule inhibitors from the cell (109). Additionally, similar to HSCs, LSCs have a low degree of oxidative stress and ROS levels and are maintained in a quiescent state of protracted dormancy (15, 19). Low-ROS AML cells, or ROS-low LSCs, require less ATP or oxygen to live and favour leukemogenesis by relying mostly on low-energy metabolic pathways (19). This is a crucial factor in why traditional chemotherapy medicines, such Ara-C, are less successful at eliminating LSCs in favour of quickly proliferating AML blasts (110). A portion of blast cells with preserved mitochondrial activity and a high rate of proliferation have been found to be less susceptible to Ara-C, suggesting that distinct kinds of haematopoietic cells have unique metabolic profiles that can be used for targeting (111).

AML METABOLIC TARGETING

AML is one of several human tumours for which metabolic targeting is thought to be a viable treatment approach. Prior research has emphasised the complexity of the metabolic pathways in AML cells, which calls for in-depth research to better illuminate their molecular mechanisms. It has taken a lot of research to find and create novel medications that target metabolism in AML. These medications primarily target the metabolism of lipids, amino acids, glucose, and mitochondria. Although metabolic treatments have been successful in destroying leukemic cells, more thorough preclinical research is required to improve treatment results and prove that these pharmacological modulations do not specifically target healthy haematopoietic cells.

GLUCOSE METABOLISM TARGETING



The dependence of AML blasts on glucose metabolism has been discussed previously, and this makes it a desirable target for AML treatment. Unsurprisingly, it has been demonstrated that suppressing glycolysis by the inhibition of glycolytic enzymes causes considerable energy loss and leukaemia cell death (38). In individuals with AML, overexpression of GLUT1 is linked to a suboptimal response to chemotherapy, and inhibition of GLUT1 is thought to be a viable therapeutic approach (43). In primary AML blasts and cell lines, 2-Deoxy-D-glucose (2-DG) significantly increased the cytotoxicity of Ara-C by inhibiting the glycolysis rate-limiting enzyme hexokinase-2 (37). A synthetic glucose analogue called 2-DG interferes with OXPHOS, N-linked glycosylation, and the activation of autophagy in addition to disrupting glucose metabolism (135). Compared to healthy haematopoietic cells, AML primary blasts and cell lines with c-KIT and FLT3-ITD mutations demonstrated sensitivity to 2-DG therapy (112). In AML cells with high glycolytic activity, such as HL-60 cells, direct inhibition of hexokinase-2 with 3-bromopyruvate is also being considered as a treatment option (43). AML cells with FLT3-ITD also shown resistance to the kinase inhibitor sorafenib, which is used to treat FLT-ITD+ cells, but were susceptible to hexokinase-2 inhibitors such as 2-DG and 3-bromopyruvic acid (113). Glycolysis inhibition is mostly studied in AML patients at diagnosis or in the majority of the AML population, and further research in relapsed AML and LSCs is required.

TARGETING PATHWAYS RELATED TO MITOCHONDRIA

In individuals with AML, inhibition of several mitochondrial metabolic pathways including OXPHOS and aerobic respiration is an emerging therapeutic approach. Patients with relapsed/refractory AML are being treated in an ongoing phase I clinical study using IACS- 010759, a strong and specific OXPHOS inhibitor (ClinicalTrials.gov Identifier NCT02882321). IACS-010759's anti-leukemic action in OXPHOS-dependent primary AML blasts and cell lines is mediated through the AMPK pathway (136). IACS-010759 caused AMPK activation in sensitive primary AML blasts with high levels of AMPK, which suppressed mTOR and decreased cell proliferation. Contrarily, treatment response was reduced in resistant initial AML blasts with low AMPK expression (136). By increasing the TCA cycle, mTORC1 suppression induces primary AML blasts to switch from glycolysis to OXPHOS, which has led to the usage of mTORC1 inhibitors (rapamycin) and OXPHOS inhibitors (metformin) in the treatment of refractory blast cells (38). Brequinar sodium, a different medication that targets the ETC, inhibits the inner mitochondrial membrane enzyme dihydroorotate dehydrogenase, which is crucial for pyrimidine production (137). Brequinar's inhibition of dihydroorotate dehydrogenase caused initial AML blasts to differentiate into myeloid cells and undergo apoptosis (114, 115). The carboxylation of pyruvate to acetyl-CoA is catalysed by the pyruvate dehydrogenase complex. Glycolysis, the TCA cycle, and OXPHOS are three separate metabolic processes, and the pyruvate dehydrogenase complex serves as a connector between them (138). Increased OXPHOS, ROS concentration, and an activated antioxidant response have been seen after inhibiting the pyruvate dehydrogenase complex with the selective inhibitor dichloroacetate, which activates DNA repair genes (138). As a result, using dichloroacetate in conjunction with genotoxic medications like doxorubicin and Ara-C caused DNA damage, ROS production, and death in AML cells (139,140). In initial blasts from AML patients and AML cell lines with FLT3- ITD, Emadi et al. discovered that consecutive treatment of dichloroacetate and arsenic trioxide had synergistic anti-leukemic effects (139). Treatment methods involving mitochondrial dysfunction include exposing AML cells to BCL-2 inhibitors. A powerful BCL-2 inhibitor, venetoclax, has demonstrated efficacy in the treatment of haematologic malignancies, either alone or in combination with other chemotherapeutic drugs (116, 141). Venetoclax treatment resulted in a favourable response in 19% of patients with 32 relapsed/refractory AML patients, while another 19% of patients had a mild anti-leukemic response (116). Likewise, two patients who received venetoclax alone in a short trial including seven patients with secondary AML went into full remission (142). Venetoclax combination therapy, however, has been shown to be much more effective than single-agent therapy (117, 118). Compared to 17.9% of patients in the control group, 36.7% of older patients receiving venetoclax and azacitidine together experienced full remission (118). In a related investigation, the combination of venetoclax with the FLT3 inhibitor quizartinib demonstrated synergistic anti-leukemic action in cell lines and primary patient samples and increased the survival of FLT-ITD+ AML mice compared to the underwhelming effects of single-agent therapies (119). It has also been demonstrated that Venetoclax and statins together have synergistic anti-leukemic effects. Statins have been shown to boost the effectiveness of venetoclax in treating AML, and this effect is caused by the overexpression of pro-apoptotic genes including PUMA, BCL-2 modulation, and protein geranyl-geranylation (133). Additionally, it has been demonstrated that the FAO inhibitor etomoxir boosts the in vivo therapeutic effectiveness of another BCL-2 inhibitor, ABT-737 (143). On the other hand, heme biosynthesis was recently identified as a major regulator of drug sensitivity in a genome-wide CRISPR/Cas9 screen and metabolomics investigation. Venetoclax treatment of AML cells increased heme production, a key regulator of mitochondrial-related apoptosis through ETC and OXPHOS (62). According to these investigations, Jones et al. found that inhibiting BCL-2 with venetoclax greatly lowered OXPHOS and specifically decreased the survival of ROS-low LSCs ex vivo, making them



sensitive to the treatment with azacitidine (18). As previously mentioned, IDH1/2 mutant AML cells produce more 2-D-hydroxyglutarate, which prevents differentiation. In patients and cell lines, targeting AML cells with mutant IDH1/2 profiles has shown positive anti-leukemic results. Enasidenib, a selective IDH2 inhibitor, exhibited an overall response rate of 40.3% when given as a single drug to AML patients who had relapsed or were resistant to therapy (122). Patients who failed to react to treatment had co-occurring mutations in the NRAS and MAPK pathways, which was consistent with the idea that RAS signalling is a main cause of therapeutic resistance (123). Enasidenib also inhibited 2-D-hydroxyglutarate synthesis and promoted cellular development in primary AML cells and xenograft models when given to mutant IDH2 cells (124). Enasidenib also improved survival in xenografts of IDH2-mutant AML, which encouraged the start of clinical studies of the drug in individuals with IDH2 mutation-positive haematologic malignancies (ClinicalTrials.gov Identifier: NCT01915498). Direct disruption of mitochondrial components has also been demonstrated to be another alluring therapeutic approach, and its significance in hematologic malignancies, including AML, is gradually being recognised. This is in addition to inhibition of mitochondria-related pathways. For instance, tigecycline's blockage of translation has had a potent antileukemic impact on primary AML cells. Tigecycline is a glycylcycline class antibiotic that binds to the 30S ribosomal subunit and perturbs mitochondrial translation. Without damaging healthy haematopoietic cells, it specifically killed CD34+CD38- LSCs and primary bulk AML cells (73). A2-32-inhibition 01's of a mitochondrial caseinolytic protein protease has had positive outcomes in AML (74). A2-32-01 is an anti-virulence medication that specifically suppressed ClpP and destroyed both primary and AML cell lines with high levels of ClpP expression without harming healthy hemopoietic cells (74). Treatment of AML patients with high mtDNA polymerase activity also involves suppressing mtDNA replication with 2',3'-dideoxy-cytidine. In AML cell lines and original samples, the nucleoside analogue 2',3'-dideoxy-cytidine selectively inhibits mtDNA polymerase, disturbs OXPHOS, and promotes cytotoxicity while sparing healthy haematopoietic cells (121). 2',3'-dideoxy-cytidine also decreases mtDNA, ETC proteins and induces tumour regression without toxicity in vivo and selectively targeted LSCs with leukaemia initiating potential in secondary xenografts (121). Overall, our findings highlight the possibility of improving AML treatment results by focusing on mitochondrial-related pathways.

AMINO ACID METABOLISM TARGETING

Significant glutamine absorption is a typical metabolic trait of AML cells (60, 62), hence it should come as no surprise that inhibiting glutamine uptake or function is an effective AML treatment method. GLS1 is an important enzyme to increase glutamine levels and its overexpression is reported to be involved in the drug resistance of AML cells. It has been demonstrated that primary AML cells and cell lines do not proliferate when glutamine levels in the culture medium are low or when glutamine production is inhibited by GLS1 knockdown (144). Additionally, CB-839, a GLS1 inhibitor, disrupts the generation of GSH in AML cell lines by inhibiting glutamine metabolism, which raises ROS and causes apoptotic cell death (145). Additionally, arsenic trioxide (ATO), a chemotherapy agent that synergistically disrupted the mitochondrial redox state and caused death in AML cell lines, raw samples, and in vivo models, rendered AML cells vulnerable to GLS1 inhibition (145). In the culture of AML cell lines, GLS1 suppression with CB-839 triggered mitochondrial apoptosis and depleted glutamine, which worked in concert with venetoclax's anti-leukemic actions (78). GLS1 mediates resistance to tyrosine kinase inhibitors, according to results of a CRISPR/Cas9 screen of MOLM-13 AML cells that have been subjected to FLT3 inhibitors (76). Quiartinib (a FLT3 inhibitor) and CB-839 were simultaneously exposed to FLT3- ITD AML cell lines, and this resulted in a potent decrease in viability and an increase in overall survival of immune-deficient mice engrafted with patient-derived AML xenografts, suggesting that AML cells depend on glutamine metabolism for drug resistance. Recent research has emphasised the link between amino acid metabolism and OXPHOS in AML cells. Venetoclax's pharmacological suppression of amino acid metabolism decreased OXPHOS and caused cell death in de novo LSCs with minimal ROS (18). The same study demonstrated that ROS-low LSCs from patients with recurrent AML were resistant to venetoclax because they do not rely on amino acid metabolism for energy and instead get their energy from fatty acid metabolism (18). Moreover, comprehensive metabolomics analysis of relapsed ROS-low LSCs indicated high levels of nicotinamide and NAD⁺, which play an important role in sustaining OXPHOS. As a result, altering nicotinamide metabolism targeted and eradicated ROS-low LSCs that had relapsed, emphasising the importance of doing so (147). According to another research, exogenous cysteine is converted by ROS-low LSCs to GSH, which then activates succinate dehydrogenase, a vital enzyme in the mitochondrial ETC complex II. The same work demonstrated that cysteine deprivation impeded GSH synthesis disturbed ETC, which in turn prevented the formation of ATP and OXPHOS, resulting in ROS-low LSC mortality (148). Another crucial amino acid produced by glutamine and aspartate in the metabolism of AML is asparagine (149). L-asparaginase is an enzyme that turns asparagine into aspartic acid. It has powerful anti-leukemic properties and has been used to treat patients with both de novo and recurrent AML (125, 126). L-asparaginase, high-dose Ara-C, and mitoxantrone have been used successfully to treat AML patients with abnormal asparagine metabolism



(125, 150). Due to these findings, a randomised phase 2b study evaluating the effectiveness of L-asparaginase encapsulated in red blood cells (ERY001) in treating elderly AML patients who are not suitable for intense chemotherapy has been started (127). The suppression of arginine has also shown promise in the therapy of AML. According to a research by Miraki-Moud et al., arginine was necessary for the survival and proliferation of AML blasts taken from patients at the time of diagnosis (81). A pegylated arginine deiminase known as ADI-PEG 20 with decreased arginosuccinate synthetase-I activity shown anti-leukemic efficacy in vitro and in vivo with only little harm on normal haematopoietic cells (81). Another pegylated recombinant arginase, BCT-100, slowed AML blast cell growth and decreased leukaemia engraftment in vivo when arginine was depleted (151). Additionally, adult AML blasts treated with single-agent BCT-100 had substantial cell death along with cytarabine action (151). Similar to this, a current trial (ClinicalTrials.gov Identifier NCT03455140) is examining the safety and effectiveness of BCT-100 in younger patients with relapsed/refractory leukaemia. Together, these trials show that targeting amino acid metabolism is a viable AML therapy approach, similar to targeting glycolysis and mitochondrial metabolism.

VI. TRYING TO STOP LIPID METABOLISM

Increased FA synthesis and FAO are two unregulated metabolic pathways that promote leukemogenesis. FA synthesis and FAO are hence ideal targets for suppression, as could be expected (84, 152). In cell line-derived AML xenografts, CPI-613's inhibition of FA production enhanced doxorubicin's anti-leukemic actions, extending the median survival from 12 days with doxorubicin alone to 16 days with the combination of both (130). FAO suppression has also been demonstrated to prevent AML. In AML cell lines, inhibiting FAO with the specific CPT1A inhibitor ST1326 decreased cell proliferation, caused apoptosis, and interacted favourably with the cytotoxic effects of Ara-C. (134). In a related research, etomoxir's suppression of CPT1A combined with arsenic trioxide to reduce leukemic activity in AML cell lines. Carnitine palmitoyl transferase 1 activity is inhibited by etomoxir, which prevents fatty acid transport into mitochondria and β -oxidation (131). Additionally, by reducing NADPH levels and increasing DNA damage-related cell death, inhibition of CPT1A with avocatin B preferentially targeted AML blasts while protecting normal HSCs (129). What's more intriguing is that, despite enhanced FAO acting as a resistance mechanism, concurrent treatment of LSCs from patients at relapse with azacitidine and venetoclax only slightly reduced viability (18). Sorbitan sesquileate, a CD36 inhibitor, reduced FA absorption, which re-sensitized ROS-low LSCs from patients experiencing recurrence to azacitidine (18). According to a different research, LSCs in the BMME are abundant in adipose tissue and are shielded by lipolysis or FAO. Comparing CD36+CD34+ LSCs to developed leukaemia cells or healthy HSCs, FAO rates are greater in CD36+CD34+ LSCs. As a result, attacking FAO may enable the selective targeting and eradication of the CD36+CD34+ LSC population. Sphingolipids have recently been proposed as a novel therapeutic approach for AML (99, 100). Sphingolipids are produced as a result of a process that is catalysed by acid ceramidase, which also increases the anti-apoptotic protein MCL-1. When NSG mice were engrafted with primary AML cells, the acid ceramidase inhibitor LCL204 decreased the leukaemic load (132). To target resistant primary AML cells with FLT3 mutations, it is now possible to suppress ceramide in AML cells carrying FLT3-ITD, which made them more sensitive to FLT3 inhibitors (153). With little effects on healthy HSCs, MP-A08, a selective sphingosine kinase inhibitor, significantly increased apoptosis in AML cell lines, primary blasts, and CD34+CD38CD123+ LSCs (99). AML patient-derived xenografts were also exposed to MP-A08, which decreased tumour burden and lengthened animal life without compromising normal murine haematopoiesis (99). In contrast to the majority of leukemic cells, normal HSCs and LSCs place a greater emphasis on FAO and FA production than on glycolytic, mitochondrial, and amino acid metabolism. These results imply that lipid metabolism is a survival mechanism for AML progenitor cells and that blocking these pathways is a potential treatment approach for the eradication of these cells in the future.

VII. CONCLUSION

Numerous efforts have been done over the past 10 years to identify the key metabolic differences between tumour cells and their normal counterparts (6, 9). These studies have shown that some malignancies, including leukaemia, are fueled by metabolic changes, necessitating the use of suitable metabolic-based therapeutic approaches (32, 33, 154). Additionally, the distinct metabolic profile of leukemic cells may be utilised to track the development and prognosis of the illness. The bulk of earlier studies on AML metabolism have revealed that over the course of the disease and during treatment, leukemic blasts can compensate for an energy deficit and adapt to different metabolic programmes. To enhance clinical outcomes and lower the likelihood of patient recurrence, however, disrupting metabolic pathways in leukemic blasts alone is ineffective. This is due to the fact that LSCs are the primary mediators of AML recurrence, whereas prior research mostly focused on leukemic blasts (3). Lack of therapeutically applicable in vivo models to



research AML metabolism is a significant obstacle (155). To increase the effectiveness and concordance between in vitro and in vivo investigations, clinically relevant mouse models are needed (155). For instance, the development of AML cells in human plasma-like media demonstrates the disparity between in vitro and in vivo models (HPLM). HPLM has physiologically significant quantities of uric acid, which prevents the creation of new pyrimidines. Uric acid can block uridine monophosphate synthase, a vital enzyme for pyrimidine synthesis, since urate concentrations in human blood are greater than in mouse serum. This has been demonstrated to decrease the susceptibility of AML cells to chemotherapy treatments like 5-fluorouracil and emphasises the significance of the tumour microenvironment on cell metabolism and the effectiveness of medications (156). Lack of effective culture medium to faithfully replicate the tumour environment in patients is another constraining factor (155). In order to more accurately reflect the biological circumstances of patients, much research has been done to enrich culture media with nutrients that are essential in human serum. This has resulted in the usage of enriched mediums like HPLM and Plasmax (156, 157). Additionally, cell co-cultures and 3D cultures provide a tumour microenvironment that is a crucial in vitro regulator of medication response and metabolic reprogramming, better simulating the cellular environment of patients. Adipose tissues and adipocytes can modify drug response in AML and offer compensatory nutrition for leukaemic cells to withstand chemotherapy, as we highlighted in this article. As a result, it is not unexpected that co-culturing AML cells with bone marrow adipocytes significantly enhanced FAO and developed resistance to CPT1a inhibitors (143, 158). Specifically in co-cultures with bone marrow adipocytes, treatment of AML cells with inhibitor dramatically boosted free FAs and glucose absorption, highlighting the critical role of the microenvironment in regulating energy needs and chemotherapy response (158). As a result, the absence of plasma and blood metabolites in cell culture may reduce the effectiveness of metabolic inhibitors and raise concerns about the therapeutic applicability of many in vitro methods. Another degree of complication in understanding AML metabolism and developing appropriate treatment plans is patient and cellular heterogeneity. Previous studies have demonstrated that AML cells change their gene expression pattern, which results in rewired metabolism, to resist treatment (22, 120). In fact, Ara-C and metabolic inhibitors treated AML patients revealed altered metabolic and transcriptional regulation. Additionally, it has been demonstrated that the antiproliferative action of metabolic inhibitors varies between individuals and that AML cells generated from various individuals are metabolically heterogenic, most likely as a result of genetic heterogeneity (22). Another study found that there was a significant amount of genome heterogeneity, which was associated with changed cellular pathways, including metabolism, when the gene expression profiles of chemotherapy responders and non-responders were compared (120). This degree of genome and metabolome heterogeneity supports the idea that a "one-size-fits-all" approach to AML therapy would not be successful, and that personalised medicine is therefore necessary to customise treatments to achieve the best possible outcome for specific patients (159). Targeting metabolic pathways in AML, however, is a promising treatment strategy and a fast developing field that merits serious consideration. To develop effective treatment plans for individuals with AML at various phases of the illness, such as diagnosis, relapse, and remission, further in vivo studies differentiating metabolic requirements of normal HSCs, AML blasts, and LSCs are required. We present a current update on the most recent discoveries of dysregulated metabolic pathways in HSCs, LSCs, and AML blasts in this review, along with information on how these pathways might be targeted for better therapeutic results. Targeting these cells might be a successful AML treatment plan, as previous research has revealed that LSCs are primarily responsible for AML. LSCs can alter their metabolic profile, avoid chemotherapy, and promote disease recurrence by living in the BMME. Conventional chemotherapy is harmful to healthy HSCs and virtually completely unsuccessful in selectively eliminating LSCs or changing metabolic pathways. Targeting metabolic pathways can therefore re-sensitize AML blasts and LSCs to traditional chemotherapy while preserving normal HSCs and healthy haematopoietic cells. Finally, because AML is metabolically and genetically diverse, in vitro investigations may not accurately predict what would happen in patients and in vivo. Therefore, further research is needed to improve patient outcomes and successfully increase survival.

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