Review

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# Bidirectional interplay between metabolism and epigenetics in hematopoietic stem cells and leukemia

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## Abstract

**During the last decades, remarkable progress has been made in further understanding the complex molecular regulatory networks that maintain hematopoietic stem cell (HSC) function. Cellular and organismal metabolisms have been shown to directly instruct epigenetic alterations, and thereby dictate stem cell fate, in the bone marrow. Epigenetic regulatory enzymes are dependent on the availability of metabolites to facilitate DNA- and histone-modifying reactions. The metabolic and epigenetic features of HSCs and their downstream progenitors can be significantly altered by environmental perturbations, dietary habits, and hematological diseases. Therefore, understanding metabolic and epigenetic mechanisms that regulate healthy HSCs can contribute to the discovery of novel metabolic therapeutic targets that specifically eliminate leukemia stem cells while sparing healthy HSCs. Here, we provide an in-depth review of the metabolic and epigenetic interplay regulating hematopoietic stem cell fate. We discuss the influence of metabolic stress stimuli, as well as alterations occurring during leukemic development. Additionally, we highlight recent therapeutic advancements toward eradicating acute myeloid leukemia cells by intervening in metabolic and epigenetic pathways.**

**Keywords** acute myeloid leukemia; epigenetics; hematopoietic stem cells; leukemia stem cells; metabolism

**Subject Categories** Chromatin, Transcription & Genomics; Metabolism; Stem Cells & Regenerative Medicine

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## Introduction

For many years, hematopoietic stem cells (HSCs) have been a valuable model for studying tissue regeneration and stem cell mechanisms. Residing at the top of a hierarchically organized system, HSCs are tighly regulated to retain the unique capability to replenish all blood cells. Cellular fitness of HSCs is attained by a deep quiescence state to prevent DNA damage and exhaustion of the stem cell pool owing to excessive cell divisions (Rossi *et al*, 2007; Weiss & Ito, 2014; Walter *et al*, 2015). Consequently, during homeostasis, almost the entire HSC compartment (~ 90%) resides in the resting phase, G0 (Cheshier *et al*, 1999; Zhang *et al*, 2022b), while the downstream multipotent progenitors are actively cycling to maintain daily turnover (Sun *et al*, 2014; Busch *et al*, 2015; Sawai *et al*, 2016). HSC quiescence is associated with glycolytic energy production rather than oxidative phosphorylation (OXPHOS), ensuring low reactive oxygen species (ROS) production, which can be harmful to the genomic integrity (Ludin *et al*, 2014; Mistry *et al*, 2023) (Box 1; Fig 1A). Additionally, low levels of metabolic activators and protein synthesis are hallmarks of quiescent HSCs (Chen *et al*, 2008; Gan *et al*, 2008; Signer *et al*, 2014; Ito *et al*, 2016; Scognamiglio *et al*, 2016; Vannini *et al*, 2016; Cabezas-Wallscheid *et al*, 2017). During emergencies such as severe bleeding, infections, or chemotherapy, HSCs must guarantee sufficient cellular compensation by exiting their quiescent state to generate the downstream progenitors (Randall & Weissman, 1997; Cheshier *et al*, 2007; Hormaechea-Agulla *et al*, 2020). Higher energy demands of proliferative activated HSCs are compensated by a reversible metabolic switch to OXPHOS (Suda *et al*, 2011). The switch of HSC functionality is governed by epigenetic regulators that modulate chromatin accessibility. Under these circumstances, chromatin remodeling complexes are essential to modulate the positioning of nucleosomes on the DNA (Yoshida *et al*, 2008; Kokavec *et al*, 2017; Lehnertz *et al*, 2017; Liu *et al*, 2018; Xu *et al*, 2018; Han *et al*, 2019; Tu *et al*, 2021). Moreover, histone tails of the nucleosome core can be subjected to posttranslational modifications (PTMs), including ac(et)ylation, methylation, phosphorylation, and ubiquitination. Next to modulating chromatin accessibility, DNA methylation reactions are indispensable to regulate stemness functions (Farlik *et al*, 2016). Malfunction of these cellular mechanisms can lead to the dysfunction of HSC survival, proliferation, and differentiation processes.

In the context of aberrant hematopoiesis including acute myeloid leukemia (AML), the metabolic state of leukemic cells remains controversial. Some studies have implicated high glycolytic activity as a driver of disease progression that can be targeted for eradicating AML (Chapuis *et al*, 2019; Kreitz *et al*, 2019). However, emerging

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evidence suggests that leukemic stem cells (LSCs), which are responsible for leukemia initiation, maintenance, and recurrence (O'Reilly *et al*, 2021), are metabolically less active compared to the blast cell population and cannot mobilize to enhance glycolysis. Instead, LSCs are dependent on OXPHOS, a more efficient method of ATP production (Lagadinou *et al*, 2013) (Box 1; Fig 1B). The distinct metabolic profiles of LSCs promote resistance to traditional chemotherapy and may represent a strong determinant for disease outcome (Sriskanthadevan *et al*, 2015). However, studying LSCs has been challenging due to the lack of reliable surface markers, making it difficult to dissect the metabolic differences between the LSC and the blast population. AML progression has also been shown to be regulated by epigenetic mechanisms. Sequencing data from The Cancer Genome Atlas (TCGA) revealed that 30% of the genes mutated in AML occur within chromatin modifiers and 44% in DNA modification genes (DNMT3A and TET2) (Ley *et al*, 2013).

Previous work has shown that the activity of numerous epigenetic modifiers relies on specific metabolic intermediates serving as cofactors and substrates to facilitate DNA- and histone-modifying reactions and modulate chromatin accessibility, eventually altering transcriptional output (Kaelin & McKnight, 2013; Keating & El-Osta, 2015; Wiese & Bannister, 2020). Subsequently, these epigenetic modifications contribute to the metabolic flux by altering the transcriptional regulation of metabolic factors. As a result, disturbances in either the epigenetic or metabolic profile actively contribute to healthy and malignant hematopoiesis. Advancements in low-input techniques combined with novel functional assays have recently provided the tools to investigate the interplay between central metabolic pathways and epigenetic-transcriptional regulation involved in stem cell fate determination (Takubo *et al*, 2013; Vannini *et al*, 2016; Agathocleous *et al*, 2017; Lozoya *et al*, 2018; Yang *et al*, 2019; Kim *et al*, 2020; Sun *et al*, 2021).

Metabolism (Chandel *et al*, 2016; Nakamura-Ishizu *et al*, 2020; Meacham *et al*, 2022) and epigenetics (Cullen *et al*, 2014; Jiang *et al*, 2019a; Rodrigues *et al*, 2020) have been intensively reviewed as separate themes. This review aims to highlight the instructive contribution of metabolic regulators to epigenetics or vice versa, which is a relatively unexplored field in HSC fate decisions. Further, this review will discuss how these processes regulate leukemia in general and specifically AML.

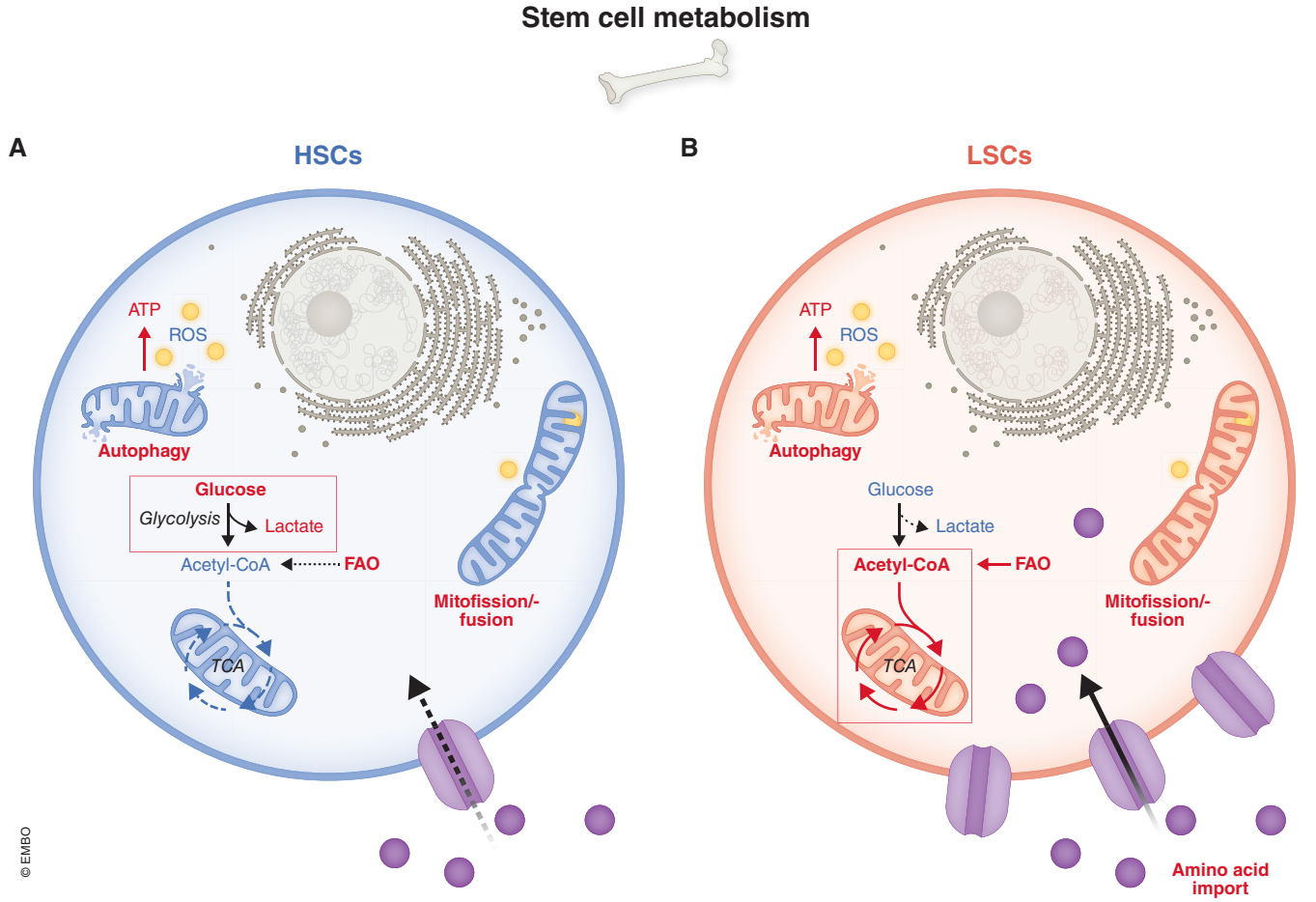


**Figure 1. Metabolic requirements of HSCs and LSCs.**
(A) Hematopoietic stem cells (HSCs) exhibit a quiescent metabolic phenotype and thus show low TCA cycle and OXPHOS activity to sustain low ROS levels. On the other hand, HSCs rely on high levels of autophagy and FAO to sequester damaged mitochondria and to maintain proper stem cell function. (B) Metabolic profiing of leukemic stem cells (LSCs) revealed that these cells are more dependent on OXPHOS, which is more effective in producing ATP. LSCs can mitigate ROS levels by upregulating the expression of ROS scavengers, regulating mitofission/fusion and autophagy. LSCs are more reliant on amino acids metabolism and fatty acid oxidation to supply the compounds to fuel OXPHOS.

**BOX 1. Metabolic requirements of hematopoietic stem cells**

**Hematopoetic stem cells (Summarized in Fig 1A)**

HSCs exhibit hypoxic metabolic profiles and therefore rely on anaerobic glycolytic energy production instead of mitochondrial oxidative phosphorylation (OXPHOS) (Simsek *et al*, 2010; Suda *et al*, 2011). Hypoxia-inducible factor 1 alpha (Hif-1α) is a metabolic master regulator, which directly senses oxygen levels within the bone marrow niche. Hypoxic conditions stabilize Hif-1α, which then hetero-dimerizes with the constitutively expressed Hif-1β and transcriptionally activates multiple glycolytic genes (Semenza, 2010; Simsek *et al*, 2010; Takubo *et al*, 2010). Although some studies suggest the dispensability of Hif proteins for HSC self-renewal (Guitart *et al*, 2013; Vukovic *et al*, 2016), there is evidence that this transcription factor is required to ensure proper HSC function (Takubo *et al*, 2010; Kocabas *et al*, 2012; Takubo *et al*, 2013). Upon activation, HSCs increase glycolysis as well as the production of acetyl-coenzyme A (acetyl-CoA) to fuel the mitochondrial tricarboxylic acid (TCA) cycle (Liang *et al*, 2020). The TCA cycle has a central role in amino acid metabolism and generates redox equivalents such as nicotinamide adenine dinucleotide hydride (NADH), which are required for OXPHOS via the five electron transport chain (ETC) complexes (Martínez-Reyes & Chandel, 2020). Several studies have highlighted the importance of distinct ETC members in maintaining HSC function (Bejarano-García *et al*, 2016; Ansó *et al*, 2017). For instance, ETC complex II activity maintains complex III in proton pumping, while ATP synthesis is kept at very low levels (Morganti *et al*, 2019). In order to meet their higher energy demands, ATP production is indispensable for HSC differentiation processes, but mitochondrial oxidation may be additionally required during homeostasis to recycle $NAD^+$/NADH+$H^+$ and FAD/$FADH_2$ and to maintain TCA cycle activity for the generation of amino acids and fatty acids. Therefore, a reduced OXPHOS capacity can inhibit HSC differentiation causing the accumulation of dysfunctional stem cells (Takubo *et al*, 2013).

Fatty acid oxidation (FAO) catabolizes fatty acids to acetyl-CoA, generating reductive equivalents for the ETC and intermediates for the TCA cycle. FAO is a critical regulator of HSC cell fate determination that controls asymmetric versus symmetric cell division and contributes to redox balancing, since it is an important source of nicotinamide dinucleotide phosphate (NADPH) (Ito *et al*, 2012; Jeon *et al*, 2012). Inhibition of carnitine palmitoyltransferase 1a (Cpt1a), the key rate-limiting enzyme of FAO, promotes HSC differentiation. On the other hand, activation of the FAO upstream regulator peroxisome proliferator-activated receptor delta (Pparδ) further supports HSC function (Ito *et al*, 2012).

In general, mitochondrial respiration produces ROS, which in physiological concentrations can be involved in normal stem cell proliferation and differentiation (Ludin *et al*, 2014). However, extensive ROS levels trigger DNA damage resulting in malfunction, exhaustion of the stem cell pool and aging (Cipolleschi *et al*, 1993; Weiss & Ito, 2014). HSCs can prevent excessive ROS levels by upregulating ROS-detoxifying enzymes like superoxide dismutase and catalase via the forkhead box protein O (FoxO) family of transcription factors. FoxO factors have been shown to prevent ROS-mediated DNA damage, promote HSC quiescence, and mediate apoptosis and autophagy (Miyamoto *et al*, 2007; Tothova *et al*, 2007; Tothova & Gilliland, 2007; Hagenbuchner & Ausserlechner, 2013; Warr *et al*, 2013; Rimmele *et al*, 2015). As mitochondria are key to various metabolic processes, it is not surprising that mitochondrial homeostasis, including mitochondria fusion, fission, and clearance via autophagy, is crucial to prevent HSC malfunction (Youle & Narendra, 2011; Luchsinger *et al*, 2016; Ho *et al*, 2017; Jin *et al*, 2018; Hinge *et al*, 2020; Murakami *et al*, 2021). For example, several studies have described important roles for the Pink/Parkin pathway and the autophagy-related conjugation system, which mediate the clearance of depolarized mitochondria (Joshi & Kundu, 2013; Romero-Moya *et al*, 2013). Remarkably, a recent study provided evidence that HSCs carrying dysfunctional mitochondria have limited their self-renewal capacity (Hinge *et al*, 2020). Based on recent studies, the mitochondrial mass content in HSCs remains controversial (de Almeida *et al*, 2017; Bonora *et al*, 2018; Morganti *et al*, 2019).

Overall, the metabolic state of HSCs determines their function by preventing stem cell exhaustion while contributing to blood homeostasis and emergency hematopoiesis.

**Leukemia and stem cells (summarized in Fig 1B)**

Leukemia stem cells (LSCs) are dependent on OXPHOS rather than on glycolysis (Lagadinou *et al*, 2013; Kuntz *et al*, 2017; Pollyea *et al*, 2018; Raffel *et al*, 2020; Jayavelu *et al*, 2022; Pulikkottil *et al*, 2022; Thomas *et al*, 2022). In contrast, blast cells are dependent on glycolysis. The expression of metabolic genes in AML has a prognostic value in predicting disease outcomes. For example, a high OXPHOS molecular signature (RNA and protein) is associated with poor prognosis in AML patients (Jayavelu *et al*, 2022). It has been speculated that the dependence of LSCs on OXPHOS may be explained by the need to increase ATP production to fuel ATP-dependent drug efflux pumps such as the multidrug resistance proteins P-glycoprotein and the multidrug resistance protein 1 (Wuchter *et al*, 2000; Robey *et al*, 2018). Relative ROS levels can be used to isolate and enrich for LSCs (ROS-low) and blasts (ROS-high) from primary AML patient specimens irrespective of the cytogenetic classification (Lagadinou *et al*, 2013). Amino acid metabolites are significantly enriched in ROS-low LSCs compared to ROS-high AML blasts. The ROS-low LSCs rely on amino acids to fuel OXPHOS. The higher abundance of intracellular amino acids is attributed to increased expression of amino acid transporters in ROS-low LSCs compared to ROS-high blast cells. The depletion of amino acids severely affects ROS-low LSCs survival, indicating that LSCs rely highly on amino acid metabolism (Jones *et al*, 2018). LSCs preserve the low ROS state by increasing the expression of multiple glutathione pathway regulatory proteins, including the ROS-scavenging enzyme *glutathione peroxidase* 3 (*GPX3*) (Herault *et al*, 2012; Pei *et al*, 2013). Deacetylating mitochondrial enzyme sirtuin 3 (SIRT3) reprograms mitochondrial metabolism toward OXPHOS, but downregulates ROS generation by activating mitochondrial antioxidant enzymes (Chen *et al*, 2011). AML cells with high SIRT3 deacetylase activity are more resistant to chemotherapy (Ma *et al*, 2019). In LSCs, high ROS levels promote mitochondrial dynamics. During mitofission and mitofusion, damaged mitochondria are isolated and degraded. Mitochondrial fission 1 (FIS1) is critical for mitophagy by clearing the dysfunctional mitochondria, and high FIS1 is associated with poor prognosis in AML patients (Tian *et al*, 2014). Therefore, the depletion of FIS1 reduces mitophagy and leads to the loss of LSC self-renewal potential (Pei *et al*, 2018).

LSCs can confer chemo-resistance by utilizing the gonadal adipose tissue as a fuel for FAO (Ye *et al*, 2016). The very long-chain acyl-CoA dehydrogenase (VLCAD) is also critical for leukemia cell mitochondrial metabolism, and when targeted can lead to increased cell death. Lipotoxicity can occur when there is an accumulation of excessive lipids, but not all lipids are equally as cytotoxic. Saturated fatty acids (SFA) have high cytotoxicity compared to unsaturated fatty acids. Stearoyl-CoA Desaturase (SCD), an enzyme that catalyzes monounsaturated fatty acids (MUFA), normalizes the MUFA/SFA ratio and protects AML cells from lipotoxicity (Subedi *et al*, 2021).

However, a current challenge in the field is to define LSCs based on markers and the limited numbers of cells to perform certain metabolic assays. Future studies might further define the metabolic features of LSCs based on new markers and low input metabolomics tools.

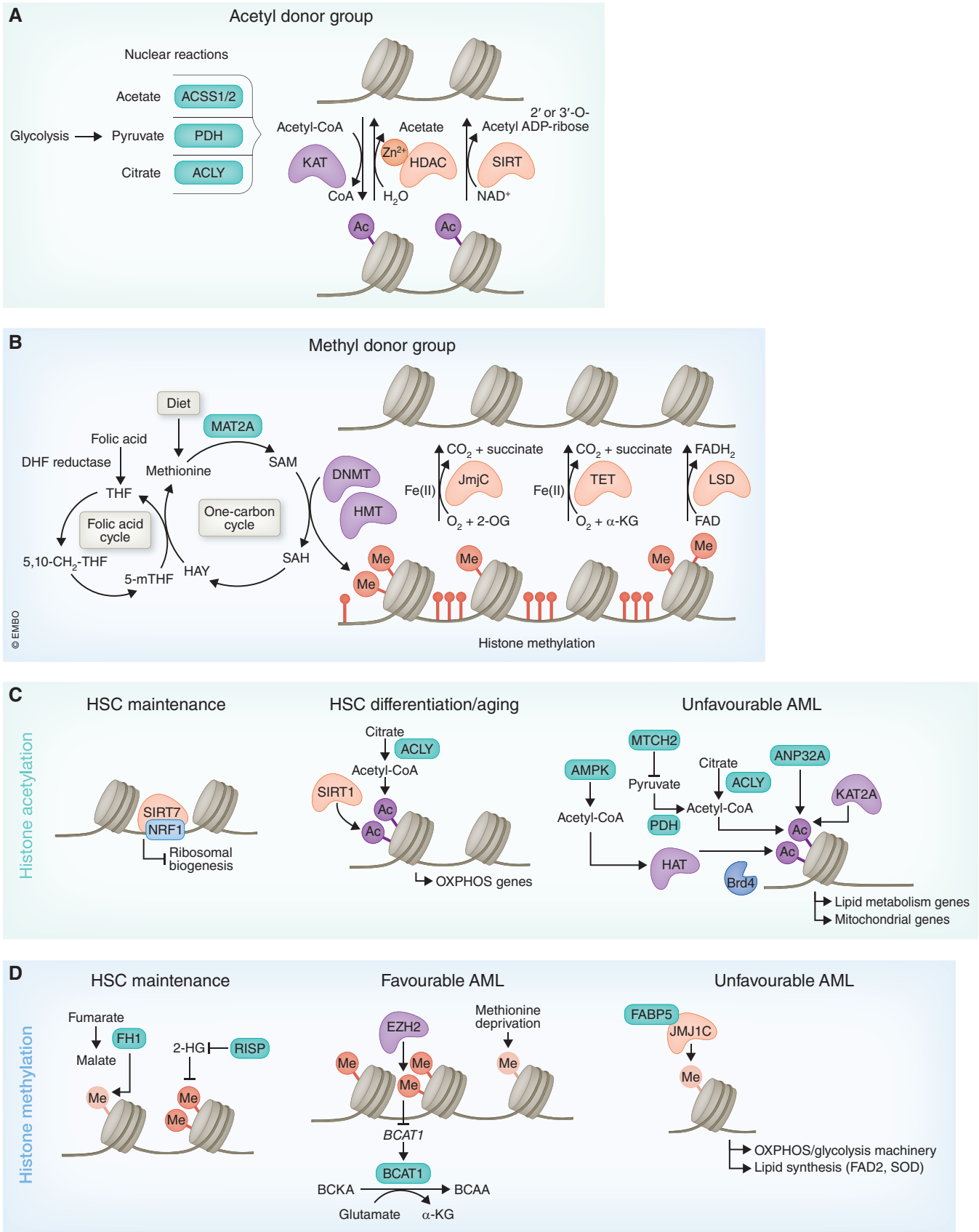


**Figure 2.**

**Figure 2. Acetyl-CoA and S-adenosyl-L-methionine are key metabolites that play additional roles in acetylation and methylation of the chromatin.**
(A) Acetyl-CoA is required as a substrate for KATs. Nuclear acetyl-CoA can be generated through several reactions, e.g., metabolization of pyruvate by the enzyme pyruvate dehydrogenase (PDH) or of acetate by acyl-CoA-synthetase short-chain family member 2 (ACSS2). Alternatively, ATP-citrate lyase (ACLY) can generate acetyl-CoA from citrate. Histone acetylation is linked to chromatin decompaction, resulting in active transcription, and usually dependent on nuclear acetyl-CoA availability. This PTM must be balanced by histone deacetylation, which is conferred by $Zn^{2+}$-dependent HDACs or $NAD^{+}$-dependent SIRT deacetylases. (B) One-carbon metabolism encompasses both the folate and one-carbon cycles to allow cells to generate the methyl groups and use them for methylation reactions. DNMTs and HMTs catalyze the transfer of a methyl group from *S*-adenosyl-L-methionine (SAM) to the C5 position of cytosine on the DNA or histone. TET proteins are iron(II)- and α-KG-dependent oxygenases that hydroxylate 5mC to 5hmC. The JmjC family uses $Fe^{2+}$and 2-oxoglutarate as cofactors, whereas LSD use FAD as a cofactor, to catalyze lysine demethylation. (C) HSC and AML regulation via the interaction between metabolism and histone acetylation HSCs can be maintained through Sirt7 repression of Nrf1 to prevent the transcription of ribosomal proteins. Although Sirt1 acts as a deacetylase, upon aging, Sirt1 is recruited to maintain histone H4 acetylation. Sirt1 knockout inhibits protein synthesis and metabolic activation. ACLY can promote histone acetylation by catalyzing acetyl-CoA from citrate. In AML, numerous metabolic pathways function to increase availability of acetyl-CoA to augment histone acetylation and contribute to disease development and poor survival. For instance, MTCH2 increases nuclear pyruvate and PDH, which increases acetyl-CoA generation. Alternatively, acetyl-CoA can be metabolized from ACLY or butyrate. AMPK increases acetyl-CoA and histone acetylation, which recruits BET proteins to initiate transcription of leukemia-initiating genes. ANP32A increases H3 acetylation and the expression of lipid metabolism genes. KAT2A affects the transcription of genes associated with mitochondrial metabolism. (D) HSC and AML regulation via the interaction between metabolism and histone methylation. Mitochondrial respiration in HSCs is regulated by FH1 and RISP. Additionally, FH1 regulates histone H3 trimethylation. RISP represses 2-HG, a metabolite known to inhibit DNA and histone demethylases. In favorable AML, EZH2 epigenetically represses genes such as BCAT1 via H3K27 methylation in a dose-dependent manner. *BCAT1* increases branched chain amino acid (BCAA). In unfavorable AML, methionine deprivation leads to a profound loss of global H3K27 methylation and H3K36 methylation. JMJD1C enhanced AML proliferation by upregulating of glycolytic and oxidative machinery.

## Histone acetylation is required for regulating stem cell function

The activity of chromatin-modifying enzymes is highly dependent on essential metabolic cofactors. For instance, acetyl-CoA is a donor of acetyl groups for histone acetylation. Therefore, histone acetylation levels are dependent on the availability of nuclear acetyl-CoA (Simithy *et al*, 2017). Lysine acetyl-transferases (KATs) catalyze the transfer of the acetyl group from acetyl-CoA to lysine residues on histones, and histone acetylation levels are typically accompanied by chromatin decompaction, resulting in active transcription (Jiang *et al*, 2019a). In contrast, $Zn^{2+}$-dependent histone deacetylases (HDACs) and $NAD^{+}$-dependent sirtuin (SIRT) deacetylases remove these groups from histones (Ryall *et al*, 2015), thereby leading to chromatin compaction and transcriptional silencing. SIRTs are regulated by the $NAD^{+}$/NADH ratio in a cell which directly links their activity to the cellular redox status (Ryall *et al*, 2015). Nuclear acetyl-CoA is generated through several enzymatic reactions. This includes acyl-CoA-synthetase short-chain family member 2 (ACSS2) which generates acetyl-CoA from acetate, and ATP-citrate lyase (ACLY) which produces acetyl-CoA from citrate. Both enzymes are present in the cytosol and nucleus. Additionally, the pyruvate dehydrogenase (PDH) complex has been shown to translocate to the nucleus during mitochondrial stress conditions and generate acetyl-CoA "onsite" from pyruvate (Sivanand *et al*, 2018) (Fig 2A).

### *Hematopoetic stem cells*

#### *Histone acetylation*

To preserve HSC function, the acetyl-CoA to $NAD^{+}$ ratio must be tightly regulated since these metabolites directly impact cellular acetylation levels. Numerous studies have examined the roles of KATs in regulating HSC function (reviewed in Rodrigues *et al*, 2020). For example, the lysine acetyltransferase, Kat6a uses acetyl-CoA as a substrate and is required to sustain a functional stem cell pool (Sheikh *et al*, 2016). Interestingly, Kat6a acts synergistically with Bmi1, a component of polycomb repressive complex 1 (PRC1) that regulates distinct repressive histone modifications, such as methylation of H3K27, to maintain HSC transplantation features and prevent aging (Sheikh *et al*, 2017; Nitta *et al*, 2020). However, very little is known about the bidirectional interplay between histone acetylation and metabolism in HSCs. To date, most studies have explored histone acetylation with regard to stem cell aging, a cellular state that is accompanied with substantial metabolic changes. Although it remains to be elucidated if cellular acetyl-CoA levels are altered during aging, various metabolic pathways, including glycolysis, FAO, and acetyl-CoA metabolism, are affected in aged hematopoietic stem and progenitor cells (HSPCs) (Brown *et al*, 2013; Mohrin *et al*, 2015; Hinge *et al*, 2020; Nakamura-Ishizu *et al*, 2020; Zhang *et al*, 2020). For instance, glycolytic carbons are redirected to pathways that branch out of the TCA cycle to fuel anabolic processes, which can ultimately lead to decreased acetylation levels (Hennrich *et al*, 2018; Poisa-Beiro *et al*, 2020). In agreement, H4K16ac levels decline upon aging and have been linked to increased Rho-GTPase Cdc42 activity resulting in the loss of HSC polarity (Florian *et al*, 2012). Moreover, in the early phase of hematopoietic regeneration after treatment with the chemotherapeutic agent 5-fluorouracil (FU), HSCs increase the activity of ACLY, and thereby enhance histone acetylation. HSCs with reduced mitochondrial metabolism and ACLY activity maintain stem cell phenotypes, whereas ACLY-dependent histone acetylation in HSCs promote differentiation (Umemoto *et al*, 2022). However, in mice, deficiency of ACLY alters chromatin accessibility of multiple C/EBP family transcription factors known to regulate myeloid differentiation and is sufficient to enhance myelopoiesis (Greenwood *et al*, 2022).

#### *Histone deacetylation*

The proliferative activation of HSCs is generally accompanied with a metabolic switch from glycolysis to OXPHOS. Higher OXPHOS activity leads to an increase in $NAD^{+}$, a cofactor of SIRT histone deacetylases. SIRTs are inextricably linked to major mitochondrial pathways, including biogenesis, metabolism, and the unfolded protein response (Verovskaya *et al*, 2019). Thus, SIRTs are indispensable for regulating HSC metabolic features and are particularly relevant for preventing mitochondrial dysfunction upon aging. For instance, Sirt7 levels decline upon aging resulting in hyperactivation of HSCs. Sirt7 acts on proximal promoters of ribosomal proteins and can mediate gene repression by directly binding to the mitochondrial master transcription factor, nuclear respiratory factor I (Nrf1) (Mohrin *et al*, 2015) (Fig 2C). On the other hand, the loss of Sirt1 suppresses the activation of genes regulating oxidative metabolism, thereby inhibiting HSC aging

(Wang *et al*, 2022c) (Fig 2C). Investigating the $NAD^+$ content during HSC aging will be of interest for the field.

Dietary intakes can also directly contribute to alterations in epigenetic enzyme activities (see Box 2). In particular, high-fat diets correlating with obesity and specific fatty acids, including cholesterol, can change HDAC activity and provoke HSC malfunction similar to aging (Zhang *et al*, 2013; Salminen *et al*, 2014; Tie *et al*, 2014). While the loss of HDAC1 or HDAC2 can be compensated by each other, simultaneous ablation leads to severe HSC defects causing anemia and cytopenia (Heideman *et al*, 2014).

Overall, acetyl-CoA provides a hub fed by various metabolic pathways, multiple cellular and environmental signals and can be integrated to modulate the transcriptional program of HSCs.

#### AML

##### *Histone acetylation*

Aberrant acetylation and deacetylation play a central role in the regulation of metabolic genes in AML. Higher expression of ACLY in AML is associated with increased levels of fatty acids and TCA intermediates and worse clinical outcome (Wang *et al*, 2019; Basappa *et al*, 2020). Higher histone acetylation is also observed in AML from higher Acidic Nuclear Phosphoprotein 32 Family Member A (ANP32A) expression, a member of the inhibitor of the histone acetyltransferase complex. ANP32A is a marker of an unfavorable disease outcome. Genome-wide histone H3 acetylation studies revealed that ANP32A deficiency reduces histone H3 acetylation to induce the expression of genes involved in lipids metabolism (Yang *et al*, 2018; Wang *et al*, 2022a). On the other hand, loss of KAT2A affects the transcription of genes associated with mitochondrial and nucleic acid metabolism and depletes leukemia stem like cells (Domingues *et al*, 2020) (Fig 2C).

Dysregulation of metabolic regulators can also influence histone acetylation levels mainly by modulating acetyl-CoA availability. In AML, inhibition of the mitochondrial carrier homolog 2 (MTCH2) increases nuclear pyruvate and PDH, which in turn augments acetyl-CoA generation. This process induces histone acetylation and subsequently promotes differentiation (Khan *et al*, 2020). Histone acetylation is also maintained by adenosine monophosphate-activated protein kinase (AMPK), a regulator of glucose metabolism and fatty acid uptake. AMPK deletion reduces histone acetylation rendering the chromatin inaccessible to bromodomain and extra-terminal (BET) proteins binding, thereby suppressing the expression of leukemic genes and disease development (Jiang *et al*, 2019b) (Fig 2C).

##### *Histone deacetylation*

In many types of leukemia, SIRTs are involved in disease aggression. For example, the mitochondrial deacetylase, SIRT3 reprograms AML cells toward cellular respiration, protecting them from chemotherapy (Ma *et al*, 2019). Similarly, reduced SIRT5 activity hinderes OXPHOS and glutamine metabolism, which is detrimental to AML. In addition, loss of SIRT5 reduces superoxide dismutase 2 (SOD2) expression, which increases mitochondrial superoxides (Yan *et al*, 2021). H3K9 acetylation levels are also suppressed by PI3K and LYN inhibitors, which prevent ACLY-mediated production of acetyl-CoA (Basappa *et al*, 2020).

While HDAC inhibitors are well-characterized antileukemia agents that show promising clinical trial results, HDAC gene mutations have not been detected in AML. There are several examples of synergies between HDAC inhibition and metabolic pathway inhibitors in the ablation of leukemic cells. For instance, RNF5 promotes the degradation of misfolded glutamine carrier proteins to regulate glutamine metabolism. The inhibition of RNF5 was shown to cause transcriptional changes that overlap with the inhibition of HDAC1, which enhances AML cell sensitivity to HDAC inhibitors (Khateb *et al*, 2021). The NAMPT inhibitor KPT-9274 confers synthetic lethality with the HDAC inhibitor AR-42. Mechanistically, an increase of histone acetylation potentiates the effect of KPT-9274 on PARP-1 suppression through abolishing mono-ADP ribosylation and attenuates homologous recombination and nonhomologous end-joining pathways in the leukemia-initiating cells (Zhang *et al*, 2021). However, in AML1-ETO leukemia, HDAC inhibition reduces autophagy, thereby limiting cell death (Torgersen *et al*, 2013).

## Stem cells require a balanced histone methylation status

S-adenosyl-Lmethionine (SAM) is the universal substrate for methyltransferase reactions, including histone and DNA methylation. It is generated by one-carbon metabolism, a series of cyclic reactions to transfer a single carbon unit, including the folate, methionine, and trans-sulfuration cycle (Ryall *et al*, 2015). In brief, tetrahydrofolate (THF) is reduced to 5-methyl THF, which donates a carbon atom to homocysteine to generate methionine, which is then adenylated into SAM (Ryall *et al*, 2015). Histone methyltransferases (HMTs) transfer the methyl group from SAM onto lysine or arginine residues, thereby generating S-adenosyl homocysteine (SAH), which in turn acts as a potent methyltransferase inhibitor. Depending on the number of methyl groups added and the amino acids modified, histone methylation can translate to either transcriptional activation (generally associated with H3K4, H3K36, and H3K79) or repression (H3K9, H3K27, and H4K20) (Oh & Humphries, 2012). Numerous histone demethylases exhibit metabolic dependencies such as demethylation reactions that can be controlled by α-ketoglutarate (α-KG) and succinate (Beerman & Rossi, 2015). α-KG may be either produced via oxidative decarboxylation of isocitrate by isocitrate dehydrogenase (IDH) or via oxidative deamination of glutamate by glutamate dehydrogenase during glutaminolysis. Succinate is mainly produced by the TCA cycle enzyme succinyl-CoA synthetase (Kaelin Jr. & McKnight, 2013) (Fig 2B).

#### Hematopoetic stem cells

##### *Histone methylation*

In HSCs, H3K4 methylation is mediated by mixed lineage leukemia 1 (Mll-1; also known as Kmt2a) and involved in the regulation of fetal and adult hematopoiesis (Jude *et al*, 2007; McMahon *et al*, 2007). Dietary methionine restriction has been shown to regulate cellular SAM levels and thus to modulate H3K4me dynamics in several tissues (Shiraki *et al*, 2014; Mentch *et al*, 2015; Dai *et al*, 2018). However, the role of dietary methionine or intracellular SAM levels have so far not been elucidated in HSCs. Additionally, H3K9, H3K27, and H3K36 methylation are other types of SAM-dependent modifications that modulate HSC fate decisions (Ugarte *et al*, 2015; Kats *et al*, 2018; Zhang *et al*, 2018). It would be interesting to investigate the direct link between SAM availability and histone methylation levels in HSCs.

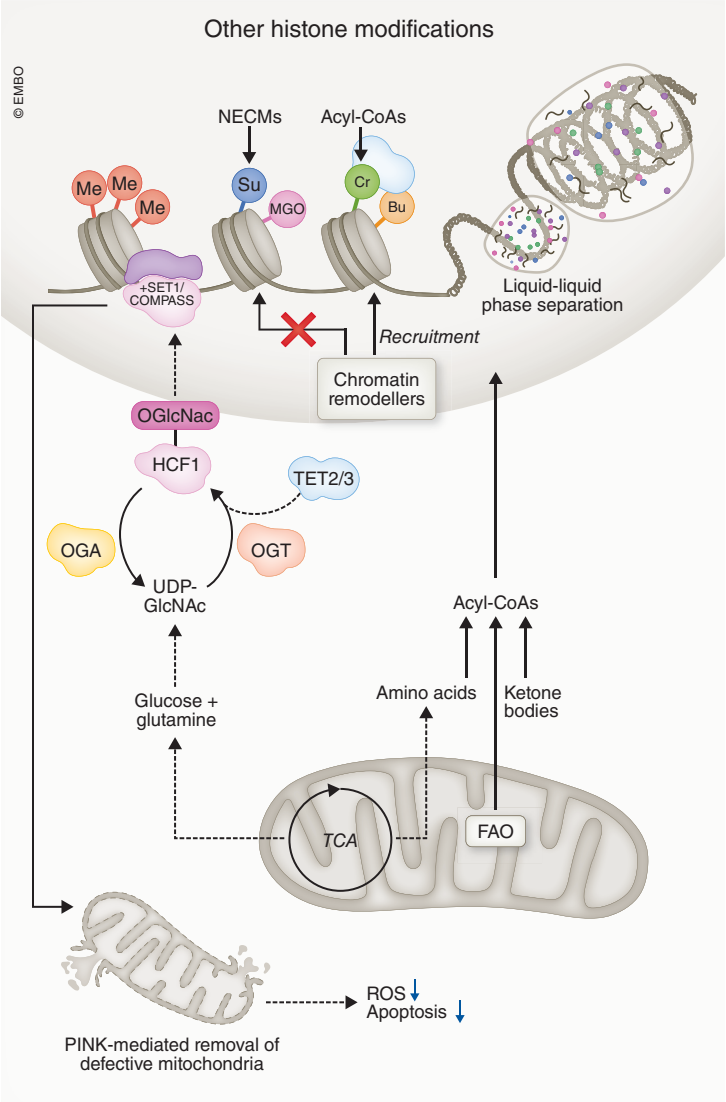


**Figure 3. Additional histone modifications impacting HSC self-renewal.**
Numerous histone PTMs have been identified throughout the last few years, including acylations, (i.e., butyrylation, crotonylation, succinylation) as well as other modifications such as O-GlcNAcylation and methylglyoxal (MGO) adduction. The corresponding substrates are produced within diverse metabolic processes including lipid metabolism, amino acid catabolism, ketone body metabolism, as well as short-chain fatty acid (SCFA) metabolism derived from intestinal microbiota. For instance, in HSCs O-GlcNActransferase (OGT), together with TET proteins, can modify histone methyltransferase complexes such as HCF1/SET1/COMPASS, which leads to changes in H3K4 methylation levels. This results in activation of the PINK pathway, which is essential to maintain HSC function by removing defective mitochondria, limiting ROS levels, and ultimately preventing apoptosis. Liquid–liquid phase separation of metabolic enzymes in the nucleus may be important to provide these subtrates in substantial amount directly at the chromatin.

*Histone demethylation*

HSCs depend on two families of histone demethylases (HDMs), the lysine demethylase (LSD) and the Jumonji C (JmjC) domain-containing family, to remove histone methylation marks. Importantly, α-KG acts as a cofactor for JmjC HDMs and TET enzymes. α-KG levels are particularly important for HSC differentiation by altering demethylation activities and modulating chromatin changes (Ko *et al*, 2011; Cimmino *et al*, 2017). Another example of regulating methylation patterns is represented by the enzyme Lsd1, which explicitly targets me1/2 of H3K4 and H3K9. Lsd1 is an important regulator of HSC expansion (Subramaniam *et al*, 2020) and requires FAD for its enzymatic activity (Forneris *et al*, 2005; Shi *et al*, 2005).

Interestingly, metabolites generated during mitochondrial respiration such as fumarate have been shown to inhibit the activity of HDMs. Fumarate hydratase (Fh1) is a component of the TCA cycle and cytosolic fumarate metabolism. Deletion of Fh1 causes HSC failure due to endogenous fumarate accumulation, which decreases maximal mitochondrial respiration and increases histone H3 trimethylation (Guitart *et al*, 2017). Similarly, when mitochondrial respiration is impaired by the loss of the mitochondrial complex III subunit Rieske iron–sulfur protein (RISP), this results in loss of quiescence of adult HSCs. Knockout of RISP results in elevated levels of 2-hydroxyglutarate (2-HG), a metabolite known to inhibit DNA and histone demethylases. Hence, the loss of RISP in HSCs

increases both DNA and histone methylation (Ansó *et al*, 2017) (Fig 2D).

### *AML*

#### *Histone methylation*

Histone methyltransferases such as *EZH2*, *MLL*, *DOT1L* are frequently mutated in primary and secondary AML (Ley *et al*, 2013). Myeloproliferative neoplasms (MPN), a precursor of AML, often exhibit loss-of-function mutations of the methyltransferase, EZH2. EZH2 represses genes such as branched-chain aminotransferase 1 (BCAT1), the enzymes responsible for the early steps of branched chain amino acid (BCAA) catabolism via H3K27 methylation in a dose-dependent manner. Thus, the loss of EZH2 elevates the expression of *BCAT1*. Enhanced expression of *BCAT1* increases BCAA metabolism and upregulates the expression of genes involved in the TCA cycle (Gu *et al*, 2019) (Fig 2D). Moreover, mutated EZH2 and oncogenic NRASG12D cooperate to increase the leukemia burden through loss of EZH2 repression of *BCAT1*. This condition is mitigated by the BCAT1 inhibitor, Gbp, which impairs EZH2-deficient leukemia-initiating cells (Gu *et al*, 2019).

#### *Histone demethylation*

JMJD1C is a JmjC containing H3K9 demethylase and, when overexpressed, increases AML proliferation through demethylase-independent upregulation of glycolytic and oxidative machinery. Targeting JMJD1C-mediated metabolism using ABT-268 and Shikonin decreases tumor growth of leukemias co-expressing *JMJD1C* and *HOXA9* (Lynch *et al*, 2019). In another study, JMJD1C was found to regulate lipid synthesis-associated genes such as fatty acid desaturase 2 (FAD2) and stearoyl-CoA desaturase (SOD) in *MLL rearranged* AML. Inversely, the authors found that lipid synthesis-associated protein fatty acid-binding protein 5 (FABP5) binds to the jumonji domain of JMJD1C to regulate expression (Qi *et al*, 2022) (Fig 2D).

In AML, dietary methionine deprivation leads to a profound loss of global H3K27 methylation but an increase of H3K27me3 on the DOT1L promoter. This results in a loss of DOT1L function and prolonged survival in MLL-rearranged leukemia xenograft mice (Barve *et al*, 2019). An additional study demonstrated that dietary methionine deprivation most heavily impacted H3K36me3 and delayed patient-derived AML progression. Methionine starvation is mimicked by chemical inhibition of SETD2, the specific H3K36 trimethyltransferase (Cunningham *et al*, 2022) (Fig 2D).

## Additional histone modifications: an understudied field in HSCs and AML

Besides the histone PTMs mentioned above, several other modifications have been identified in recent years. These include acylations, including propionylation, butyrylation, and crotonylation, and other modifications such as ubiquitinylation, succinylation, glycosylation, or ADP-ribosylation, which are important for modulating gene expression (reviewed in Dutta *et al*, 2016, Dai *et al*, 2020, Nitsch *et al*, 2021) (Fig 3). However, very little is known about the function of these PTMs and their regulation by metabolites in the context of HSCs and AML. One of the few examples that has been evaluated in HSCs to date is uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), produced by the hexosamine biosynthetic pathway. This

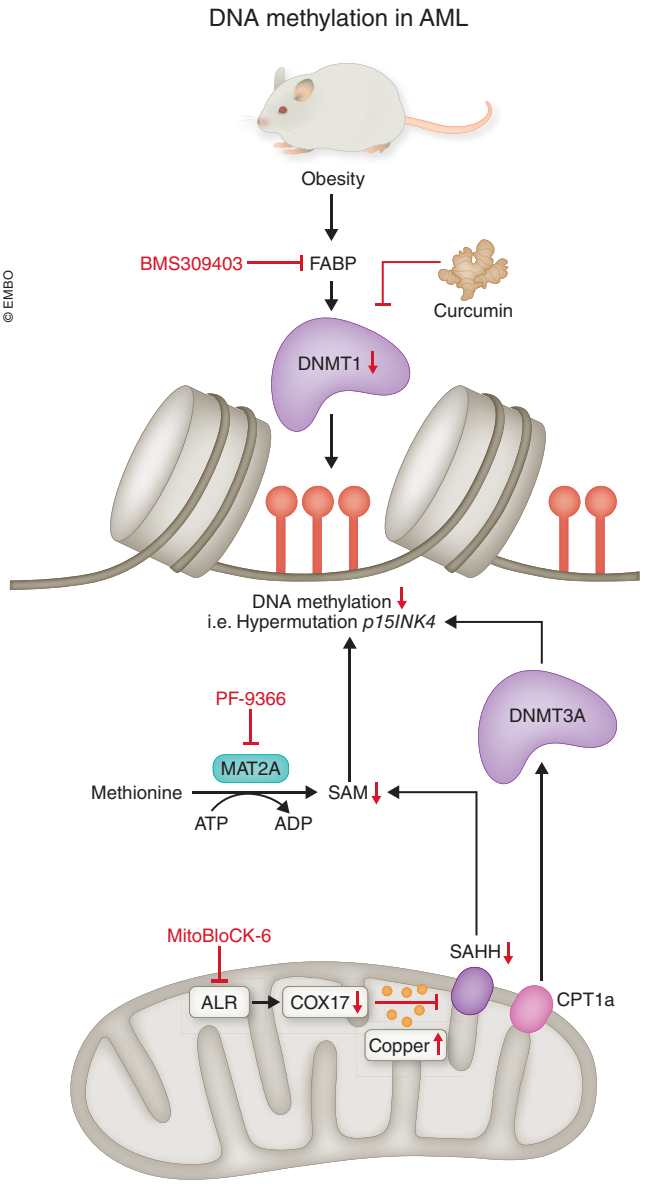


**Figure 4. DNA methylation enzymes can be triggered to alleviate and treat AML.**
FABP4 enhances the expression of DNMT1. Inhibition of FABP4 by BMS309403 downregulates DNMT1 and global DNA methylation to re-expression p15INK4. MitoBloCK6 can increase mitochondrial copper, which negatively regulates the activity of SAHH, decreasing SAM levels and global DNA methylation to prolong survival. MAT2A catalyzes the formation of SAM from methionine and ATP. MAT2A inhibition by PF-9366 depletes SAM levels to decreases growth and survival in MLL-rearranged AML.

modification is critical for the formation of glycoproteins and glycolipids and reflects the global nutritional status of a cell. Via O-linked addition of N-GlcNAc (O-GlcNAcylation), serine and threonine residues are reversibly modified by the O-GlcNAc transferase (Ogt). This PTM is removed by an enzyme called O-GlcNAcase, as soon as substrate availability decreases. In HSPCs, the deletion of Ogt leads to the disruption of H3K4me3 patterns resulting in defective Pink-dependent mitophagy, and thus to high ROS levels accompanied with increased apoptosis (Murakami *et al*, 2021). It is worth

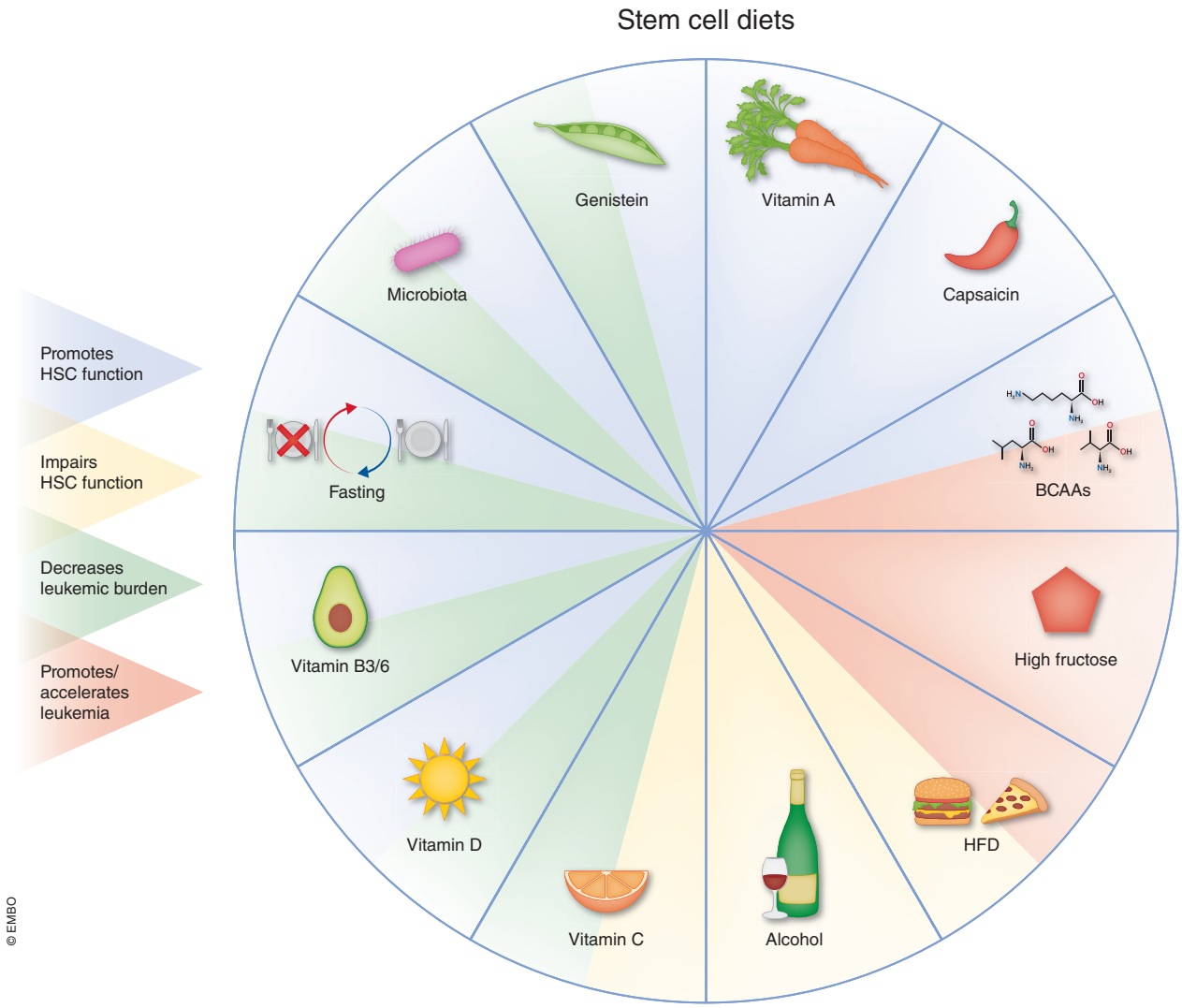


**Figure 5. Stem cell diets influence HSC and LSC functions.**
Dietary preferences can have a large impact on the epigenetic control of cellular programs in HSCs, but also contribute to leukemia development and malignant progression. In turn, nutritional interventions can be also applied to treat leukemia.

mentioning that O-GlcNAcylation has been previously reported in the context of cell cycle transitioning. O-GlcNAcylation thereby regulates mitosis-specific phosphorylation on H3 to orchestrate G2-M transition; however, its role in HSC cell cycle regulation remains to be elucidated (Sakabe *et al*, 2010; Fong *et al*, 2012).

## Metabolism tightly regulates DNA methylation

Next to histone methylation, SAM also serves as a methyl donor to DNA methyltransferase reactions. DNA methylation is generally associated with transcriptional repression and is mainly established by DNA methyltransferases (DNMTs) on CpG sites and long stretches of CpG repeats known as CpG islands. Conversely, DNA demethylation is catalyzed by TET enzymes, which oxidize 5-methyl-cytosine (5mC) to 5-hydroxymethyl-cytosine (5hmC) (Fig 2B).

### *Hematopoetic stem cells*

#### *DNA methylation*

Dnmt1 maintains DNA methylation patterns after DNA replication, and its genetic deletion causes reduced self-renewal capacity, niche retention, and defective multi-lineage hematopoiesis (Bröske *et al*, 2009; Trowbridge *et al*, 2009). Dnmt3a and Dnmt3b establish *de novo* DNA methylation and are essential to ensure proper lineage differentiation capacities. For example, loss of Dnmt3a leads to the downregulation of lineage differentiation factors, thereby generating "immortalized" HSCs to retain reconstitution potential over 12 generations of transplantation (Challen *et al*, 2011, 2014; Jeong *et al*, 2018). Dietary changes in methionine and polyamine metabolism can alter DNA methylation levels in various other cell types (Bröske *et al*, 2009). However, whether the lack of methionine in the diet can mimic the loss of Dnmt activity in HSCs remains to be answered.

*DNA demethylation*

Recently, large under-methylated regions, termed canyons, have been described in HSCs. These depend on the cooperative function of Dnmt3a and Tet1. Importantly, TET enzymatic activity is dependent on the availability of α-KG. Additionally, vitamin C (ascorbate) and iron serve as an important enzymatic cofactors (Yue & Rao, 2020). When Tet1 binds to these canyons, Dnmt3a-mediated DNA methylation is prevented. This also influences H3K27me3 levels at bivalent promoters, which further impacts gene expression (Gu *et al*, 2018). Moreover, Tet2 plays an important role in HSC maintenance. Loss of Tet2 results in drastic methylation changes at CpG sites that are contained within lineage-specific transcription factor-binding motifs causing a skew toward myelomonocytic progenitors (Izzo *et al*, 2020). Already, Tet2 haploinsufficiency rewires hematopoietic transformation by increasing HSC self-renewal and extramedullary hematopoiesis. Under ambient air (∼ 21% $O_2$), the deletion of Tet2 reduces the expression of oxidative phosphorylation genes, indicating more reliance on anaerobic glycolysis. However,

**Table 1. Metabolic and epigenetic interplay in HSCs and AML. Metabolic factors including metabolites, enzymes, and translational factors can influence the regulation of several epigenetic players. Inversely, epigenetic players influence the expression of metabolic factors to regulate HSCs and AML activity.**

**(a) Interplay: metabolism—epigenetics**

| Metabolic partner | Epigenetic partner | HSC | AML |
|---|---|---|---|
| MTCH2 | Histone acetylation | | Accelerates/maintains (Khan *et al*, 2020) |
| ACLY | Histon acetylation (H3K9) | Impairs (Umemoto *et al*, 2022) | Accelerates/maintains (Wang *et al*, 2019; Basappa *et al*, 2020) |
| AMPK | Histone acetylation | | Accelerates/maintains (Jiang *et al*, 2019b) |
| Butyrate | Acetyl-CoA for histone acetylation | | Decreases (Pulliam *et al*, 2016; Witt *et al*, 2000; Wang *et al*, 2022b) |
| COX17 + ALR | DNA methylation (SAHH:SAM ratio) | | Accelerates/maintains (Singh *et al*, 2020) |
| Curcumin | DNMT1 | | Decreases (Yu *et al*, 2013) |
| Dietary methionine deprivation | H3K27 and H3K36 methylation | | Decreases (Barve *et al*, 2019; Cunningham *et al*, 2022) |
| Fh1/Furamate metabolism | Histone trimethylation | Promotes/maintains (Guitart *et al*, 2017) | Accelerates/maintains (Guitart *et al*, 2017) |
| MAT2A | DNA methylation | | Accelerates/maintains (Secker *et al*, 2010) |
| RISP | DNA and histone methylation | Promotes/maintains (Ansó *et al*, 2017) | |

**(b) Interplay: epigenetics—metabolism**

| Epigenetic partner | Metabolic partner | HSC | AML |
|---|---|---|---|
| ANP32A | Lipid metabolism genes | | Accelerates/maintains (Wang *et al*, 2022a) |
| DNMT1 | FABP4 | | Accelerates/maintains (Yan *et al*, 2017) |
| DNMT3A/B | CPT1 | | Accelerates/maintains (Shi *et al*, 2016) |
| EZH2 | BCAT1/BCAA metabolism | | Decreases (Gu *et al*, 2019) |
| IDH1 R132H | Phosphatidylinositol, sphingolipids | | Accelerates/maintains (Stuani *et al*, 2018) |
| IDH1/2 | 2-HG | | Accelerates/maintains (Figueroa *et al*, 2010a) |
| JMJD1C | Glycolysis/respiration/fatty acid synthesis genes | | Accelerates/maintains (Lynch *et al*, 2019) |
| KAT2A | Mitochondrial and nucleic acid genes | | Accelerates/maintains (Domingues *et al*, 2020) |
| OGT | Pink-dependent mitophagy | Promotes/maintains (Murakami *et al*, 2021) | |
| SIRT1 | OXPHOS genes | Impairs (Wang *et al*, 2022c) | |
| SIRT7 | Nuclear respiratory factor 1 | Promotes/maintains (Mohrin *et al*, 2015) | |

under physioxia conditions (3% $O_2$), Tet2 deletion does not alter Hif-1α-regulated pathways (Aljoufi *et al*, 2022). Overall, DNA methylation states underlie dynamic metabolic regulatory mechanisms to maintain key stem cell functions.

### AML

#### *DNA methylation*

DNMT1 mutations are rare in AML. Nonetheless, the inhibition of DNMT1 through metabolic factors improves survival in AML mice (Pappalardi *et al*, 2021). For instance, curcumin reduces the expression of DNMT1 and leads to DNA hypomethylation of *p15*INK4, a tumor suppressor, to suppress AML growth (Yu *et al*, 2013) (Fig 4). Further, in obese mice, DNMT1 regulates FABP4 in a positive metabolic-epigenetic feedback loop. The selective inhibition of FABP4 by BMS309403 downregulates DNMT1 and global DNA methylation to re-expression p15INK4B (Yan *et al*, 2017). Mutations in DNMT3A occur in about 20% of AML patients. Typically, impaired methyltransferase activity is associated with poor disease outcome (Russler-Germain *et al*, 2014). However, hypermethylation from increased expression of *DNMT3A* can also be detrimental. For instance, high expression of *DNMT3A and DNMT3B is* accompanied by higher *CPT1A*, an enzyme responsible for mitochondrial uptake of long-chain fatty acids, whose expression is accompanied with an adverse AML outcome (Shi *et al*, 2016).

Mitochondrial sulfhydryl oxidase, ALR, and the copper chaperone, COX17, regulate AML stem cells by controlling the levels and distribution of mitochondrial copper. Copper negatively regulates the activity of S-adenosylhomocysteinine hydrolase (SAHH), a cytoplasmic and mitochondrial enzyme involved in preserving the SAM/SAH ratio. COX17 and ALR inhibition prolong survival by decreasing SAM levels and global DNA methylation, but histone methylation levels are not reduced (Singh *et al*, 2020) (Fig 4). S-adenosylmethionine synthetase isoform type 2 (MAT2A) is an enzyme that catalyzes the formation of SAM from methionine and ATP. Inhibition of MAT2A depletes SAM levels to decrease growth and enhances apoptosis in MLL-rearranged AML (Secker *et al*, 2020).

Approximately 20% of AML harbor mutations for IDH1 or IDH2. Gain-of-function in IDH1 or IDH2 leads to increased production of the metabolite, 2-hydroxyglutarate (2-HG), which promotes leukemogenesis by blocking myeloid differentiation. 2-HG is a competitive inhibitor of α-KG, an essential cofactor for certain histone and DNA demethylases. The reduction of α-KG from IDH1 or IDH2 mutation is thought to result in hypermethylated histones and at the DNA promoter (Figueroa *et al*, 2010a). Considerable metabolic reprogramming is observed in IDH1/2 mutant AML. For instance, the IDH1 R132H mutation in AML increases phosphatidylinositol, sphingolipids (ceramide, sphingosine, and sphinganine), free cholesterol, and monounsaturated fatty acids (Stuani *et al*, 2018). Additonally, IDH mutations increase TCA cycle intermediates and enhance mitochondrial oxidative metabolism (Stuani *et al*, 2021). Interestingly, the acetylation of K413 of mitochondrial IDH2 negatively regulates IDH2 activity by preventing dimerization and blocking the binding of α-KG and cofactor NADPH (Chen *et al*, 2021). Currently, patients with relapsed or refractory AML are treated with R140 and R172 IDH2 isoforms which increases 5hmC levels and consequently reactivate TET activity.

#### *DNA demethylation*

Loss of function mutations of TET2 occur in 10–20% of AML, resulting in an unfavorable disease outcome, and is mutually exclusive to IDH1/2 mutations. Almost all patients with low 5hmC exhibit TET2 mutations since these mutations can impair the production of 5hmC. BCAT1 converts BCAAs into branched-chain keto acids by transferring the BCAA amino group onto α-KG to generate glutamate (Raffel *et al*, 2017). In *de novo* AML, high BCAT1 levels are associated with poor patient outcomes in $IDH^{WT}TET2^{WT}$, but not $IDH^{mut}$ or $TET2^{mut}$ AML. In the latter, high BCAT1 levels in leukemia cells decrease intracellular α-KG levels and lead to a hypermethylated phenotype through altered TET activity that increases leukemia-initiating potential by influencing gene transcription (Raffel *et al*, 2017). This phenotype is similar to AML cells with the $IDH^{mut}$, where TET2 is inhibited by 2-HG. In contrast, the knockdown of BCAT1 in leukemia cells causes accumulation of α-KG and results in Egl-9 family hypoxia inducible factor 1 (EGLN1)-mediated HIF-1α degradation, a protein associated with poor progonosis (Deeb *et al*, 2011; Jabari *et al*, 2019). In summary, several metabolites are highly relevant to modulate DNA methylation levels in AML.

## Conclusions and future directions

It has become evident during the last few years that metabolites are not only a consequence of a cellular state but rather play an active role in regulating cell fate. As described above, metabolites can act as co-factors of epigenetic enzymes and thus regulate HSC function and AML development (see Table 1). Nevertheless, mechanistic insights on the role of numerous metabolites regulating epigenetic features in HSCs and AML are largely lacking. For instance, it remains unknown if and how stem cells can buffer smaller or larger environmental pertubations, which affect metabolism and ultimately may also alter chromatin accessibilty. Global epigenetic modifications must be stably maintained when encountering small metabolic fluctuations. Thus, transcriptional regulation is mediated by a combination of several histone modifications instead of relying on single methylation or acetylation marks (Trefely *et al*, 2020). Intriguingly, in other cell types, chromatin can act as reservoir for metabolites responding to a metabolite surplus or supplement cellular pools when needed (Martinez-Pastor *et al*, 2013; Ye & Tu, 2018). However, large metabolic fluctuations may result in the hyperactivation of gene loci that are generally maintained as heterochromatin, including satellite repeats and LINE retrotransposons, and thus, lead to cellular malfunctions. It will be of great interest to address whether chromatin can act as a metabolic reservoir in HSCs upon distinct stresses such as aging and leukemia. Another intriguing question remaining unanswered is how HSCs regulate local metabolite availability. In order to participate in chromatin modification, epigenetic substrates must be provided in sufficient concentrations within the nucleus; however, many acyl-CoAs are produced within mitochondria and cannot directly cross mitochondrial membranes. The mechanisms of acyl-CoA generation and transport to the nuclear-cytoplasmic compartment remain poorly investigated, especially in the context of HSCs. Remarkably, there is growing evidence that metabolic enzymes can be recruited to chromatin and metabolic substrates may be generated onsite for epigenetic acylation and

**BOX 2. Dietary habits control stem cell fate and leukemic burden (summarized in Fig 5)**

Nutritional preferences can significantly impact cell fate. This observation has been widely described in the context of diseases such as obesity, diabetes, and cancer. A growing body of research reports on the effects of dietary habits on key characteristics of HSCs and LSCs driven by metabolism and epigenetics. For example, several dietary interventions have been shown to play important roles in healthy hematopoiesis and can be applied to treat or improve leukemia burden.

**Vitamin A**

Vitamin A is an essential metabolite that cannot be produced from our bodies and is critical for the maintenance of HSC dormancy. For instance, vitamin A-free diets in mice caused declined HSC numbers accompanied with reduced *in vivo* blood reconstitution capacities and disrupted metabolic and epigenetic features (Cabezas-Wallscheid *et al*, 2017; Schönberger *et al*, 2022b). In human, vitamin A deficiency is linked to immunodeficiency. However, current therapies based on vitamin A supplementation exhibit a full immune recovery rate of only 20% of the cases (Kilic *et al*, 2005; Villamor & Fawzi, 2005; Ross *et al*, 2011). It is tempting to speculate that this may be attributed to dysfunctional HSCs. Nevertheless, further studies are needed to understand the role of vitamin A in the context of human.

**Vitamin B3 and B6**

Similarly, nicotinamide riboside, a form of vitamin B3, was shown to attenuate HSC aging and accelerate blood recovery after murine lethal irradiation (Vannini *et al*, 2019; Sun *et al*, 2021). By boosting $NAD^+$ production, nicotinamide riboside supplementation decreases mitochondrial stress levels, augments mitochondrial clearance, and thus supports asymmetric HSC divisions via metabolic and epigenetic control mechanisms (Vannini *et al*, 2019, Sun *et al*, 2021). Supplementation of nicotinamide riboside in the water prevents HSC aging by preserving a youthful metabolic capacity (Sun *et al*, 2021).
In MLL-AF9 mice, dietary vitamin B6 deficiency decreases disease progression without manifestation of systemic toxicity. Pyroxidal kinase (PDXK) is an enzyme that synthesizes pyridoxal phosphate (PLP) from vitamin B6, which regulates enzymes such as GOT2 that are required to produce amino acids and nucleic acids for AML proliferation. Pharmacological disruption of the vitamin B6 pathways by targeting PDXK and PLP levels decreases disease progression (Chen *et al*, 2020).

**Vitamin C**

In contrast to the aforementioned vitamins, vitamin C (ascorbate) is a negative regulator of HSC self-renewal. Depletion of dietary vitamin C in mice was shown to increase HSC frequency and function (Agathocleous *et al*, 2017). Generally, ascorbate acts as a cofactor of TET enzymes and contributes to DNA demethylation, thereby limiting self-renewal potential. However, during leukemogenesis, it is advantageous to actively block LSC self-renewal potential and restore mutated TET function by supplementing vitamin C (Moran-Crusio *et al*, 2011; Agathocleous *et al*, 2017; Cimmino *et al*, 2017; Schonberger & Cabezas-Wallscheid, 2017).

**Vitamin D**

Vitamin D has been demonstrated to be involved in myeloid differentiation and the ability to accumulate ROS (Cortes *et al*, 2016; Paubelle *et al*, 2020). Elevated *Vitamin D receptor* (*VDR*) expression in AML4-5 patients is associated with prolonged survival. The VDR promoter is frequently methylated; thereby, when VDR agonists are combined with hypomethylating agents, VDR-target gene expression is induced. This combination has been suggested to promote LSC exhaustion and decrease tumor burden (Paubelle *et al*, 2020). VDR agonists can also upregulate the expression of fructose-1,6-bisphosphatase (*FBP1*), a gluconeogenesis enzyme involved in the pathway that opposes glycolysis by transforming substrates into glucose. *FBP1* expression blocks glycolysis in the blast population, which leads them to cell death (Xu *et al*, 2022).

**Other vitamins**

Other vitamins are known to act as enzymatic cofactors, including folate (i.e important for transferring methyl-groups), cobalamin (vitamin B12; required for methionine synthase and methyl-malonyl-CoA-mutase), and phyllochinone (carboxylation of glutamyl residues). While vitamin deficiencies are known to cause numerous hematological diseases, the effects on HSCs and LSCs remain largely unknown.

**Genistein**

Genistein is a phytoestrogen found in soy and interacts with estrogen receptors $\alpha$ and $\beta$. Interestingly, genistein has been shown to provide significant radioprotection to HSPCs before irradiation (Davis *et al*, 2007) while selectively limiting G-CSF-induced DNA damage in HSPCs but not downstream progenitors when administered as a dietary supplement (Souza *et al*, 2014). A genistein-rich diet in AML has been shown to improve the survival of leukemic mice (Raynal *et al*, 2008). Mechanistically, genistein arrests cell cycle, reduces protein synthesis through inhibition of mTOR, increases ROS, mitochondrial membrane polarization, and the ratio of BAX/BCL2, thereby inducing apoptosis (Narasimhan *et al*, 2015; Hsiao *et al*, 2019; Hasan *et al*, 2020). Further, genistein enhances the anti-leukemia effect of the glycolysis inhibitor 2-deoxy-d-glucose (2-DG) by targeting the compensatory activation of the PI3K/Akt and MEK/ERK pathways (de Blas *et al*, 2016). Genistein can also synergize with chemotherapy to elicit anti-leukemia through targeting MAPK signaling (Shen *et al*, 2007). It would be interesting to address whether genistein exerts its effect through HSCs or by niche cells.

**Calorie restriction**

Although still debated, some studies suggest a positive effect of fasting on HSC function. For instance, prolonged fasting in 48 h cycles promotes HSC regeneration via inhibition of insulin growth factor 1 signaling (Cheng *et al*, 2014). Another positive effect of dietary restriction was documented in aged HSCs where regenerative capacities are alleviated but at the expenditure of lymphoid differentiation capabilities (Tang *et al*, 2016). In contrast, an independent study demonstrated that life-long calorific restriction prevents the age-related increase of the bone marrow cellularity and ablates functional benefits for aged HSCs, implying a significant role for fasting kinetics (Lazare *et al*, 2017). It would be interesting to assess if repeated fasting intervals combined with regular dieting could impact HSC reconstitution capabilities more durably.
Interestingly, periodic starvation was shown to prevent the development of B- and T-ALL by promoting rapid proliferation, apoptosis, and differentiation. However, in AML development, periodic starvation or dietary restriction is ineffective (Saito *et al*, 2015). Only in AMP-deficient AML, dietary restriction extends the survival (Saito *et al*, 2015).

**BOX 2.** (continued)

**High fat diets**

High-fat diets (HFD) show a vastly negative impact on HSCs. Most HFD models lead to obesity and exhibit reduced HSC activity by stimulating myeloid differentiation and provoking poor stress recovery responses, as demonstrated by 5-fluorouracil treatment (Singer *et al*, 2014; van den Berg *et al*, 2016; Li *et al*, 2018). A second effect is provoked by augmented adipocyte numbers in the bone marrow niche, which has been suggested to negatively regulate hematopoietic function (Ambrosi *et al*, 2017). Similarly, in the MLL-AF9 mouse model, the consumption of a HFD enhances AML development (Hermetet *et al*, 2020). Nonetheless, particular fatty acids instruct positive epigenetic and transcriptional changes in the bone marrow microenvironment. For example, fish oil-derived omega-3 polyunsaturated fatty acids increase the activity of matrix metalloproteinase in the bone marrow microenvironment, which is accompanied by an expansion of the stem cell pool (Xia *et al*, 2015).

**Fructose**

Rapidly dividing AML cells consume substantial amounts of glucose, leading to glucose insufficiency. To compensate, AML cells upregulate glucose transporter-like protein 5 (GLUT5), a fructose transporter. In general, patients with high expression of the GLUT5-encoding gene *SLC2A5* or high serum fructose concentration have poorer outcomes (Chen *et al*, 2016). In fructose-rich conditions, leukemia cells become dependent on the serine synthesis pathway (SSP). The higher SSP flux, driven by a higher ratio of $NAD^+$/NADH in fructose-rich conditions, contributes to the generation of α-KG from glutamine and facilitates TCA anaplerosis. Targeting PHGDH, the rate-limiting enzyme in the SSP reduces the AML burden in high fructose conditions (Jeong *et al*, 2021).

**Branched chain amino acids**

Dietary amino acids contribute to HSC function. For example, valine, which is an essential branched-chain amino acid (BCAA), plays an important role in the maintenance of stem cells by regulating the HSC proliferative capacity, survival, and apoptosis, as well as HSC self-renewal (Taya *et al*, 2016; Nakauchi, 2017; Wilkinson *et al*, 2017; Naidu *et al*, 2022). Dietary valine restriction leads to a dramatic reduction of HSPCs and has been suggested as a metabolic conditioning approach for HSC transplantations, thereby preventing iatrogenic complications caused by chemo-irradiative myeloablation (Taya *et al*, 2016; Nakauchi, 2017). In T-cell acute lymphoblastic leukemia (T-ALL), dietary restriction of valine decreases disease burden and increases *in vivo* survival (Taya *et al*, 2016; Wilkinson *et al*, 2018). In CML, dietary supplementation with BCAAs reverses the defects caused by the loss of BCAT1 activity (Hattori *et al*, 2017).

**Gut microbiota**

Recently, it was shown that accurate HSC function is dependent on the crosstalk between nutrient availability and the microbiome. Mechanistically, microbiota produces short chain fatty acids (SCFAs) important to bone marrow macrophage function and thus enable recycling of red blood cells to provide iron for HSC regeneration during stress conditions (Zhang *et al*, 2022a). Interestingly, HSC self-renewal and expansion can also be modulated independently of the microbiome by restricting iron availability in the diet (Zhang *et al*, 2022a). Decreased diversity in the gut microbiota has been reported in AML patients and is linked to accelerated disease progression. In particular, butyrate produced by the gut microbiota is reduced in feces of AML patients. In murine AML, the supplementation of butyrate or Faecalibacterium, *which produces* butyrate, postpones murine AML progression (Wang *et al*, 2022b). Overall, this demonstrates that targeting the gut microbiota is a therapeutic option for AML. Perhaps, the supplementation with a microbiota following antibiotic treatment in AML patients might represent one method to reduce disease burden.

**Other dietary influence**

Intriguingly, the natural component of chili peppers capsaicin has been shown to activate nociceptive neurons resulting in an HSPC egress from the bone marrow niche via CGRP—Ramp-1/ CALCRL signaling (Gao *et al*, 2021). Although not surprising, alcohol intake also infers toxic effects on stem cells. In HSCs, acetaldehyde causes impaired blood production due to DNA damage and chromosomal rearrangements in HSCs (Garaycoechea *et al*, 2018).

methylation reactions (Mews *et al*, 2017; Wang *et al*, 2017). Thus, the generation of so-called "nuclear micro-domains" may generally contribute to the accurate control of gene expression (Prouteau & Loewith, 2018). It is tempting to speculate that the formation of nuclear condensates by liquid–liquid phase separation play a major role in metabo-epigenetic control mechanisms regulating HSC function. Novel techniques such as mass spectrometry imaging, RNA aptamers, and super-resolution microscopy may help to observe this phenomenon also in rare stem cell populations. Additionally, future studies should address how metabolism can dynamically influence the high-level architecture of chromatin, i.e., nucleosome density and chromosomal looping. For instance, the switch/sucrose nonfermentable (Swi/Snf) complex coordinates nucleosome density and phasing and is critical for HSC function (Han *et al*, 2019). Interestingly, the Swi/Snf complex retains two different protein domains, YEATS and Taf14, which enable its recruitment to distinct histone acylation marks (Han *et al*, 2019). Dietary intake and certain metabolite ratios thus may influence higher chromatin structures in HSCs and AML and help to fine-tune their spatio-temporal transcriptional outputs.

Recent technological advancements (highlighted in Box 3) will accelerate the development of "metabolo-epigenetics" in hematology. Novel technologies, such as spatial and single-cell metabolomics, are currently exploited and will help to better characterize the hematopoietic heterogeneity and to understand the role of single metabolites in regulating stem cell fate. Combined spatial omics analyses (transcriptome-epigenome-metabolome on tissue sections) and the development of corresponding analyses tools will serve as a breakthrough technology to ultimately decipher the complex networks that regulate stemness. Moreover, our knowledge needs to progress beyond the (homeostatic) adult bone marrow. The metabo-epigenetic link still needs to be explored in neonatal/fetal HSCs and under proliferative stress conditions and physiological aging. In addition, we are only at the beginning of understanding the metabolic fingerprints of the bone marrow niche and the influence of niche-derived metabolites on HSC function and vice versa. There are additional layers of complexity, where extrinsic metabolites influencing HSCs goes beyond the niche.

Based on the evidence presented in this review and elsewhere, metabolites can shape the epigenomic landscape and vice versa,

**BOX 3. Deciphering the metabolome through technological advancements: from low input to single cell analyses**

Metabolome analyses, i.e., metabolomics, provide a unique platform to unravel how stemness is regulated. Due to the scarcity of HSCs and LSCs, performing metabolome analyses on these cells has been particularly challenging. In addition, the cellular metabolome is highly dynamic and undergoes rapid alterations within milliseconds. Recently, significant technological advancements have been made in the field of low-input bulk metabolomics in stem cells. DeVilbiss *et al* (2021) developed a new method involving hydrophilic liquid interaction chromatography (HILIC) and high-sensitivity orbitrap mass spectrometry (MS) that detects 160 metabolites in only 10,000 mouse HSCs. Using an alternative HILIC-MS approach and comparable cell numbers, Schönberger *et al* provided insights into the metabolic differences between mouse HSCs and their immediate downstream multipotent progenitors (Schönberger *et al*, 2022a,b, 2023). With these established methodologies, it would be now interesting to address the metabolic fingerprints of human HSCs and LSCs. Further, establishing a method that requires even less material would be beneficial to minimize the time of isolating cells and reduce the number of animals needed for each experiment.

Next to bulk metabolomics approaches, the field of single-cell metabolomics is rapidly evolving (Petras *et al*, 2017; Alexandrov, 2020). Various mass spectrometric methods have been developed and can be distinguished based on sampling strategies and ionization techniques. Thereby, metabolites can be sampled and ionized from a solid surface using matrix-assisted laser desorption ionization (MALDI), secondary ion mass spectrometry (SIMS), and laser ablation electrospray ionization (LAESI) or may derive from the cell in liquid phase and include electrospray ionization (ESI) with or without a prior separation step by capillary electrophoresis (CE) or liquid chromatography (LC). While direct-infusion mass spectrometry enables a straight injection of sample mixtures into the ionization source of the mass spectrometer, separation-based mass spectrometry may improve sensitivity and remove spectral interferences in many cases (Clish, 2015; Saoi & Britz-McKibbin, 2021). Alternatively, mass cytometry (also called CyTOF), a method based on single-cell labeling using antibodies joint to transition elements and detected by inductively coupled plasma mass spectrometry, has been used to identify metabolic adaptations (Hartmann *et al*, 2021; Levine *et al*, 2021). Yet, single-cell metabolomics tools have not been applied in neither HSCs nor in LSCs. This might be due to the small size of HSCs and LSCs making the use of single-cell tools even more challenging. An enhanced sensitivity of single-cell metabolomics tools would unravel the heterogeneity and relationships between metabolism and cell function.

Mass spectrometry imaging provides data on the quality and quantity of metabolites combined with spatial information (Petras *et al*, 2017; Buchberger *et al*, 2018). MALDI-imaging mass spectrometry is one of the most popular techniques established by Alexandrov and colleagues (Rappez *et al*, 2021). Space M was developed to precisely match mass spectrometry and light microscopy. GCIB–SIMS is an alternative method that does not require special sample preparation and allows a second mass spectrometry detection round since this technique detects metabolites without damaging the samples (Tian *et al*, 2021). NanoSIMS is a method that allows the interpretation of subcellular metabolome data (Thomen *et al*, 2020), which is invaluable data since some metabolites are exclusively localized in specific organelles, and their detection may be restricted to certain tissue parts or organs and thus have distinct implications for the cellular function. However, 2-dimensional or even 3-dimensional spatial metabolomics imaging approaches exhibit a number of technical challenges and require extensive computational power for data analysis (Alexandrov, 2020). Technological progress but also advances in machine learning, deep learning, and artificial intelligence will be critical to establishing spatial metabolomics, combined with other omics techniques to unravel the metabolic heterogeneity of HSCs, LSCs, and their niche.

Overall, these metabolomics techniques hold great potential to decipher the spatial distribution and functional role of metabolites in HSCs and LSCs and to improve our understanding of homeostatic and pathological processes in the hematopoietic context. Furthermore, they could greatly improve our ability to expand HSCs *ex vivo* and advance HSC transplantation efficacies.

thereby contributing to healthy and diseased hematopoiesis (see Table 1). In AML, dietary modulation is becoming an increasingly popular therapeutic approach and may serve in future studies to manipulate epigenetic cellular features and improve patient survival (see Box 2). Additonally, pharmacological inhibition of epigenetic modulators and metabolic proteins has been proposed to treat AML and continues to show promosing therapeutic responses. Thus, targeting the metabo-epigenetic vulnerabilities is a promising strategy for personalized cancer therapy.

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## Author contributions

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## Disclosure and competing interests statement

The authors declare that they have no conflict of interest.

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