

Review

Metabolism of Young and Aged Hematopoietic and Acute Myeloid Leukemia Stem Cells: Insights for Rejuvenation and Therapy

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ABSTRACT: Hematopoietic stem cells (HSCs) reside in the adult bone marrow and sustain the lifelong production of blood and immune cells. The processes of HSC quiescence, activation, and aging are complex and are orchestrated by a combination of intrinsic and extrinsic stimuli. Similarly, leukemic stem cells (LSCs) are responsible for the initiation of leukemia and drug resistance. Metabolic adaptations are critical for these processes, and research in this area is rapidly evolving. In this review, the metabolic programs, including glycolysis, mitochondrial metabolism, and amino acid and lipid metabolism, of young HSCs, aged HSCs, leukemia blasts, and LSCs are comparatively presented, with a greater focus on aged HSCs and LSCs, as aging and leukemia represent substantial health challenges. The clinical implications of metabolic vulnerabilities, either for rejuvenating aged HSCs or selectively killing LSCs, are also discussed.

Keywords: hematopoietic stem cells (HSCs), aging, leukemia stem cells (LSCs), metabolism

1. Introduction

Hematopoietic stem cells (HSCs) are rare cells that reside in the hypoxic bone marrow niche of adult vertebrates and are responsible for sustaining the lifelong production of blood and immune cells [1, 2]. While most HSCs remain quiescent in their specialized niche, some enter the cell cycle in response to physiological demands. They are highly regulated by intrinsic and extrinsic factors that maintain quiescence, self-renewal, and multilineage differentiation. Factors that influence HSC function include transcriptional programs, signaling pathways, signals from specialized BM niches, epigenetics, and metabolic cues [1–3]. The metabolic regulation of HSCs is a complex process that involves energy production, redox balance, and protein turnover and orchestrates the balance between HSC self-renewal and differentiation, contributing to their maintenance and the preservation of stemness [3].

Young HSCs in their hypoxic niches in the bone marrow are mostly quiescent and preferentially rely on anaerobic glycolysis for energy production instead of mitochondrial oxidative phosphorylation (OXPHOS), thereby reducing the production of reactive oxygen species (ROS) and preserving cellular integrity by minimizing oxidative damage [4, 5]. They also possess low mitochondrial mass, regulated membrane potential, and effective mitophagy. NAD⁺-dependent sirtuins enhance mitochondrial integrity and stress resistance, ensuring a stable reserve of HSCs capable of responding to hematopoietic demands while accumulating minimal damage [6, 7]. To meet physiological needs, a small proportion of young quiescent HSCs are activated and enter the cell cycle to proliferate and differentiate, producing all blood cell lineages. Activated young HSCs preferentially use OXPHOS for energy production. This results in increased ROS levels and the accumulation of dysfunctional mitochondria, thereby affecting HSC stemness [8]. Thus, young quiescent HSCs, which

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comprise the majority of HSCs in the body, use metabolic programs that are different from those used by activated young HSCs, emphasizing the importance of choosing an immunophenotypically and metabolically appropriate population when studying HSC metabolism.

The metabolic profile of HSCs changes with age. Aged HSCs are characterized by high mitochondrial activity, decreased NAD⁺-sirtuin activity, decreased glycolytic flux, and impaired autophagy and mitophagy,

which lead to redox imbalance, accumulation of ROS, DNA damage, and dysfunctional mitochondria (Fig. 1) [6, 7, 9]. Functionally, aged HSCs demonstrate reduced regenerative potential, a skew toward myeloid differentiation, and heightened susceptibility to clonal hematopoiesis driven by mutations in genes, such as *DNMT3A* and *TET2*. These metabolic and functional changes compromise hematopoietic fitness and increase the risk of malignant transformation [10–12].

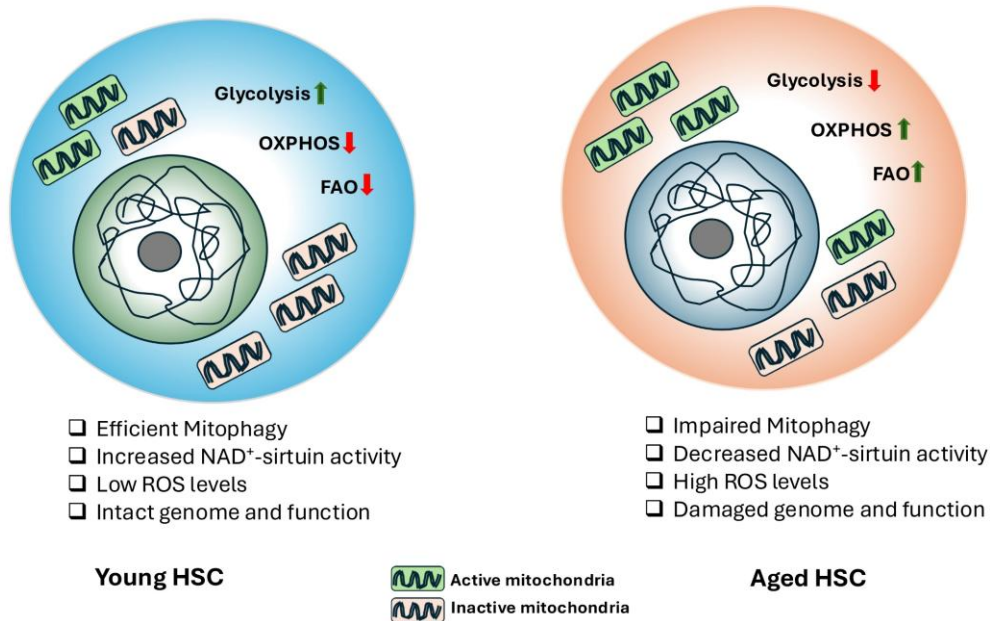


Figure 1. The metabolic changes in young and aged HSCs.

In aged mice, HSCs have been found to be transcriptionally, immunophenotypically, and metabolically heterogeneous [13]. While most aged HSCs show altered metabolic programs and functional decline, around one-third of them exhibit a low metabolic profile with activated autophagy and preserved functionality comparable to that of young HSCs [6]. This was further elucidated when a subset of aged HSCs was found in proximity to sinusoidal niches and showed enhanced regenerative capacity compared with those found farther away from the sinusoids [14]. Additionally, high expression of CD61 in aged murine HSCs identifies a quiescent subpopulation with a low metabolic state and enhanced self-renewal and functionality after transplantation compared with observations in young HSCs [15]. Furthermore, low expression of CD150 (CD150^{Low}) in aged HSCs marks a subpopulation that shows better functionality after transplantation, with distinct transcriptional and epigenetic profiles compared with those of aged HSCs with high CD150 expression (CD150^{High}) [16]. When functionally compared with

young HSCs, CD150^{Low} aged HSCs showed approximately 73% repopulation capacity relative to young HSCs, despite having different molecular signatures, whereas CD150^{High} aged HSCs retained approximately 6% functionality [16]. Interestingly, CD150 is a SLAM-family marker that is commonly used to isolate murine young long-term HSCs along with lineage⁻ Sca1⁺ c-kit⁺ flt3⁻ CD34⁻, in which CD150^{High} marks myeloid-biased HSCs, whereas CD150^{Low} identifies lymphoid-biased HSCs and balanced HSCs [11]. CD150^{High} myeloid-biased HSCs have been shown to expand with age and exhibit altered functionality [11], suggesting that the relatively few CD150^{Low} HSCs are responsible for maintaining hematopoiesis in older adults, whereas the observed phenotypic changes in aged hematopoiesis are driven by the predominant CD150^{High} HSC population. A recent study showed that clusterin (Clu) expression defines heterogeneity in aged murine HSCs. Clu^{High} aged HSCs have been found to be myeloid- and platelet-biased, predominate in the HSC pool, and be responsible for age-related hematopoietic changes,

whereas Clu^{Low} aged HSCs retain balanced differentiation potential, exhibit a youthful transcriptional program, and demonstrate superior functionality after transplantation compared with that of Clu^{High} HSCs; however, their functionality remains lower than that of their young counterparts [17]. Another report found that GPR183 is exclusively expressed in a subset of aged murine HSCs with high self-renewal capacity and high mitochondrial mass compared with aged HSCs lacking GPR183 [18]. Thus, careful consideration of this heterogeneity, together with further spatial investigation of aged HSCs within the bone marrow niche accompanied by functional, molecular, and immunophenotypic analyses, is needed to better understand the aging hematopoietic system, with the long-term goal of developing clinically translatable rejuvenation strategies.

Leukemia stem cells (LSCs) are a rare population that is primarily quiescent and can self-renew to continuously propagate leukemia and resist chemotherapy [19]. In contrast to young HSCs, LSCs are highly dependent on OXPHOS for energy production, which is fueled by amino acid metabolism in *de novo* acute myeloid leukemia (AML) and by fatty acid oxidation (FAO) in patients with relapsed AML [20].

This review addresses these complexities by comparing the metabolic properties, including glycolysis, mitochondrial metabolism, and amino acid and lipid metabolism, of young HSCs, aged HSCs, AML blasts, and AML LSCs (hereafter, the terms LSCs and leukemia blasts refer to AML), with a focus on aged HSCs and LSCs, as aging and leukemia pose substantial health burdens. It also highlights the clinical implications of these metabolic vulnerabilities for rejuvenating aged HSCs and selectively eliminating LSCs.

2. Metabolic traits of young HSCs, aged HSCs, and LSCs

Metabolic pathways in HSCs and leukemia cells are flexible and adapt to different cellular states, including quiescence, proliferation, differentiation, aging, and leukemogenesis. In their hypoxic bone marrow niche, HSCs depend on low metabolic activity to maintain stemness, genomic stability, and long-term regenerative capacity [9, 21]. With age, these programs become altered, resulting in functional decline despite increased cell numbers and a greater propensity to develop clonal hematopoiesis [10, 11].

To frame the metabolic changes discussed throughout this section and draw on the tripartite organization of the hallmarks of the aging framework [22], I propose that metabolic alterations in aged HSCs can be organized into a causal hierarchy comprising primary drivers, adaptive responses, and downstream consequences. The likely

candidate primary drivers include increased reliance on OXPHOS for energy production, NAD⁺ depletion, reduced sirtuin activity, and failure of mitochondrial quality-control mechanisms (mitophagy, biogenesis, fission, fusion, and transfer) [23–26]. NAD⁺ depletion is mediated by the NADase CD38 in a SIRT3-dependent manner, and ablation of CD38 in aged mice has been shown to preserve NAD⁺ levels, mitochondrial respiratory rates, and metabolic function [25, 27]. These defects may induce compensatory mechanisms, such as activation of the pentose phosphate pathway (PPP) and the mitochondrial unfolded protein response. Although these adaptive responses initially protect against metabolic stress, sustained activation may become maladaptive and contribute to downstream consequences, including mitochondrial ROS accumulation, DNA damage, myeloid-biased hematopoiesis, and functional impairment. Support for this emerging model comes from *in vivo* studies in mouse models showing that nicotinamide riboside (NR) restores aged HSC functionality by increasing NAD⁺ levels, reducing mitochondrial stress and mass, enhancing mitochondrial clearance, and shifting the aged transcriptional signature toward a youthful state, suggesting that NAD⁺ depletion may be a major driver of metabolic dysfunction in aged HSCs [28, 29].

Although LSCs share fundamental properties with HSCs, such as self-renewal and quiescence, they utilize distinct metabolic pathways to drive leukemia progression and resist chemotherapy [30, 31]. Identifying both the similarities and differences between HSCs and LSCs provides valuable insights into vulnerabilities that may be targeted for therapy or rejuvenation. A comparison of these features is presented in Table 1.

2.1 Cytosolic glycolysis and mitochondrial OXPHOS

Young quiescent HSCs in their hypoxic niche in the bone marrow preferentially rely on glycolysis for energy production and maintenance of a low metabolic state. Upon activation, HSCs become metabolically active and switch to another energy source: mitochondrial OXPHOS. As an indispensable adaptive response, activated HSCs activate the PPP to reduce ROS production and thereby preserve genomic integrity and functionality [5, 32, 33]. Glycolysis in HSCs is regulated by hypoxia-inducible factor-1 α , which promotes glycolysis by activating glycolytic metabolism and limiting the influx of pyruvate into mitochondria through activation of pyruvate dehydrogenase (PDH) kinase via Cited2 [32, 34, 35]. As hypoxia-inducible factor-1 α activity decreases in aged HSCs, expression of glycolytic enzymes declines and glycolytic flux is reduced, shifting aged HSCs toward greater reliance on OXPHOS for

energy production [32]. Despite its greater efficiency in energy production, OXPHOS increases ROS generation, which promotes DNA damage and contributes to the functional decline of aged HSCs [6, 26, 36]. However, as an adaptive response, aged HSCs activate the PPP to support survival and function and ameliorate oxidative

stress by inducing expression of succinate dehydrogenase assembly factor 1 [37]. Furthermore, glycolysis in aged HSCs is suppressed by chronic inflammation in the bone marrow niche through activation of suppressor of cytokine signaling 3 (Socs3), which impairs the AKT-FoxO cascade [38].

Table 1. Comparative overview of metabolic alterations in young hematopoietic stem cells (HSCs), aged HSCs, and leukemic stem cells (LSCs).

Metabolic Pathway	Young HSCs	Aged HSCs	LSCs and leukemia blasts
Glycolysis	Quiescent HSCs preferentially depend on glycolysis for energy production, whereas activated HSCs often rely on OXPHOS.	Reduced expression of glycolytic enzymes is often associated with decreased glycolysis and a shift toward OXPHOS. Approximately one-third of HSCs in aged mice resemble young HSCs.	LSCs show reduced dependence on glycolysis for energy production, whereas leukemia blasts preferentially utilize glycolysis.
Mitochondrial OXPHOS and ROS levels	Quiescent HSCs often show reduced OXPHOS and low ROS levels, whereas activated HSCs often switch to OXPHOS with high ROS production	Often exhibit increased OXPHOS activity, elevated ROS levels, and increased DNA damage. Approximately one-third of HSCs in aged mice resemble young HSCs.	LSCs often rely on OXPHOS for energy production and survival while maintaining low ROS levels. Leukemia blasts often show reduced dependence on OXPHOS.
Fatty acid oxidation (FAO)	Balanced FAO supports quiescence. FAO inhibition causes only modest impairment of HSC function.	Often exhibit increased FAO, lipid accumulation, mitochondrial overload, and functional exhaustion.	Dependence on FAO through CPT1A and FABP4 may support survival and therapy resistance. Inhibition of FAO can re-sensitize LSCs to venetoclax and azacitidine.
Amino acid metabolism	Quiescent HSCs typically exhibit low amino acid metabolism and low protein synthesis, whereas activated HSCs often exhibit increased protein synthesis.	Altered protein synthesis. Aged HSCs often activate the heat shock response to maintain proteostasis and alleviate functional decline.	LSCs often exhibit enhanced amino acid metabolism, including metabolism of cysteine, glutamine, valine, leucine, and isoleucine, to support OXPHOS, survival, and chemoresistance.
Mitochondrial activity and autophagy	Quiescent HSCs generally have suppressed mitochondrial activity, low mitochondrial mass, and tightly regulated mitochondrial membrane potential. Basal autophagy preserves quiescence and mitochondrial quality through efficient mitophagy.	Often exhibit increased mitochondrial biogenesis and mitochondrial mass, accumulation of dysfunctional mitochondria, increased mitochondrial protein-folding stress, reduced mitochondrial membrane potential, and decreased autophagy.	LSCs often exhibit high autophagic activity. Leukemia blasts often exhibit increased mitochondrial mass and biogenesis together with reduced respiratory chain complex activity.
NAD⁺/Sirtuins	Optimal NAD ⁺ levels and sirtuin activity support HSC proliferation.	Reduced NAD ⁺ levels and sirtuin activity. Supplementation with NAD ⁺ precursors such as nicotinamide riboside can improve HSC function.	LSCs often maintain high NAD ⁺ levels and sirtuin activity through NAMPT and NMNAT1, which support survival. Inhibition of NAMPT or NMNAT1 can induce apoptosis in LSCs and acute myeloid leukemia cells.

Given the heterogeneity of aged HSCs, most exhibit altered metabolic programs and functional decline relative to young HSCs, whereas a small subset exhibits a low metabolic profile with activated autophagy and preserved functionality comparable to that of young HSCs [6]. Consistent with this observation, Clu^{Low} aged HSCs exhibit balanced differentiation potential and greater regenerative capacity after transplantation than that of

Clu^{High} aged HSCs [17]. Deletion of Clu in aged HSCs reduces OXPHOS, ROS levels, and DNA damage through the Mfn2-OXPHOS-p38-Cebpb axis [39]. These findings indicate that aged HSCs are heterogeneous and that the metabolic profiles of distinct aged HSC subsets require further elucidation [40]. Efforts are ongoing to understand how HSCs utilize glycolysis during steady-state hematopoiesis and under stress. Recently, using a

tracking system in murine HSCs, PFKFB3 was found to accelerate glycolysis in proliferating HSCs under OXPHOS inhibition in an AMPK-dependent manner and contribute to glycolytic ATP production [41]. This finding highlights the plasticity of HSC metabolism and demonstrates how HSCs can exploit different metabolic programs to support survival and function, a capacity that may also be utilized by aged HSCs.

Chemoresistant LSCs and leukemia blasts exhibit distinct metabolic patterns, which account for their different kinetics and roles in leukemogenesis [42]. LSCs maintain a low metabolic state with reduced ROS levels and preferentially depend on OXPHOS for energy production [43]. They can also switch to alternative metabolic pathways, such as lipid and amino acid metabolism, to resist chemotherapy and preserve quiescence [42, 44]. LSCs with low ROS levels (ROS^{low} LSCs) upregulate BCL-2. Pharmacological BCL-2 inhibitors (ABT-737 and ABT-263) have been shown to reduce OXPHOS and selectively target ROS^{low} LSCs in primary AML populations and xenograft mouse models while sparing normal CD34⁺ bone marrow cells [43]. Interestingly, following pharmacological inhibition, ROS^{low} LSCs could not switch to glycolysis, unlike HSCs, which retain the flexibility to adapt to alternative metabolic programs and survive [20, 43]. The dependence of LSCs on OXPHOS can therefore be further exploited therapeutically. By contrast, leukemia blasts utilize glycolysis to create a hypoxic bone marrow environment that supports their proliferation, thereby promoting leukemia progression and chemoresistance [42, 45]. They are metabolically more flexible than LSCs and can adapt to alternative metabolic programs under stress to sustain proliferation [20]. Interestingly, LSCs exhibit distinct metabolic phenotypes in patients with AML. Following treatment with venetoclax and azacitidine (ven/aza), which induce amino acid depletion, LSCs from patients with de novo AML showed reduced OXPHOS activity and increased cell death, whereas LSCs from patients with relapsed AML compensated for amino acid depletion by increasing fatty acid metabolism, thereby maintaining OXPHOS activity [20].

2.2 Lipid metabolism

Lipids play various roles in cells, including regulation of energy production, cell membrane composition, and signaling pathways. Lipid metabolism plays distinct roles in young HSCs, aged HSCs, and LSCs. Although its activity is minimal in young HSCs, it is elevated in aged HSCs and LSCs. In the bulk population of young HSCs and multipotent progenitors (HSPCs), loss of FAO resulting from deletion of carnitine palmitoyltransferase 1A (CPT1A), a key enzyme in FAO, does not alter HSPC

function in young mice during steady state or after transplantation [46]. Young HSPCs exhibit reduced PDH phosphorylation and retain the ability to oxidize other substrates, including glutamine, which may compensate for the loss of FAO [46]. By contrast, another study found that deletion of CPT1A in young long-term HSCs resulted in reduced HSC numbers during steady state and after primary and secondary transplantation in mice, accompanied by modest functional impairment associated with suppression of fatty acid metabolism, adipogenesis, and cholesterol metabolism pathways [47]. This discrepancy between the findings of Li et al. and Merchant et al. may be attributable to differences in the cell populations investigated, as Merchant et al. studied HSPCs, a highly heterogeneous population of stem and progenitor cells, whereas Li et al. studied long-term HSCs, a relatively homogeneous population with long-term repopulating capacity. However, deletion of CPT1A or hydroxyacyl-CoA dehydrogenase in 12-month-old middle-aged HSCs disrupted HSC numbers and function after transplantation [46]. This finding suggests that the metabolic plasticity of HSCs declines with age and that the compensatory mechanisms used by young HSCs to overcome FAO deficiency are impaired in aged HSPCs, despite the similar capacity of young and aged HSPCs for long-chain FAO [46]. However, unlike young HSCs, aged HSPCs exhibit increased levels of phosphorylated PDH, which is thought to inhibit PDH-mediated generation of acetyl-CoA from pyruvate, thereby limiting adaptation to FAO loss [46].

Similar to physiologically stressed aged HSCs, HSCs subjected to acute infection exhibit increased free fatty acid uptake and greater reliance on OXPHOS and β -oxidation. This process is mediated by upregulation of CD36, which increases CPT1A expression [48]. Interestingly, loss of CD36 in young mice has a limited impact on normal hematopoiesis, suggesting a potentially important role for CD36 in aged HSCs [49]. Therefore, further investigation of the precise role of CD36 in aged HSCs is warranted.

Choline has also been found to be critical for HSC function in vitro. Its levels are high in young HSCs from both mice and humans but decrease during aging and differentiation, resulting in altered lipid composition in aged HSPCs [50]. Treatment of aged human HSPCs with choline restores function in vitro and increases self-renewal capacity, possibly through the upregulation of membrane lipids, phosphatidylcholine, and sphingomyelin [50]. These findings suggest that choline supplementation may serve as a rejuvenating intervention for aged HSCs.

Alterations in steroid metabolism have also been reported in the context of HSC aging. Metabolic modeling of multiple reactions in aged HSCs identified cholesterol

sulfate (CS) hydrolysis as one of the most significantly altered steps [51]. Treatment of aged mice with CS rejuvenated aged HSCs, reduced DNA damage, and enhanced their proliferative capacity. Mechanistically, CS was identified as a ligand for the nuclear receptor RORA, which is downregulated in aged HSCs; activation of the CS–RORA axis was shown to contribute to HSC function *in vivo* [51]. Collectively, these findings establish the CS–RORA axis as a promising therapeutic target for HSC rejuvenation.

Lipid metabolism is also critical for the function and survival of LSCs and leukemia blasts [52]. Fatty acid breakdown through FAO serves as an important source of energy for OXPHOS in LSCs, thereby supporting their survival [53]. Therefore, FAO represents an attractive therapeutic target for eliminating LSCs. Effective ven/aza treatment in patients with AML inhibits amino acid metabolism [20]; however, ven/aza-resistant LSCs upregulate FAO as a compensatory response to amino acid depletion, and inhibition of FAO re-sensitizes these cells to ven/aza [54]. Choline levels have also been found to be decreased in patients with AML, suggesting a potential role for choline metabolism and lipid metabolism in AML [50]. Although the focus of this section is lipid metabolism in LSCs, comprehensive reviews addressing the roles of lipids in mitochondria and cell membranes, as well as their contribution to AML, have been published elsewhere [52].

2.3 Amino acid metabolism and proteostasis

Quiescent young HSCs exhibit low amino acid metabolism, consistent with the overall low metabolic activity required for their maintenance. To preserve stemness, HSCs often exhibit restricted protein synthesis, low intracellular amino acid levels, and increased amino acid catabolism regulated by the GCN2–eIF2 α axis [55, 56]. In addition, they maintain high proteome quality, containing fewer misfolded and unfolded proteins than those of myeloid progenitors [57]. Conversely, upon activation, young HSCs predominantly exhibit increased protein synthesis and intracellular amino acid levels, along with reduced amino acid catabolism, leading to proteotoxic stress that impairs HSC function [56, 58]. Similar to HSC activation, HSC aging is also a form of cellular stress. During aging, HSCs expand and exhibit altered protein synthesis [59]. However, as an adaptive response to maintain protein homeostasis (proteostasis) and mitigate age-associated functional decline, aged HSCs activate the heat shock response through heat shock factor 1 (Hsf1), which is dispensable in young adult HSCs [60]. Activation of Hsf1 *in vitro* using small molecules partially suppressed protein synthesis, restored proteostasis, and sustained *ex vivo* HSC maintenance

[60]. Mechanistically, Hsf1 has been identified as an upstream regulator of melanoma differentiation-associated protein 5 (Mda5) in aged HSCs [61]. Genetic ablation of Mda5 in aged murine HSCs improved proteostasis, as evidenced by reduced accumulation of misfolded and unfolded proteins, along with a more youthful metabolic profile and enhanced repopulation capacity [61]. These findings indicate that Hsf1 is required to preserve proteostasis and fitness during hematopoietic aging. Aggresomes, which are responsible for sequestering misfolded proteins for degradation, are largely absent in aged murine HSCs, which instead exhibit increased proteasome activity to maintain proteostasis [62]. By contrast, young murine HSCs predominantly traffic misfolded proteins to aggresomes in a Bag3-dependent manner *in vivo* [62]. These observations suggest that young and aged HSCs employ distinct mechanisms to maintain proteostasis, although protein aggregation during aging may contribute to the functional decline of aged HSCs. Regulation of proteostasis and amino acid metabolism requires further investigation to determine whether these processes are key determinants of HSC aging and hematopoietic aging.

LSCs exhibit enhanced amino acid metabolism to fuel OXPHOS and support survival and chemoresistance [20, 63]. Cysteine is essential for LSC metabolism because it contributes to glutathione synthesis and electron transport chain complex activity, thereby supporting OXPHOS and LSC survival [64]. Branched-chain amino acids (BCAAs), including valine, leucine, and isoleucine, have also been found to play important roles in LSC metabolism and leukemogenesis. BCAA transaminase 1 (BCAT1), a cytosolic enzyme that catalyzes BCAA catabolism by transferring α -amino groups from BCAAs to α -ketoglutarate to generate glutamate, is overexpressed in LSCs [65]. Inhibition of BCAT1 in LSCs results in accumulation of α -ketoglutarate and reduced cell survival [65]. BCAT1 and BCAT2 are also upregulated by the m6A methyltransferase METTL16, which promotes LSC survival through reprogramming of BCAA metabolism [66]. Glutamine also contributes to the tricarboxylic acid (TCA) cycle, glutathione synthesis, and redox homeostasis in leukemia cells [67]. Pharmacological inhibition of glutaminase with CB-839 in AML cell lines, primary AML cells, and AML mouse models resulted in increased ROS production and cell death [67].

2.4 Mitochondrial metabolism

Mitochondrial activity is highly suppressed in young quiescent HSCs. Reduced mitochondrial mass, tightly regulated mitochondrial membrane potential (MMP), and active mitophagy minimize ROS generation and maintain quiescence [26, 68]. By contrast, aged HSCs accumulate

dysfunctional mitochondria characterized by increased mitochondrial mass, greater reliance on OXPHOS, increased mitochondrial protein-folding stress, impaired mitochondrial quality control (mitophagy/autophagy), and altered metabolism accompanied by elevated ROS levels that promote oxidative stress [36, 69].

NAD⁺ is central to mitochondrial metabolism because it serves both as a coenzyme in metabolic reactions and as a regulator of mitochondrial stress [70]. NAD⁺ maintains proliferation of young HSCs through CD38-dependent NAD⁺ metabolism [25]. With age, NAD⁺ levels decline, resulting in reduced sirtuin activity, increased CD38 expression, elevated oxidative stress, and decreased HSC self-renewal, ultimately leading to functional defects and genomic instability in aged HSCs [25, 26, 29]. Supplementation with NAD⁺ precursors, such as NR, has been shown to mitigate age-associated hematopoietic phenotypes and improve HSC function in vivo [29].

Phenotypically defined aged HSCs exhibit heterogeneous mitochondrial activity. Approximately one-third of aged HSCs exhibit high levels of autophagy and functionality comparable to that of young HSCs [6]. MMP has also been found to differ between young and aged HSCs, with important functional consequences. Most aged murine HSCs exhibit lower MMP than that of young HSCs; however, 10%–15% of aged HSCs exhibit high MMP and are transcriptionally similar to young HSCs [71]. The presence of this small subset within the aged HSC population suggests that it may help maintain hematopoiesis in an impaired aging environment and supports efforts to exploit these metabolic features to reverse age-associated hematopoietic dysfunction [6, 71]. Mitochondrial dysfunction has also been observed in leukemia. AML blasts exhibit increased mitochondrial mass and biogenesis accompanied by reduced respiratory chain complex activity [72]. LSCs retain robust NAD⁺ biosynthetic activity to support their survival. Nicotinamide phosphoribosyltransferase (NAMPT) maintains the NAD⁺ salvage pathway, ensuring sufficient NAD⁺ levels to support sirtuins and poly (ADP-ribose) polymerases, which are NAD⁺-dependent enzymes with diverse biological functions, including metabolic regulation [73]. Selective depletion of LSCs, but not normal hematopoietic stem and progenitor cells, was achieved through pharmacological inhibition of NAMPT using KPT-9274. Treatment with KPT-9274 reduced NAD⁺ levels, impaired mitochondrial respiration and lipid homeostasis, and ultimately induced apoptosis in LSCs and AML cells in vivo [73, 74].

2.5 Autophagy and lysosomes

HSC maintenance is highly dependent on lysosome-mediated autophagy (cellular recycling) and mitophagy

(removal of damaged mitochondria), which degrade intracellular components and damaged mitochondria and recycle their constituents for macromolecule synthesis and energy production [23, 75]. Basal autophagy maintains metabolic dormancy and long-term stemness in young HSCs [75, 76]. Deletion of the autophagy-related proteins Atg7 and Atg5 results in impaired HSC survival and function, accompanied by mitochondrial accumulation, increased ROS levels, and DNA damage [77, 78]. Aged HSCs exhibit reduced autophagic flux and mitochondrial accumulation, which contribute to myeloid skewing and functional decline [6]. However, approximately one-third of aged HSCs exhibit increased autophagy and functionality comparable to that of young HSCs, suggesting a critical role in maintaining hematopoiesis during aging [6]. Experimental interventions, such as caloric restriction, rapamycin treatment, and induction of autophagy using the mitochondrial modulator urolithin A, can restore autophagy and partially rejuvenate aged HSCs [38, 79, 80]. Although suppression of lysosomal activity preserves HSC stemness, lysosomal integrity is impaired in aged HSCs [81, 82]. Aged HSCs exhibit reduced, hyperactivated, and dysfunctional lysosomes, and inhibition of lysosomal hyperactivity restores lysosomal integrity and improves aged HSC function [81].

Autophagy is also induced in leukemia and LSCs, where it functions as a survival mechanism and contributes to chemoresistance [83, 84]. Deletion of Atg7 in leukemia-initiating cells resulted in mitochondrial accumulation, increased ROS levels, and induction of cell death [85]. Similarly, inhibition of autophagy in LSCs from AML with FLT3-ITD mutations resulted in increased ROS levels and mitochondrial accumulation [86]. Autophagy inhibitors effectively target LSCs, reducing both LSC numbers and leukemia burden [87].

3. Balancing rejuvenation, the risk of clonal expansion, and AML targeting

HSCs and LSCs exhibit distinct metabolic profiles. Aging impairs HSC function, whereas LSCs exploit metabolic alterations to support malignant growth. This highlights metabolism as a critical regulator that can shift hematopoietic balance from regeneration to leukemogenesis. Consequently, metabolic pathways have emerged as important therapeutic targets. Strategies for restoring HSC function include NAD⁺ enhancers that stimulate sirtuin activity, AMPK agonists that enhance energy production, mTOR inhibitors that reinvigorate autophagy, and antioxidants that mitigate oxidative stress [88, 89]. By contrast, LSC-targeted therapies aim to disrupt metabolic dependencies. Venetoclax disrupts

OXPHOS, FAO can be inhibited by targeting CPT1A or FABP4, and amino acid metabolism can be blocked using glutaminase inhibitors, such as CB-839 [90–92]. Additional targets include pathways regulated by oncometabolites, such as mutant IDH enzymes [93]. A major challenge is how to rejuvenate aged HSCs without promoting leukemogenesis and, conversely, eliminate LSCs without impairing normal hematopoiesis.

Although HSC rejuvenation strategies may restore HSC function, they may also confer a competitive advantage on preexisting mutant hematopoietic clones, most commonly those harboring mutations in *DNMT3A*, *TET2*, and *ASXL1*, collectively referred to as clonal hematopoiesis of indeterminate potential (CHIP). CHIP becomes increasingly common with age and is detectable in more than 10% of individuals older than 70 years; it is associated with an increased risk of myeloid malignancies, cardiovascular disease, and other adverse outcomes [10, 94–96]. Therefore, all HSC rejuvenation strategies, including those targeting metabolic pathways, must be carefully evaluated in the context of this risk.

Continuous NR supplementation has been shown to reduce mitochondrial activity by enhancing mitochondrial clearance in HSCs, resulting in a more youthful metabolic profile and improved HSC engraftment after transplantation in mouse models [28, 29]. Similarly, overexpression of NAD⁺-regulated sirtuins, including SIRT2, SIRT3, and SIRT7, in aged murine HSCs reduced mitochondrial stress and improved regenerative capacity [24, 26, 97]. However, NR supplementation has been linked to brain metastasis of triple-negative breast cancer in animal models [98]. *DNMT3A* mutations lead to increased expression of NAMPT, resulting in elevated NAD⁺ production [99]. LSCs preferentially rely on NAD⁺ for survival, and inhibition of NAMPT using KPT-9274 reduces NAD⁺ levels and induces apoptosis in LSCs and AML cells in vivo [73, 74]. Furthermore, nicotinamide nucleotide adenyltransferase 1 (NMNAT1) has been identified as a key regulator of NAD⁺ biosynthesis in LSCs. Notably, deletion of NMNAT1 in LSCs reduced NAD⁺ levels, induced apoptosis, and increased sensitivity to venetoclax in vivo, whereas NMNAT1 was dispensable for HSC function [100]. Therefore, these findings warrant careful consideration when NR is supplemented in older individuals at risk for CHIP, particularly those harboring *DNMT3A* mutations.

Activation of mTOR is a feature of aged HSCs, and inhibition of mTOR with rapamycin preserves HSC function in mouse models [75, 80]. Similarly, rapamycin inhibits proliferation of *DNMT3A*-mutant leukemic cells in vivo [101]. These findings highlight rapamycin and other mTOR inhibitors as promising agents for both rejuvenation of aged HSCs and treatment of leukemia. Dosing of mTOR inhibitors is critical, as partial inhibition

of mTOR has been found to be beneficial during aging, whereas chronic administration is immunosuppressive [102]. The use of mTOR inhibitors in preclinical and clinical settings has been reviewed elsewhere [102].

Aged HSCs exhibit low MMP, elevated ROS levels, and myeloid skewing, characteristics that are also observed in AML and other myeloid neoplasms. Targeting aged HSCs in vivo with mitoquinol, a mitochondria-targeted coenzyme Q10 derivative, enhances MMP and reduces ROS levels resulting in increased regeneration potential after transplantation and balanced hematopoietic output [71]. Antioxidants have also been investigated for the treatment of AML [103]. Therefore, antioxidants may have utility in both rejuvenation of aged HSCs and treatment of AML. However, increased oxidative stress and ROS levels are associated with enhanced senescence and apoptosis in aged HSCs as adaptive responses, whereas physiologically low ROS levels are required for normal HSC function [104, 105]. Thus, excessive suppression of ROS as a rejuvenation or AML treatment strategy could confer a survival advantage on functionally impaired aged HSCs and mutant clones, potentially predisposing them to hematologic disorders. This suggests that modulation of ROS levels may be more appropriate as an adjunctive rather than a primary intervention, and careful monitoring of ROS levels is warranted following rejuvenation or AML treatment.

Autophagy induction can be used to rejuvenate aged HSCs; however, LSCs also utilize autophagy to support survival and chemoresistance [6, 83]. Although evidence regarding the state of autophagy in CHIP is lacking, autophagy may also be altered in aged mutant clones. Therefore, intermittent induction of autophagy should be approached with caution when considered for rejuvenation purposes. Understanding how HSCs and LSCs utilize both selective and bulk autophagy is critical [106].

Another promising rejuvenation strategy targets inflammatory signaling within the bone marrow niche. Tet2-mutant HSPCs have been found to expand preferentially in response to key mediators of niche inflammation, including interleukin-1 (IL-1) and IL-6 [107, 108]. Targeting the IL-1 pathway improves aged murine HSC function [109]. Thus, such interventions may selectively suppress mutant clones while promoting rejuvenation of aged HSCs and limiting clonal expansion. It is now possible to predict AML years before diagnosis by quantifying variant allele frequencies of recurrently mutated AML-associated genes, thereby distinguishing individuals at risk of developing AML from those with benign clonal hematopoiesis [110]. This approach allows identification of individuals at risk for AML before implementation of rejuvenation strategies.

Targeting metabolic vulnerabilities in AML often produces initial therapeutic responses; however, durable remission remains challenging because AML is genetically, morphologically, and metabolically heterogeneous. Furthermore, AML blasts and LSCs utilize distinct metabolic programs and may rewire substrate utilization in response to therapeutic stress [111, 112]. In patients with *de novo* AML, LSCs depend on amino acid metabolism to sustain OXPHOS. Treatment with ven/aza disrupts amino acid uptake and reduces OXPHOS-dependent survival [20]. In patients with relapsed or refractory AML, LSCs exhibit elevated nicotinamide metabolism, which simultaneously reactivates amino acid metabolism and FAO to sustain OXPHOS and evade ven/aza-induced cytotoxicity [54, 113]. This metabolic flexibility, namely the shift from amino acids to fatty acids as the primary fuel source for OXPHOS, is a major mechanism of therapeutic escape in AML and helps explain why a single metabolic intervention often produces only transient responses. In addition to these cell-intrinsic mechanisms, the bone marrow microenvironment also contributes to AML resistance. Osteolineage cells and nestin⁺ bone marrow mesenchymal stem cells support AML survival and chemoresistance *in vivo* and in primary AML cells through taurine signaling, increase OXPHOS and TCA cycle activity, and elevate glutathione levels, thereby reducing ROS burden [114, 115].

AML metabolic therapies may adversely affect HSPCs because HSPCs utilize metabolic programs similar to those used by LSCs for maintenance and energy production. Targeting FAO can induce toxicity in HSPCs. Deletion of CPT1A and CD36 had only limited negative effects on murine HSPC function [47, 49]. Similarly, *in vivo* pharmacological inhibition of CPT1A with etomoxir reduced FAO and led to HSC exhaustion after transplantation in a mouse model [116]. Nevertheless, a potential therapeutic window has been identified. Pharmacological inhibition of FAO with etomoxir in combination with ven/aza selectively reduces leukemic burden in resistant AML cells, likely because CPT1A and CD36 are expressed at substantially higher levels in primary AML cells [54]. This strategy may therefore result in less toxicity to HSCs, as loss of CPT1A or CD36 in HSCs and HSPCs does not produce profound functional defects [47, 49].

Inhibition of OXPHOS has been investigated as a therapeutic strategy in the treatment of AML. However, no such therapeutic window has been achieved clinically. A phase I trial of IACS-010759, a potent mitochondrial complex I inhibitor, was conducted in patients with relapsed/refractory AML to target OXPHOS. Although IACS-010759 demonstrated strong preclinical activity against AML, its clinical development was terminated

because of dose-limiting lactic acidosis and nephrotoxicity [117]. To overcome the metabolic plasticity of AML cells following OXPHOS inhibition, treatment with a combination of artesunate (ART), an antimalarial agent, and arsenic trioxide (ATO), which inhibits glycolysis, exhibited antileukemic effects in AML cell lines and primary AML samples [118]. Mechanistically, ART induces uncoupled respiration and mitochondrial damage through mitochondrial iron and calcium overload in AML cells, whereas ATO inhibits glycolysis and induces apoptosis. Furthermore, when ART and ATO were combined with azacitidine (ART-ATO-Aza), a marked reduction in leukemia burden was observed in a THP-1 AML cell line-derived luciferase xenograft model, while having minimal effects on normal peripheral blood cells [118]. Thus, the ART-ATO-Aza combination may provide a strategy to overcome the toxicities and therapeutic limitations associated with IACS-010759.

IDH inhibitors (ivosidenib, enasidenib, and olutasidenib) are small-molecule inhibitors of IDH1 and IDH2 that have been approved by the US Food and Drug Administration for the treatment of adults with relapsed or refractory IDH1- or IDH2-mutated AML [119–121]. These agents inhibit production of the oncometabolite 2-hydroxyglutarate by IDH-mutant AML cells. The main clinically relevant toxicity is differentiation syndrome, which occurs in a small subset of patients and is generally manageable with corticosteroids [122]. In addition, inhibition of α -ketoglutarate dehydrogenase in MLL-AF9 and p53-mutant AML mouse models impaired AML progression and induced differentiation by disrupting the TCA cycle, thereby inhibiting the nucleotide synthesis required for AML cell expansion [123]. Regarding clinical translation, ven/aza and the IDH inhibitors ivosidenib, enasidenib, and olutasidenib represent the most advanced metabolic-targeting strategies and have demonstrated survival benefits [122, 124]. Collectively, these findings indicate that durable LSC eradication will likely require combination strategies that simultaneously target multiple metabolic vulnerabilities while sparing normal HSPCs. In addition, single-cell metabolomics approaches will be essential for mapping the full metabolic heterogeneity of LSCs and leukemia blasts across different stages of AML.

The strategies discussed above for HSC rejuvenation or AML targeting differ markedly in terms of their translational maturity. Currently, the metabolic interventions that have received regulatory approval and are in clinical use are directed at AML rather than HSC rejuvenation: ven in combination with aza, together with the mutant IDH inhibitors ivosidenib, enasidenib, and olutasidenib. A second group of interventions is supported by robust preclinical evidence but has not been validated

in humans. These include NAD⁺ precursors, mTOR inhibition, antioxidants, autophagy induction, IL-1 blockade, cholesterol sulfate supplementation, and FAO inhibition. A final and more preliminary category rests on the in vitro evidence alone: choline supplementation in aged HSPCs. Overall, the rejuvenation arm remains less developed than the AML-targeting arm, which underscores the need to advance this effort, while ensuring that any clinical attempt at rejuvenation is combined with the aforementioned clonal expansion precautions.

4. Conclusion

The switch from glycolysis to OXPHOS, mitochondrial hyperactivation, ROS accumulation, NAD⁺ depletion, and impaired autophagy contribute to lineage bias, functional defects, and susceptibility to clonal hematopoiesis in aged HSCs. By contrast, LSCs adapt to diverse metabolic programs, including oxidative phosphorylation, FAO, amino acid metabolism, autophagy, and NAD⁺ salvage pathways, to support survival, chemoresistance, and leukemia initiation. Therefore, these metabolic alterations in aged HSCs and LSCs represent potential therapeutic targets for either rejuvenating aged HSCs or eliminating LSCs. In addition, it is essential to better understand the metabolic adaptations of young quiescent HSCs relative to activated HSCs and to compare these adaptations with those of LSCs and leukemia blasts. Such understanding may facilitate selective targeting of leukemia cells while sparing normal hematopoietic cells. These efforts can be further advanced through developments in single-cell metabolomics, multiomics, and combination therapies [125]. Furthermore, the heterogeneity of aged HSCs should be considered when studying metabolic regulation in hematopoiesis to avoid masking small subsets of aged HSCs that retain functionality comparable to that of young HSCs, with the long-term goal of developing clinically translatable rejuvenation strategies.

Conflicts of interest

The author declares no conflicts of interest.

Author contributions

A.A designed and wrote the manuscript.

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References

- [1] Rettkowski J, Cabezas-Wallscheid N (2025). Regulation of Hematopoietic Stem Cell Dormancy and Quiescence: Insights into Regeneration and Disease. *Annu Rev Cell Dev Biol*, 41:231–258.
- [2] Nakamura-Ishizu A, Ito K, Suda T (2020). Hematopoietic Stem Cell Metabolism during Development and Aging. *Dev Cell*, 54:239–255.
- [3] Ito K, Bonora M, Ito K (2019). Metabolism as master of hematopoietic stem cell fate. *Int J Hematol*, 109:18–27.
- [4] Prakash A, Inamdar MS (2025). Mitochondrial-activity-driven hematopoietic stem cell fate and lineage choice is first established in the aorta-gonad-mesonephros. *Cell Rep*, 44:116296.
- [5] Simsek T, Kocabas F, Zheng J, DeBerardinis RJ, Mahmoud AI, Olson EN, et al. (2010). The Distinct Metabolic Profile of Hematopoietic Stem Cells Reflects Their Location in a Hypoxic Niche. *Cell Stem Cell*, 7:380–390.
- [6] Ho TT, Warr MR, Adelman ER, Lansinger OM, Flach J, Verovskaya E V, et al. (2017). Autophagy maintains the metabolism and function of young and old stem cells. *Nature*, 543:205–210.
- [7] Vannini N, Girotra M, Naveiras O, Nikitin G, Campos V, Giger S, et al. (2016). Specification of haematopoietic stem cell fate via modulation of mitochondrial activity. *Nat Commun*, 7:13125.
- [8] Man CH, Li C, Xu X, Zhao M (2024). Metabolic regulation in normal and leukemic stem cells. *Trends Pharmacol Sci*, 45:919–930.
- [9] Keller A, Temple T, Sayanjali B, Mihaylova MM (2021). Metabolic Regulation of Stem Cells in Aging. *Curr Stem Cell Rep*, 7:72–84.
- [10] Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman P V, Mar BG, et al. (2014). Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes. *N Engl J Med*, 371:2488–2498.
- [11] Beerman I, Bhattacharya D, Zandi S, Sigvardsson M, Weissman IL, Bryder D, et al. (2010). Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. *Proc Natl Acad Sci U S A*, 107:5465–5470.
- [12] Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoun SF, et al. (2014). Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence. *N Engl J Med*, 371:2477–2487.
- [13] Flohr Svendsen A, Yang D, Kim KM, Lazare S, Skinder N, Zwart E, et al. (2021). A comprehensive transcriptome signature of murine hematopoietic stem cell aging. *Blood*, 138:439–451.
- [14] Saçma M, Pospiech J, Bogeska R, de Back W, Mallm JP, Sakk V, et al. (2019). Haematopoietic stem cells in perisinusoidal niches are protected from ageing. *Nat Cell Biol*, 21:1309–1320.
- [15] Skinder N, Fernández IS, Dethmers-Ausema A, Weersing E, Haan G de (2024). CD61 identifies a superior population of aged murine HSCs and is required

- to preserve quiescence and self-renewal. *Blood Adv*, 8:99–111.
- [16] Wang Y, Zhang W, Zhang C, Van HQT, Seino T, Zhang Y (2025). Reducing functionally defective old HSCs alleviates aging-related phenotypes in old recipient mice. *Cell Res*, 35:45–58.
- [17] Koide S, Oshima M, Kamiya T, Zheng Z, Liu Z, Rizq O, et al. (2025). Tracking clusterin expression in hematopoietic stem cells reveals their heterogeneous composition across the life span. *Blood*, 146:62–75.
- [18] Totani H, Matsumura T, Yokomori R, Umemoto T, Takihara Y, Yang C, et al. (2025). Mitochondria-enriched hematopoietic stem cells exhibit elevated self-renewal capabilities, thriving within the context of aged bone marrow. *Nat Aging*, 5:831–847.
- [19] Stelmach P, Trumpp A (2023). Leukemic stem cells and therapy resistance in acute myeloid leukemia. *Haematologica*, 108:353–366.
- [20] Jones CL, Stevens BM, D'Alessandro A, Reisz JA, Culp-Hill R, Nemkov T, et al. (2018). Inhibition of Amino Acid Metabolism Selectively Targets Human Leukemia Stem Cells. *Cancer Cell*, 34:724–740.e4.
- [21] Ito K, Suda T (2014). Metabolic requirements for the maintenance of self-renewing stem cells. *Nat Rev Mol Cell Biol*, 15:243–256.
- [22] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023). Hallmarks of aging: An expanding universe. *Cell*, 186:243–278.
- [23] Liao Y, Octaviani S, Tian Z, Wang SR, Huang C, Huang J (2025). Mitochondrial quality control in hematopoietic stem cells: mechanisms, implications, and therapeutic opportunities. *Stem Cell Res Ther*, 16:180.
- [24] Brown K, Xie S, Qiu X, Mohrin M, Shin J, Liu Y, et al. (2013). SIRT3 Reverses Aging-Associated Degeneration. *Cell Rep*, 3:319–327.
- [25] Song Z, Park SH, Mu WC, Feng Y, Wang CL, Wang Y, et al. (2024). An NAD⁺-dependent metabolic checkpoint regulates hematopoietic stem cell activation and aging. *Nat Aging*, 4:1384–1393.
- [26] Mohrin M, Shin J, Liu Y, Brown K, Luo H, Xi Y, et al. (2015). A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. *Science*, 347:1374–1377.
- [27] Camacho-Pereira J, Tarragó MG, Chini CCS, Nin V, Escande C, Warner GM, et al. (2016). CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. *Cell Metab*, 23:1127–1139.
- [28] Vannini N, Campos V, Girotra M, Trachsel V, Rojas-Sutterlin S, Tratwal J, et al. (2019). The NAD-Booster Nicotinamide Riboside Potently Stimulates Hematopoiesis through Increased Mitochondrial Clearance. *Cell Stem Cell*, 24:405–418.e7.
- [29] Sun X, Cao B, Naval-Sanchez M, Pham T, Sun YBY, Williams B, et al. (2021). Nicotinamide riboside attenuates age-associated metabolic and functional changes in hematopoietic stem cells. *Nat Commun*, 12:2665.
- [30] Thomas D, Majeti R (2017). Biology and relevance of human acute myeloid leukemia stem cells. *Blood*, 129:1577–1585.
- [31] Pollyea DA, Jordan CT (2017). Therapeutic targeting of acute myeloid leukemia stem cells. *Blood*, 129:1627–1635.
- [32] Takubo K, Nagamatsu G, Kobayashi CI, Nakamura-Ishizu A, Kobayashi H, Ikeda E, et al. (2013). Regulation of Glycolysis by Pdk Functions as a Metabolic Checkpoint for Cell Cycle Quiescence in Hematopoietic Stem Cells. *Cell Stem Cell*, 12:49–61.
- [33] Cao J, Yao QJ, Wu J, Chen X, Huang L, Liu W, et al. (2024). Deciphering the metabolic heterogeneity of hematopoietic stem cells with single-cell resolution. *Cell Metab*, 36:209–221.e6.
- [34] Du J, Li Q, Tang F, Puchowitz MA, Fujioka H, Dunwoodie SL, et al. (2014). Cited2 is required for the maintenance of glycolytic metabolism in adult hematopoietic stem cells. *Stem Cells Dev*, 23:83–94.
- [35] Suda T, Takubo K, Semenza GL (2011). Metabolic Regulation of Hematopoietic Stem Cells in the Hypoxic Niche. *Cell Stem Cell*, 9:298–310.
- [36] Ito K, Hirao A, Arai F, Takubo K, Matsuoka S, Miyamoto K, et al. (2006). Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. *Nat Med*, 12:446–451.
- [37] Watanuki S, Kobayashi H, Sugiura Y, Yamamoto M, Karigane D, Shiroshta K, et al. (2024). SDHAF1 confers metabolic resilience to aging hematopoietic stem cells by promoting mitochondrial ATP production. *Cell Stem Cell*, 31:1145–1161.e15.
- [38] Dellorusso P V., Proven MA, Calero-Nieto FJ, Wang X, Mitchell CA, Hartmann F, et al. (2024). Autophagy counters inflammation-driven glycolytic impairment in aging hematopoietic stem cells. *Cell Stem Cell*, 31:1020–1037.e9.
- [39] Sun N, Lin CH, Li MY, Wang Y, Chen D, Ren X, et al. (2025). Clusterin drives myeloid bias in aged hematopoietic stem cells by regulating mitochondrial function. *Nat Aging*, 5:1510–1527.
- [40] Yang F, Nourse C, Helgason GV, Kirschner K (2023). Unraveling Heterogeneity in the Aging Hematopoietic Stem Cell Compartment: An Insight From Single-cell Approaches. *Hemasphere*, 7:E895.
- [41] Watanuki S, Kobayashi H, Sugiura Y, Yamamoto M, Karigane D, Shiroshta K, et al. (2024). Context-dependent modification of PFKFB3 in hematopoietic stem cells promotes anaerobic glycolysis and ensures stress hematopoiesis. *Elife*, 12:RP87674.
- [42] Mesbahi Y, Trahair TN, Lock RB, Connerty P (2022). Exploring the Metabolic Landscape of AML: From Haematopoietic Stem Cells to Myeloblasts and Leukaemic Stem Cells. *Front Oncol*, 12:807266.
- [43] Lagadinou ED, Sach A, Callahan K, Rossi RM, Neering SJ, Minhajuddin M, et al. (2013). BCL-2 Inhibition Targets Oxidative Phosphorylation and Selectively Eradicates Quiescent Human Leukemia Stem Cells. *Cell Stem Cell*, 12:329–341.
- [44] Ye H, Adane B, Khan N, Sullivan T, Minhajuddin M, Gasparetto M, et al. (2016). Leukemic Stem Cells Evade

- Chemotherapy by Metabolic Adaptation to an Adipose Tissue Niche. *Cell Stem Cell*, 19:23–37.
- [45] Chen WL, Wang JH, Zhao AH, Xu X, Wang YH, Chen TL, et al. (2014). A distinct glucose metabolism signature of acute myeloid leukemia with prognostic value. *Blood*, 124:1645–1654.
- [46] Merchant S, Paul A, Reyes A, Cassidy D, Leach A, Kim D, et al. (2025). Different effects of fatty acid oxidation on hematopoietic stem cells based on age and diet. *Cell Stem Cell*, 32:263–275.e5.
- [47] Li J, Bai J, Pham VT, Hashimoto M, Sezaki M, Shi Q, et al. (2025). Loss of Cpt1a results in elevated glucose-fueled mitochondrial oxidative phosphorylation and defective hematopoietic stem cells. *J Clin Invest*, 135: e184069.
- [48] Mistry JJ, Hellmich C, Moore JA, Jibril A, Macaulay I, Moreno-Gonzalez M, et al. (2021). Free fatty-acid transport via CD36 drives β -oxidation-mediated hematopoietic stem cell response to infection. *Nat Commun*, 12: 7130.
- [49] Meng Y, Pospiech M, Ali A, Chandwani R, Vergel M, Onyemaechi S, et al. (2023). Deletion of CD36 exhibits limited impact on normal hematopoiesis and the leukemia microenvironment. *Cell Mol Biol Lett*, 28:45.
- [50] Lalioti ME, Romero-Mulero MC, Karabacz N, Mess J, Demollin H, Rettowski J, et al. (2025). Differentiation, ageing and leukaemia alter the metabolic profile of human bone marrow haematopoietic stem and progenitor cells. *Nat Cell Biol*, 27:1367–1380.
- [51] Feng Y, Li N, Wang N, He W, Li H, Cui X, et al. (2026). Cholesterol sulfate replenishment rejuvenates aged hematopoietic stem cell phenomes. *Theranostics*, 16:5501–5517.
- [52] O'Brien C, Jones CL (2025). Unraveling lipid metabolism for acute myeloid leukemia therapy. *Curr Opin Hematol*, 32:77–86.
- [53] Tcheng M, Roma A, Ahmed N, Smith RW, Jayanth P, Minden MD, et al. (2021). Very long chain fatty acid metabolism is required in acute myeloid leukemia. *Blood*, 137:3518–3532.
- [54] Stevens BM, Jones CL, Pollyea DA, Culp-Hill R, D'Alessandro A, Winters A, et al. (2020). Fatty acid metabolism underlies venetoclax resistance in acute myeloid leukemia stem cells. *Nat Cancer*, 1:1176–1187.
- [55] Signer RAJ, Magee JA, Salic A, Morrison SJ (2014). Haematopoietic stem cells require a highly regulated protein synthesis rate. *Nature*, 509:49–54.
- [56] Li C, Wu B, Li Y, Chen J, Ye Z, Tian X, et al. (2022). Amino acid catabolism regulates hematopoietic stem cell proteostasis via a GCN2-eIF2 α axis. *Cell Stem Cell*, 29:1119–1134.e7.
- [57] Hidalgo San Jose L, Sunshine MJ, Dillingham CH, Chua BA, Kruta M, Hong Y, et al. (2020). Modest Declines in Proteome Quality Impair Hematopoietic Stem Cell Self-Renewal. *Cell Rep*, 30:69–80.e6.
- [58] Chua BA, Signer RAJ (2020). Hematopoietic stem cell regulation by the proteostasis network. *Curr Opin Hematol*, 27:254–263.
- [59] Sun D, Luo M, Jeong M, Rodriguez B, Xia Z, Hannah R, et al. (2014). Epigenomic Profiling of Young and Aged HSCs Reveals Concerted Changes during Aging that Reinforce Self-Renewal. *Cell Stem Cell*, 14:673–688.
- [60] Kruta M, Sunshine MJ, Chua BA, Fu Y, Chawla A, Dillingham CH, et al. (2021). Hsf1 promotes hematopoietic stem cell fitness and proteostasis in response to ex vivo culture stress and aging. *Cell Stem Cell*, 28:1950–1965.e6.
- [61] Bergo V, Bousounis P, To Vu G, Douté M, Polyzou A, Lalioti ME, et al. (2026). Lack of MDA5 delays hematopoietic aging by modulating inflammaging and proteostasis in mice. *Nat Commun*, 17:1645.
- [62] Chua BA, Lennan CJ, Sunshine MJ, Dreifke D, Chawla A, Bennett EJ, et al. (2023). Hematopoietic stem cells preferentially traffic misfolded proteins to aggresomes and depend on aggrephagy to maintain protein homeostasis. *Cell Stem Cell*, 30:460–472.e6.
- [63] Wang M, Zhao A, Li M, Niu T (2023). Amino acids in hematologic malignancies: Current status and future perspective. *Front Nutr*, 10:113228.
- [64] Jones CL, Stevens BM, D'Alessandro A, Culp-Hill R, Reisz JA, Pei S, et al. (2019). Cysteine depletion targets leukemia stem cells through inhibition of electron transport complex II. *Blood*, 134:389–394.
- [65] Raffel S, Falcone M, Kneisel N, Hansson J, Wang W, Lutz C, et al. (2017). BCAT1 restricts α KG levels in AML stem cells leading to IDHmut-like DNA hypermethylation. *Nature*, 551:384–388.
- [66] Han L, Dong L, Leung K, Zhao Z, Li Y, Gao L, et al. (2023). METTL16 drives leukemogenesis and leukemia stem cell self-renewal by reprogramming BCAA metabolism. *Cell Stem Cell*, 30:52–68.e13.
- [67] Gregory MA, Nemkov T, Park HJ, Zaberezhnyy V, Gehrke S, Adane B, et al. (2019). Targeting Glutamine Metabolism and Redox State for Leukemia Therapy. *Clin Cancer Res*, 25:4079–4090.
- [68] Papa L, Djedaini M, Hoffman R (2019). Mitochondrial Role in Stemness and Differentiation of Hematopoietic Stem Cells. *Stem Cells Int*, 2019:1–10.
- [69] Morganti C, Ito K (2021). Mitochondrial Contributions to Hematopoietic Stem Cell Aging. *Int J Mol Sci*, 22:11117.
- [70] Imai S, Guarente L (2016). It takes two to tango: NAD⁺ and sirtuins in aging/longevity control. *NPJ Aging Mech Dis*, 2:16017.
- [71] Mansell E, Sigurdsson V, Deltcheva E, Brown J, James C, Miharada K, et al. (2021). Mitochondrial Potentiation Ameliorates Age-Related Heterogeneity in Hematopoietic Stem Cell Function. *Cell Stem Cell*, 28:241–256.e6.
- [72] Srisanthadevan S, Jeyaraju D V., Chung TE, Prabha S, Xu W, Skrtic M, et al. (2015). AML cells have low spare reserve capacity in their respiratory chain that renders them susceptible to oxidative metabolic stress. *Blood*, 125:2120–2130.
- [73] Subedi A, Liu Q, Ayyathan DM, Sharon D, Cathelin S, Hosseini M, et al. (2021). Nicotinamide phosphoribosyltransferase inhibitors selectively induce apoptosis of AML stem cells by disrupting lipid homeostasis. *Cell Stem Cell*, 28:1851–1867.e8.

- [74] Mitchell SR, Larkin K, Grieselhuber NR, Lai T-H, Cannon M, Orwick S, et al. (2019). Selective targeting of NAMPT by KPT-9274 in acute myeloid leukemia. *Blood Adv*, 3:242–255.
- [75] Borsa M, Obba S, Richter FC, Zhang H, Riffelmacher T, Carrelha J, et al. (2024). Autophagy preserves hematopoietic stem cells by restraining mTORC1-mediated cellular anabolism. *Autophagy*, 20:45–57.
- [76] Mortensen M, Watson AS, Simon AK (2011). Lack of autophagy in the hematopoietic system leads to loss of hematopoietic stem cell function and dysregulated myeloid proliferation. *Autophagy*, 7:1069–1070.
- [77] Mortensen M, Soilleux EJ, Djordjevic G, Tripp R, Lutteropp M, Sadighi-Akha E, et al. (2011). The autophagy protein Atg7 is essential for hematopoietic stem cell maintenance. *J Exp Med*, 208:455–467.
- [78] Jung HE, Shim YR, Oh JE, Oh DS, Lee HK (2019). The autophagy Protein Atg5 Plays a Crucial Role in the Maintenance and Reconstitution Ability of Hematopoietic Stem Cells. *Immune Netw*, 19:e12.
- [79] Girotra M, Chiang YH, Charmoy M, Ginefra P, Hope HC, Bataclan C, et al. (2023). Induction of mitochondrial recycling reverts age-associated decline of the hematopoietic and immune systems. *Nat Aging*, 3:1057–1066.
- [80] Chen C, Liu Y, Liu Y, Zheng P (2009). mTOR Regulation and Therapeutic Rejuvenation of Aging Hematopoietic Stem Cells. *Sci Signal*, 2:ra75.
- [81] Arif T, Qiu J, Khademian H, Lohithakshan A, Menon A, Menon V, et al. (2025). Reversing lysosomal dysfunction restores youthful state in aged hematopoietic stem cells. *Cell Stem Cell*, 32:1904–1922.e7.
- [82] Liang R, Arif T, Kalmykova S, Kasianov A, Lin M, Menon V, et al. (2020). Restraining Lysosomal Activity Preserves Hematopoietic Stem Cell Quiescence and Potency. *Cell Stem Cell*, 26:359–376.e7.
- [83] Dykstra KM, Fay HRS, Massey AC, Yang N, Johnson M, Portwood S, et al. (2021). Inhibiting autophagy targets human leukemic stem cells and hypoxic AML blasts by disrupting mitochondrial homeostasis. *Blood Adv*, 5:2087–2100.
- [84] Chen Y, Chen J, Zou Z, Xu L, Li J (2024). Crosstalk between autophagy and metabolism: implications for cell survival in acute myeloid leukemia. *Cell Death Discov*, 10:46.
- [85] Sumitomo Y, Koya J, Nakazaki K, Kataoka K, Tsuruta-Kishino T, Morita K, et al. (2016). Cytoprotective autophagy maintains leukemia-initiating cells in murine myeloid leukemia. *Blood*, 128:1614–1624.
- [86] Qiu S, Kumar H, Yan C, Li H, Paterson AJ, Anderson NR, et al. (2022). Autophagy inhibition impairs leukemia stem cell function in FLT3-ITD AML but has antagonistic interactions with tyrosine kinase inhibition. *Leukemia*, 36:2621–2633.
- [87] Baquero P, Dawson A, Mukhopadhyay A, Kuntz EM, Mitchell R, Olivares O, et al. (2019). Targeting quiescent leukemic stem cells using second generation autophagy inhibitors. *Leukemia*, 33:981–994.
- [88] Chini CCS, Cordeiro HS, Tran NLK, Chini EN (2024). NAD metabolism: Role in senescence regulation and aging. *Aging Cell*, 23:e13920.
- [89] Karimnia N, Harris J, Heazlewood SY, Cao B, Nilsson SK (2023). Metabolic regulation of aged hematopoietic stem cells: key players and mechanisms. *Exp Hematol*, 128:2–9.
- [90] Pollyea DA, Stevens BM, Jones CL, Winters A, Pei S, Minhajuddin M, et al. (2018). Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. *Nat Med*, 24:1859–1866.
- [91] Ricciardi MR, Mirabilii S, Allegretti M, Licchetta R, Calarco A, Torrisi MR, et al. (2015). Targeting the leukemia cell metabolism by the CPT1a inhibition: functional preclinical effects in leukemias. *Blood*, 126:1925–1929.
- [92] Matre P, Velez J, Jacamo R, Qi Y, Su X, Cai T, et al. (2016). Inhibiting glutaminase in acute myeloid leukemia: metabolic dependency of selected AML subtypes. *Oncotarget*, 7:79722–79735.
- [93] Fruchtmann H, Avigan ZM, Waksal JA, Brennan N, Mascarenhas JO (2024). Management of isocitrate dehydrogenase 1/2 mutated acute myeloid leukemia. *Leukemia*, 38:927–935.
- [94] Florez MA, Tran BT, Wathan TK, DeGregori J, Pietras EM, King KY (2022). Clonal hematopoiesis: Mutation-specific adaptation to environmental change. *Cell Stem Cell*, 29:882–904.
- [95] Mitchell E, Spencer Chapman M, Williams N, Dawson KJ, Mende N, Calderbank EF, et al. (2022). Clonal dynamics of haematopoiesis across the human lifespan. *Nature*, 606:343–350.
- [96] Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, et al. (2015). Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood*, 126:9–16.
- [97] Luo H, Mu WC, Karki R, Chiang HH, Mohrin M, Shin JJ, et al. (2019). Mitochondrial Stress-Initiated Aberrant Activation of the NLRP3 Inflammasome Regulates the Functional Deterioration of Hematopoietic Stem Cell Aging. *Cell Rep*, 26:945–954.e4.
- [98] Maric T, Bazhin A, Khodakivskyi P, Mikhaylov G, Solodnikova E, Yevtdiyenko A, et al. (2023). A bioluminescent-based probe for in vivo non-invasive monitoring of nicotinamide riboside uptake reveals a link between metastasis and NAD⁺ metabolism. *Biosens Bioelectron*, 220:114826.
- [99] Yang X, Wang X, Yang Y, Li Z, Chen Y, Shang S, et al. (2023). DNMT3A mutation promotes leukemia development through NAM-NAD metabolic reprogramming. *J Transl Med*, 21:481.
- [100] Shi X, Jiang Y, Kitano A, Hu T, Murdaugh RL, Li Y, et al. (2021). Nuclear NAD⁺ homeostasis governed by NMNAT1 prevents apoptosis of acute myeloid leukemia stem cells. *Sci Adv*, 7:3895–3916.
- [101] Dai YJ, Wang YY, Huang JY, Xia L, Shi XD, Xu J, et al. (2017). Conditional knockin of Dnmt3a R878H initiates acute myeloid leukemia with mTOR pathway involvement. *Proc Natl Acad Sci U S A*, 114:5237–5242.

- [102] Mannick JB, Lamming DW (2023). Targeting the biology of aging with mTOR inhibitors. *Nat Aging*, 3:642–660.
- [103] Dong C, Zhang NJ, Zhang LJ (2021). Oxidative stress in leukemia and antioxidant treatment. *Chin Med J (Engl)*, 134:1897–1907.
- [104] Jang YY, Sharkis SJ (2007). A low level of reactive oxygen species selects for primitive hematopoietic stem cells that may reside in the low-oxygenic niche. *Blood*, 110:3056–3063.
- [105] Porto ML, Rodrigues BP, Menezes TN, Ceschim SL, Casarini DE, Gava AL, et al. (2015). Reactive oxygen species contribute to dysfunction of bone marrow hematopoietic stem cells in aged C57BL/6 J mice. *J Biomed Sci*, 22:97.
- [106] Koschade SE, Brandts CH (2020). Selective Autophagy in Normal and Malignant Hematopoiesis. *J Mol Biol*, 432:261–282.
- [107] Caiado F, Kovtonyuk L V., Gonullu NG, Fullin J, Boettcher S, Manz MG (2023). Aging drives Tet2^{+/}-clonal hematopoiesis via IL-1 signaling. *Blood*, 141:886–903.
- [108] Cai Z, Kotzin JJ, Ramdas B, Chen S, Nelanuthala S, Palam LR, et al. (2018). Inhibition of Inflammatory Signaling in Tet2 Mutant Preleukemic Cells Mitigates Stress-Induced Abnormalities and Clonal Hematopoiesis. *Cell Stem Cell*, 23:833–849.e5.
- [109] Mitchell CA, Verovskaya E V., Calero-Nieto FJ, Olson OC, Swann JW, Wang X, et al. (2023). Stromal niche inflammation mediated by IL-1 signalling is a targetable driver of haematopoietic ageing. *Nat Cell Biol*, 25:30–41.
- [110] Abelson S, Collord G, Ng SWK, Weissbrod O, Mendelson Cohen N, Niemeyer E, et al. (2018). Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature*, 559:400–404.
- [111] Castro I, Sampaio-Marques B, Ludovico P (2019). Targeting Metabolic Reprogramming in Acute Myeloid Leukemia. *Cells*, 8:967.
- [112] Addanki S, Kim L, Stevens A (2025). Understanding and Targeting Metabolic Vulnerabilities in Acute Myeloid Leukemia: An Updated Comprehensive Review. *Cancers (Basel)*, 17:1355.
- [113] Jones CL, Stevens BM, Pollyea DA, Culp-Hill R, Reis JA, Nemkov T, et al. (2020). Nicotinamide Metabolism Mediates Resistance to Venetoclax in Relapsed Acute Myeloid Leukemia Stem Cells. *Cell Stem Cell*, 27:748–764.e4.
- [114] Forte D, García-Fernández M, Sánchez-Aguilera A, Stavropoulou V, Fielding C, Martín-Pérez D, et al. (2020). Bone Marrow Mesenchymal Stem Cells Support Acute Myeloid Leukemia Bioenergetics and Enhance Antioxidant Defense and Escape from Chemotherapy. *Cell Metab*, 32:829–843.e9.
- [115] Sharma S, Rodems BJ, Baker CD, Kaszuba CM, Franco EI, Smith BR, et al. (2025). Taurine from tumour niche drives glycolysis to promote leukaemogenesis. *Nature*, 644:263–272.
- [116] Ito K, Carracedo A, Weiss D, Arai F, Ala U, Avigan DE, et al. (2012). A PML–PPAR- δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. *Nat Med*, 18:1350–1358.
- [117] Yap TA, Daver N, Mahendra M, Zhang J, Kamiya-Matsuoka C, Meric-Bernstam F, et al. (2023). Complex I inhibitor of oxidative phosphorylation in advanced solid tumors and acute myeloid leukemia: phase I trials. *Nat Med*, 29:115–126.
- [118] Balasundaram N, Palani HK, Venkatraman A, Augustin Y, Pichandi S, Regnault C, et al. (2025). A novel strategy to target metabolic dependencies in acute myeloid leukemia. *Cell Death Dis*, 16:792.
- [119] Dugan J, Pollyea D (2018). Enasidenib for the treatment of acute myeloid leukemia. *Expert Rev Clin Pharmacol*, 11:755–760.
- [120] Norsworthy KJ, Luo L, Hsu V, Gudi R, Dorff SE, Przepiorka D, et al. (2019). FDA Approval Summary: Ivosidenib for Relapsed or Refractory Acute Myeloid Leukemia with an Isocitrate Dehydrogenase-1 Mutation. *Clin Cancer Res*, 25:3205–3209.
- [121] Cortes JE (2024). Olutasidenib: a novel mutant IDH1 inhibitor for the treatment of relapsed or refractory acute myeloid leukemia. *Expert Rev Hematol*, 17:211–221.
- [122] Norsworthy KJ, Mulkey F, Scott EC, Ward AF, Przepiorka D, Charlab R, et al. (2020). Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis. *Clin Cancer Res*, 26:4280–4288.
- [123] Millman SE, Chaves-Perez A, Janaki-Raman S, Ho YJ, Morris JP, Narendra V, et al. (2025). α -Ketoglutarate dehydrogenase is a therapeutic vulnerability in acute myeloid leukemia. *Blood*, 145:1422–1436.
- [124] DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. (2020). Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med*, 383:617–629.
- [125] Haring E, Buescher JM, Apostolova P (2025). Metabolism in hematology: Technological advances open new perspectives on disease biology and treatment. *Hemasphere*, 9:e70134.