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Review

The Role of ZBTB7A in the Metabolic Landscape of t(8;21) Acute Myeloid Leukemia (AML): A Comprehensive Review of Current Evidence

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ABSTRACT

Introduction: The *RUNX1::RUNX1T1* (also known as *RUNX1::ETO*) fusion oncogene generated by the t(8;21)(q22;q22) chromosomal translocation initiates leukemogenesis but requires additional cooperating mutations to induce overt t(8;21) acute myeloid leukemia (AML). Zinc finger and BTB domain-containing protein 7A (ZBTB7A, also known as POKEMON or LRF) is a transcriptional repressor that regulates multiple cellular processes, including hematopoiesis and energy metabolism. Somatic *ZBTB7A* mutations occur preferentially in t(8;21) AML compared with other AML subtypes, suggesting a distinct cooperative role in this cytogenetic subgroup. Because metabolic reprogramming is a hallmark mechanism through which leukemic cells sustain proliferation and resist therapy, defining the metabolic impact of *ZBTB7A* inactivation is of high clinical relevance. **Methods:** A narrative literature search of PubMed and Google Scholar was conducted up to December 2025 to identify studies investigating whether *ZBTB7A* mutations drive metabolic reprogramming and cooperate with *RUNX1::ETO* in the pathogenesis of t(8;21) AML. **Results:** All somatic *ZBTB7A* alterations characterized in t(8;21) AML act as loss-of-function or dominant-negative mutations. Evidence across *in silico*, *in vitro*, and *in vivo* models demonstrates that loss of ZBTB7A de-represses key glycolytic target genes—including *SLC2A3* (*GLUT3*), *PFKP*, and *PKM*—resulting in elevated glycolytic flux that supports leukemic cell survival and clonal expansion. Furthermore, *ZBTB7A* deficiency alters lipid homeostasis by upregulating de novo fatty acid synthesis, fatty acid beta-oxidation, and ketogenesis, thereby providing metabolic flexibility under nutrient-restricted or hypoxic bone marrow conditions. **Conclusion:** Loss-of-function mutations in *ZBTB7A* promote metabolic reprogramming in t(8;21) AML by increasing cellular dependence on glycolysis and lipid metabolism, which facilitates leukemic cell survival, differentiation arrest, and disease progression. These metabolic dependencies represent promising therapeutic vulnerabilities that may be exploited through targeted inhibition of glycolytic and lipid metabolic pathways.

Key words: Acute myeloid leukemia, ZBTB7A, Core-binding factor leukemia, Metabolomics, Lipidomics, Metabolic reprogramming

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INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive hematological malignancy characterized by the arrest of myeloid differentiation and the clonal accumulation of immature myeloblasts. The balanced chromosomal translocation t(8;21)(q22;q22) defines a distinct clinical subtype of core-binding factor (CBF) AML and generates the *RUNX1::RUNX1T1* (commonly termed RUNX1::ETO or AML1::ETO) fusion oncogene, which impairs erythropoiesis and blocks myeloid maturation[1]. However, murine models have demonstrated that expression of *RUNX1::ETO* alone is insufficient to induce overt leukemogenesis[2]. Instead, secondary genetic alterations are required to cooperate with RUNX1::ETO to drive full-blown t(8;21) AML[2,3].

Leukemic cells extensively reprogram their metabolome to sustain rapid proliferation, survive within the hypoxic bone marrow niche, and mediate disease relapse[4]. This metabolic rewiring correlates strongly with clinical prognosis in AML, as specific metabolites and enzymatic regulators govern multiple pro-survival pathways[5]. In particular, metabolic adaptation is a principal mechanism through which dormant leukemic stem and progenitor cells evade chemotherapy and drive relapse following remission[6]. This phenomenon is especially prominent in t(8;21) AML, which exhibits a pronounced reliance on glucose metabolism mediated by key glycolytic regulators such as solute carrier family 2 member 3 (*SLC2A3*, encoding GLUT3) and platelet-type phosphofructokinase (*PFKP*)[7–9]. Notably, multiple rate-limiting glycolytic enzymes and glucose

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transporters are transcriptionally repressed by zinc finger and BTB domain-containing protein 7A (ZBTB7A).

ZBTB7A belongs to the ZBTB7 transcription factor subfamily, which also includes ZBTB7B and ZBTB7C, and plays an essential role in regulating gene transcription across hematopoiesis, oncogenesis, and cellular metabolism [10]. In normal hematopoiesis, loss of ZBTB7A reduces myeloid progenitor populations and impairs the repression of premature lymphoid differentiation [11,12]. Clinically, elevated ZBTB7A expression has been associated with favorable prognosis, even among patients with cytogenetically normal AML (CN-AML) [13]. In this review, we synthesize current evidence on how somatic ZBTB7A mutations cooperate with the RUNX1::ETO fusion oncoprotein to drive metabolic reprogramming and leukemogenesis in t(8;21) AML.

METHODOLOGY

This article is a narrative review based on a comprehensive literature search conducted in PubMed and Google Scholar up to December 2025. Search terms included combinations and synonyms of "ZBTB7A" (including ZBTB7, POKEMON, LRF, and FBI-1), "metabolism", and "t(8;21) AML" (including *RUNX1::RUNX1T1*, *RUNX1::ETO*, *RUNX1/RUNX1T1*, *RUNX1/ETO*, *AML1/ETO*, *AML1/MTG8*, *AML1::ETO*, and *AML1::MTG8*). Peer-reviewed original research articles and published conference abstracts fulfilling all three search domains were selected for primary analysis. For studies matching two or fewer search domains, flexible inclusion criteria were applied to capture mechanistic findings in solid tumor or hematopoietic models with direct translational relevance to t(8;21) AML. The experimental models, specific *ZBTB7A* genetic alterations, metabolomic assays, and functional outcomes identified across the selected studies are summarized in Table 1 and illustrated schematically in Figure 1.

ZBTB7A STRUCTURE AND FUNCTION

ZBTB7A—also referred to as POKEMON, FBI-1, LRF, and OCZF—is a transcriptional repressor encoded by the *ZBTB7A* gene located on human chromosome 19p13.3 [21]. The gene produces two transcript variants that encode an identical 584-amino-acid protein with an approximate molecular weight of 86 kDa [22]. ZBTB7A is a member of the BTB/POZ and Krüppel-type (POK) family of transcription factors, which are structurally defined by two conserved functional regions: an N-terminal broad-complex, tramtrack, and bric-à-brac/poxvirus and zinc finger (BTB/POZ) domain (residues 34–101) and a C-terminal array of four Krüppel-like C2H2 zinc finger (ZF) domains (ZF1–ZF4; residues 382–490). The BTB/POZ domain mediates homodimerization, heterodimerization, and the recruitment of transcriptional co-repressor complexes, whereas the C-terminal ZF domains recognize and bind specific promoter DNA sequences to repress target gene transcription [23].

Proper nuclear import of ZBTB7A is governed by a nuclear localization signal (NLS), which is indispensable for its transcriptional regulatory activity [10]. Ren et al. (2023) mapped this NLS to an arginine- and lysine-rich motif located immediately downstream of the fourth ZF domain at residues 497–504 [10]. Like other POK family members such as BCL6 and PLZF, ZBTB7A orchestrates diverse biological processes, most notably lineage commitment in hematopoiesis, tumorigenesis, and cellular energy metabolism [24].

Somatic mutations in ZBTB7A can disrupt its subcellular localization and DNA-binding capacity, thereby abrogating its transcriptional repressor function [13]. Because the C-terminal region harbors both the ZF array and the NLS, truncating mutations upstream of residue 497 eliminate both DNA binding and nuclear targeting. Specifically, the frameshift variant ZBTB7A A175fs and the nonsense variant ZBTB7A R377X, both of which terminate the polypeptide prior to ZF1, exhibit pronounced cytoplasmic mislocalization in U2OS osteosarcoma cells compared with wild-type (WT) ZBTB7A [13,25].

Conversely, missense mutations within the ZF domains preserve the downstream NLS and largely retain normal nuclear localization. In fluorescence localization assays, R402 missense variants (ZBTB7A R402C and ZBTB7A R402H) localized predominantly to the nucleus, with only a minor fraction detected in the cytoplasm compared with truncating mutants [13]. Consistently, the ZF1 missense variants R399L, R402H, and H404R localized to the nucleus in HEK293 cells [15]. Despite intact nuclear import, these ZF1 variants failed to bind the promoter regions of *GLUT3* (*SLC2A3*) and *PFKP*, whereas the N-terminal non-ZF variant P14S retained promoter-binding activity, demonstrating that ZF missense mutations cause loss of function by abolishing DNA recognition rather than altering nuclear localization [15]. An earlier study similarly established that ZBTB7A R399L is defective in binding the *GLUT3*, *PFKP*, and *PKM* promoters [14]. This mechanistic distinction is corroborated by quantitative biophysical DNA-binding analyses reported by Ren et al. (2023), in which DNA-binding affinity was reduced by more

Table 1: Summary of experimental models, *ZBTB7A* genetic alterations, metabolomic assays, and functional consequences across reviewed studies.

Study	Reported / Studied ZBTB7A Alterations	Experimental Models	Key Metabolomic and Functional Assays	Significant Metabolic Consequences of ZBTB7A Loss	Other Phenotypic and Clinical Consequences of ZBTB7A Loss
Liu et al., 2014 [14]	R399L; KD via sh*ZBTB7A* and si*ZBTB7A*	*In silico* (multi-cancer human genome database mining); *in vitro* (MEF, human fibroblasts, HEK293T, M14, SW48, U2OS, and MCF7 cells); *in vivo* (nude mouse xenografts)	Gene expression profiling; glucose uptake and lactate production assays; LC-MS/MS; microarray analysis; luciferase promoter reporter assay; ChIP; cell proliferation and nude mouse subcutaneous xenograft assays with and without 2-DG	Elevated aerobic glycolysis; transcriptional de-repression and overexpression of *GLUT3* (*SLC2A3*), *PFKP*, and *PKM*; increased glucose flux into the PPP	—
Liu et al., 2016 [15]	P14S, S22R, R49H, K60R, D78E, R112C, P184S, Q322L, S326L, S357R, R377L, C387F, I391L, R399L, R402H, T403N, H404R, G406V, P409S, C412Y, K424N, K424T, R430W, T461M, L463M, Y466D, A522T, E541K, G562D, and D576V expressed via pcDNA-*ZBTB7A*; stable expression of ZBTB7A R399L and R402H	*In silico* (multi-cancer human genome database mining); *in vitro* (HEK293 and SW48 colon carcinoma cells); *in vivo* (nude mouse xenografts and PDX)	Gene expression profiling; luciferase promoter reporter assay; glucose uptake and lactate production measurements; ChIP; cell proliferation and nude mouse tumor formation assays with and without 2-DG	Loss or reduction of transcriptional repression of *GLUT3*, *PFKP*, and/or *PKM* (in R49H, P184S, Q322L, C387F, R399L, R402H, T403N, H404R, G406V, P409S, C412Y, K424N, R430W, and Y466D variants); elevated glycolytic flux in ZBTB7A R49H and R399L	Reduced steady-state protein stability in the BTB/POZ domain mutant ZBTB7A R49H
Hartmann et al., 2016 [13]	Patient-derived mutations mapped via IBS software: R49H, S50L, F79L, L85R, P168fs, A175fs, D364X, R377X, G395C, R402H, R402C, and R458fs; functional expression of A175fs, R377X, R402C, and R402H via pcDNA3.1-His-*ZBTB7A*	*In silico* (IBS domain mapping); *in vitro* (primary t(8;21) AML patient blasts, Kasumi-1, U2OS, and HEK293T cells); *in vivo* (murine bone marrow cells)	Whole-exome and targeted amplicon sequencing; gene expression profiling; luciferase promoter reporter assay; immunofluorescence localization; cell proliferation and serial CFC assays	Elevated glycolysis; significant overexpression of *PFKP* (with upward trends in *SLC2A3* and *PKM*) in *ZBTB7A*-mutant t(8;21) AML	Loss of DNA-binding activity and cytoplasmic mislocalization (A175fs, R377X); loss of *ARF* promoter repression; attenuation of antiproliferative activity; low *ZBTB7A* expression associated with inferior clinical outcomes

Redondo Monte et al., 2018 [16]	R402C and A175fs	*In vitro* (primary hCD34$^+$ cells, K562, and HL60 cell lines)	Lentiviral/retroviral hCD34$^+$ transduction and clonal expansion assays; 2-DG glycolysis inhibition assay; flow cytometric granulocytic and monocytic differentiation assays	Heightened sensitivity to pharmacological glycolytic inhibition with 2-DG	Enhanced *RUNX1::ETO*-dependent clonal expansion of hCD34$^+$ cells; impaired erythroid differentiation (decreased CD235a); reduced repression of monocytic differentiation (decreased CD11b and increased CD14)
Redondo Monte et al., 2019 [17]	CRISPR/Cas9-mediated *ZBTB7A* KO (plus primary *ZBTB7A*-mutant t(8;21) AML patient cohort)	*In vitro* (K562 cell line and primary t(8;21) AML patient samples)	RNA-Seq; ChIP-Seq; extracellular flux analysis (ECAR and OCR); etomoxir FAO inhibition assay	Elevated glycolysis and mitochondrial beta-oxidation; direct de-repression of *SLC2A3*; upregulation of glycolytic genes (*PGM2*, *PGM3*, *SLC2A1*, and *ENO2*); upregulation of FAO genes (*ACAA2*, *ACOX1*, *ACSL1*, *ACADVL*, *CPT1A*, and *CPT1B*) and FA desaturase/epoxide hydrolase genes (*EPHX2*, *FADS2*, and *FADS1*); increased sensitivity to FAO inhibition (etomoxir)	—
Redondo Monte et al., 2020 [18,19]	R402C, A175fs, and CRISPR/Cas9-mediated *ZBTB7A* KO	*In vitro* (K562, HL60, Kasumi-1, and primary hCD34$^+$ cells); *in vivo* (PDX)	Myeloid differentiation assays; extracellular metabolic flux analysis; 2-DG drug sensitivity assay; hCD34$^+$ competitive growth and cell cycle analyses	Elevated glycolytic flux via *SLC2A3* de-repression and overexpression of *PGM2*, *PGM3*, *SLC2A1*, and *ENO2*; sensitization to 2-DG glycolysis inhibition	Promotion of monocytic differentiation and blockade of granulocytic/erythroid maturation in HL60 cells; facilitation of *RUNX1::ETO*tr-driven clonal expansion; abrogation of G0/G1 cell cycle arrest
Arfelli et al., 2023 [20]	CRISPR/Cas9-mediated *ZBTB7A* KO	*In vitro* (K562 cell line and primary CBF AML patient transcriptomes); *in vivo* (*RUNX1::ETO* / *ZBTB7A* KO murine model)	Extracellular metabolic flux analysis; stable-isotope metabolic tracing; palmitate oxidation assay; etomoxir FAO inhibition assay; RNA-Seq	Upregulation of *FASN*, de novo palmitate synthesis, and acetoacetate (ketone body) synthesis; upregulation of glycolysis and PPP; downregulation of mitochondrial ETC genes and ketolysis genes (*HMGCS1* and *ACAT1*); lack of dependence on OXPHOS or exogenous FAO	Accelerated leukemogenesis in *RUNX1::ETO* / *ZBTB7A*-KO mice with 100% leukemia penetrance

Literature search results encompassing *in silico*, *in vitro*, and *in vivo* studies investigating the metabolic and hematopoietic consequences of somatic *ZBTB7A* loss-of-function mutations, knockdown (KD), or knockout (KO) in t(8;21) acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and solid tumor models up to December 2025. A dash (—) indicates that non-metabolic phenotypic outcomes were not reported in the corresponding study. **Abbreviations**: 2-DG, 2-deoxy-D-glucose; AML, acute myeloid leukemia; CBF, core-binding factor; CFC, colony-forming cell; ChIP, chromatin immunoprecipitation; ChIP-Seq, chromatin immunoprecipitation sequencing; ECAR, extracellular acidification rate; ETC, electron transport chain; FA, fatty acid; FAO, fatty acid oxidation; fs, frameshift mutation; GLUT3, glucose transporter 3; hCD34$^+$, human CD34-positive hematopoietic stem and progenitor cells; IBS, Illustrator of Biological Sequences; KD, knockdown; KO, knockout; LC-MS/MS, liquid chromatography–tandem mass spectrometry; MEF, mouse embryonic fibroblast; OCR, oxygen consumption rate; OXPHOS, oxidative phosphorylation; PDX, patient-derived xenograft; PFKP, platelet-type phosphofructokinase; PKM, pyruvate kinase M1/2; PPP, pentose phosphate pathway; RNA-Seq, RNA sequencing; shZBTB7A, short hairpin RNA targeting ZBTB7A; siZBTB7A, small interfering RNA targeting ZBTB7A; X, nonsense (stop-gain) mutation

than 50-fold for R402C and more than 12-fold for G395C (both within ZF1), by approximately 5- to 6-fold for R402H (ZF1) and K424T (ZF2), and by approximately 4-fold for the frameshift variant R458fs (within ZF3)[10]. Notably, R458fs exhibited the mildest intrinsic DNA-binding defect among the tested mutants but lacked the downstream NLS, underscoring that cytoplasmic mislocalization is a specific consequence of NLS loss rather than a general feature of ZF domain mutations.

ZBTB7A MUTATIONS: INCIDENCE AND CLINICAL CONSEQUENCES IN t(8;21) AML

Somatic *ZBTB7A* mutations show a striking specificity for t(8;21) AML. Hartmann et al. (2016) identified ZBTB7A mutations in 23.2% (13/56) of patients with t(8;21) AML[13]. In that cohort, a numerically higher proportion of patients with mutated ZBTB7A experienced disease relapse (4/13; 30.8%) compared with patients harboring WT *ZBTB7A* (5/43; 11.6%); however, this difference did not reach statistical significance (Fisher's exact test, p = 0.189; odds ratio 3.38, 95% confidence interval 0.75–15.17) and warrants validation in larger prospective cohorts. By contrast, within the other major CBF AML subtype—inv(16) AML—only 1 of 22 patients (4.5%) harbored a *ZBTB7A* mutation, and no *ZBTB7A* mutations were detected among patients with CN-AML (n = 50) or non-CBF AML (n = 14)[13].

Independent cohorts have confirmed this subtype specificity. In a Japanese study of patients with CBF AML enrolled in the JALSG AML201 trial, *ZBTB7A* mutations occurred exclusively in the t(8;21) subgroup, accounting for 9.8% (4/41) of cases[26]. Similarly, integrative multi-omics profiling revealed an enrichment of ZBTB7A mutations among high-risk t(8;21) AML patients exhibiting aberrant leukemic stem and progenitor gene expression signatures[27]. Furthermore, Lavallée et al. (2016) identified novel somatic ZBTB7A mutations in 15.0% (3/20) of patients with t(8;21) AML, whereas none were observed in inv(16) AML or non-CBF AML control cohorts; notably, patients carrying frameshift ZBTB7A alleles also displayed the lowest *ZBTB7A* transcript levels[28].

CONTEXT-DEPENDENT ROLES OF ZBTB7A IN HUMAN MALIGNANCIES

Although originally designated as an oncogene in certain solid tumors, ZBTB7A exhibits context-dependent functions as either a tumor promoter or a tumor suppressor depending on tissue lineage. In breast cancer cell lines and clinical tumor specimens, ZBTB7A is frequently overexpressed and promotes cellular migration, invasion, and metastasis via NF-κB-mediated epithelial–mesenchymal transition[29,30]. Elevated ZBTB7A expression is likewise associated with shorter overall survival in patients with colorectal cancer, where it enhances *in vitro* cell proliferation and *in vivo* xenograft tumorigenicity[31]. Conversely, compelling evidence establishes ZBTB7A as a bona fide tumor suppressor in endometrial and myeloid malignancies. In uterine corpus endometrial carcinoma (UCEC), downregulation of ZBTB7A accelerates cancer cell proliferation and migration *in vitro* and correlates with poorer clinical prognosis[32]. In the hematopoietic compartment, knockdown of ZBTB7A in mononuclear cells derived from healthy mobilized peripheral blood delays terminal erythroid maturation[33]. Crucially, this erythroid differentiation block cooperates directly with RUNX1::ETO in murine leukemogenesis: Arfelli et al. (2023) reported that conditional *ZBTB7A* knockout (KO) in *RUNX1::ETO*-expressing mice resulted in 100% penetrance of acute leukemia[20]. The spectrum of somatic loss-of-function (LOF) *ZBTB7A* mutations compiled from the literature and their domain distribution are depicted in Figure 1.

Functionally, WT ZBTB7A counteracts RUNX1::ETO-driven hematopoietic stem and progenitor cell (HSPC) expansion. In human $CD34^+$ ($hCD34^+$) cells transduced with a C-terminally truncated, leukemogenic isoform of RUNX1::ETO *(RUNX1::ETOtr)*, co-expression of WT ZBTB7A completely abrogated clonal expansion[18]. By contrast, co-expression of LOF *ZBTB7A* mutants (ZBTB7A R402C or ZBTB7A A175fs) failed to restrain *RUNX1::ETO*tr-driven clonal outgrowth. Moreover, ectopic expression of WT *ZBTB7A* in both the t(8;21)-positive Kasumi-1 cell line and primary $hCD34^+$ cells induced cell cycle arrest, increasing the proportion of cells in the G0/G1 phase and reducing the S-phase fraction relative to ZBTB7A-mutant cells[18]. With respect to myeloid lineage commitment, WT ZBTB7A promotes granulopoiesis while repressing monocytic differentiation. Loss-of-function mutations in ZBTB7A abolish this lineage control and cooperate with RUNX1::ETO to block granulocytic maturation, accompanied by upregulated surface CD14 expression indicative of monocytic skewing[16,18].

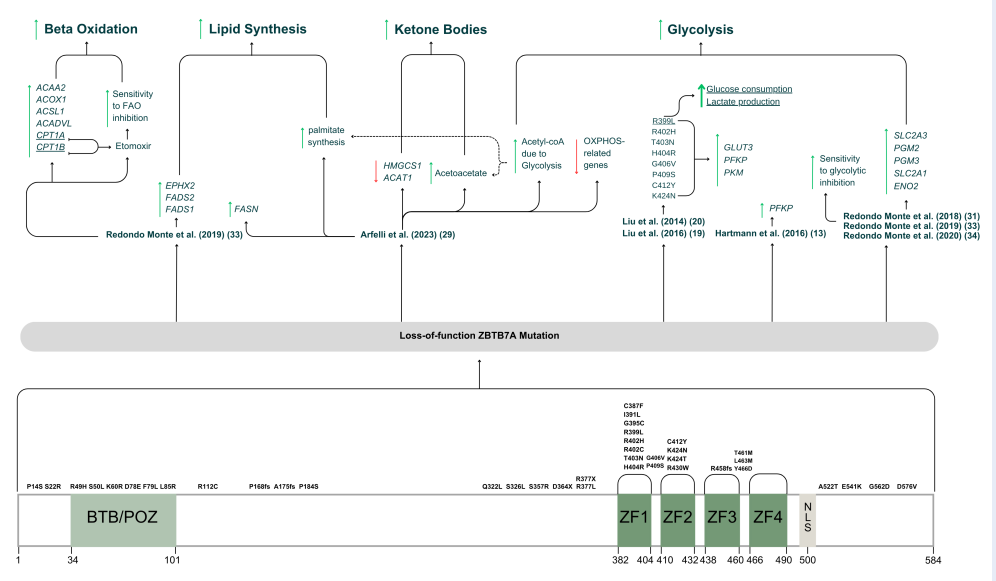


Figure 1: **Structural distribution of loss-of-function *ZBTB7A* mutations and their downstream metabolic consequences in myeloid leukemia and solid tumor models.** The lower schematic illustrates the linear domain architecture of the 584-amino-acid human ZBTB7A protein, comprising the N-terminal BTB/POZ protein–protein interaction domain (amino acids 34–101), four C-terminal Krüppel-like C2H2 zinc finger DNA-binding domains—ZF1 (amino acids 382–404), ZF2 (amino acids 410–432), ZF3 (amino acids 438–460), and ZF4 (amino acids 466–490)—and the C-terminal nuclear localization signal (NLS; approximately amino acids 497–504). Somatic missense, nonsense (X), and frameshift (fs) mutations identified across clinical cohorts and experimental studies are mapped above their corresponding structural regions, showing mutational clustering within ZF1 and ZF2. The upper schematic summarizes the four principal metabolic pathways reprogrammed following *ZBTB7A* loss-of-function mutation or genetic knockout across key studies: **(i) Beta Oxidation (left):** Upregulation of mitochondrial and peroxisomal fatty acid oxidation (FAO) genes (*ACAA2*, *ACOX1*, *ACSL1*, *ACADVL*, *CPT1A*, and *CPT1B*) in *ZBTB7A*-deficient myeloid leukemia cells, conferring heightened sensitivity to the carnitine palmitoyltransferase 1 (CPT1A/CPT1B) inhibitor etomoxir (Redondo Monte et al., 2019)[17]. **(ii) Lipid Synthesis (center-left):** Transcriptional upregulation of polyunsaturated fatty acid metabolism genes (*EPHX2*, *FADS2*, and *FADS1*) and fatty acid synthase (*FASN*), driving de novo palmitate synthesis from glycolytic acetyl-CoA (Redondo Monte et al., 2019; Arfelli et al., 2023)[17,20]. **(iii) Ketone Bodies (center-right):** Diversion of excess glycolytic acetyl-CoA toward acetoacetate production accompanied by downregulation of ketogenic/ketolytic enzymes (*HMGCS1* and *ACAT1*) (Arfelli et al., 2023)[20]. **(iv) Glycolysis (right):** Loss of ZBTB7A-mediated transcriptional repression of key glucose transporters and glycolytic enzymes (*GLUT3*/*SLC2A3*, *PFKP*, *PKM*, *PGM2*, *PGM3*, *SLC2A1*, and *ENO2*) across ZF1/ZF2 missense mutants (R399L, R402H, T403N, H404R, G406V, P409S, C412Y, and K424N) and truncating/knockout models, resulting in increased glucose consumption, elevated lactate production, downregulation of oxidative phosphorylation (OXPHOS)-related genes, and heightened sensitivity to pharmacological glycolytic inhibition (Liu et al., 2014; Liu et al., 2016; Hartmann et al., 2016; Redondo Monte et al., 2018, 2019, 2020; Arfelli et al., 2023)[13–20]. **Symbols and conventions:** Upward green arrows (↑) indicate increased gene expression, metabolite production, or drug sensitivity; downward red arrows (↓) denote decreased gene expression; solid black arrows indicate experimental findings and regulatory pathways; dashed black arrows represent metabolic flux of glycolytic acetyl-CoA into acetoacetate and palmitate synthesis; and blunted bars (⊥) indicate pharmacological inhibition of CPT1A and CPT1B by etomoxir. **Abbreviations:** BTB/POZ, broad-complex, tramtrack, and bric-à-brac/poxvirus and zinc finger domain; FAO, fatty acid oxidation; fs, frameshift mutation; NLS, nuclear localization signal; OXPHOS, oxidative phosphorylation; X, nonsense (stop-gain) mutation; ZF1–ZF4, zinc finger domains 1–4.

ZBTB7A MUTATIONS AND METABOLIC REPROGRAMMING

The experimental designs, studied ZBTB7A variants, and metabolic phenotypes reported across the reviewed literature are detailed in Table 1 and integrated in Figure 1.

ZBTB7A Mutations and Glucose Metabolism in Solid Tumors

Because multiple rate-limiting glycolytic genes are direct transcriptional targets of ZBTB7A, somatic ZBTB7A inactivation profoundly alters cellular glucose utilization and downstream biosynthetic path-

ways. Liu et al. (2014) first elucidated the glycolytic repressor function of ZBTB7A in solid tumor models, demonstrating in U2OS osteosarcoma cells and mouse embryonic fibroblasts that ZBTB7A directly binds the promoter regions and represses the transcription of three critical glycolytic genes: *GLUT3* (*SLC2A3*), *PFKP*, and *PKM*[14].

Subsequent functional screening of cancer-associated somatic ZBTB7A variants revealed that missense mutations clustering within ZF1 (R399L, R402H, T403N, and H404R) and ZF2 (K424N) completely abolish transcriptional repression of *GLUT3*, *PFKP*, and *PKM*[15]. Mechanistically, these mutant ZBTB7A proteins form heterodimers with WT ZBTB7A and act in a dominant-negative manner to impair promoter repression despite unchanged total protein abundance[15]. Consequently, colon carcinoma cells expressing ZBTB7A R399L exhibited significantly elevated glucose uptake, lactate secretion, and flux into the pentose phosphate pathway (PPP), which accelerated xenograft tumor growth in mice while rendering the tumor cells hypersensitive to pharmacological glycolysis inhibition with 2-deoxy-D-glucose (2-DG)[14,15].

ZBTB7A Mutations and Glucose Metabolism in t(8;21) AML

Hartmann et al. (2016) extended these findings to human t(8;21) AML, demonstrating that genetic inactivation of *ZBTB7A* is associated with significantly elevated *PFKP* transcript levels in primary t(8;21) AML patient samples compared with *ZBTB7A*-WT t(8;21) AML cases, alongside a similar upward trend in *SLC2A3* and *PKM* expression[13]. In t(8;21)-positive Kasumi-1 cells, retroviral restoration of WT *ZBTB7A* exerted a potent antiproliferative effect that was completely abolished by the truncating A175fs mutation and partially attenuated by the missense R402C mutation[13]. Furthermore, in serial colony-forming cell (CFC) assays using murine bone marrow cells co-expressing *RUNX1::ETO* and either WT or mutant ZBTB7A, the A175fs and R402C variants significantly increased primary colony numbers, indicating that *ZBTB7A* inactivation enhances leukemic self-renewal and stemness[13,34].

Subsequent investigations by Redondo Monte et al. (2018, 2019, 2020) demonstrated that ZBTB7A-deficient myeloid leukemia cells exhibit marked glycolytic dependency alongside heightened metabolic plasticity under stress[16–19]. While WT ZBTB7A restricts RUNX1::ETO-driven clonal expansion, ZBTB7A loss confers a competitive proliferative advantage to myeloid progenitors by upregulating glycolytic ATP and biomass production[16,18]. In chronic myeloid leukemia (CML)-derived K562 cells, CRISPR/Cas9-mediated ZBTB7A KO resulted in pronounced de-repression of *SLC2A3* and significant upregulation of additional glycolytic enzymes, including PGM2, PGM3, SLC2A1, and ENO2, whereas *PKM* and *PFKP* levels were not significantly altered in this specific cellular background[16–18]. Functionally, ZBTB7A KO cells displayed an elevated extracellular acidification rate (ECAR), reflecting enhanced aerobic glycolysis—a classic manifestation of the Warburg effect[16,35]. Notably, this glycolytic surge became even more pronounced upon pharmacological inhibition of the mitochondrial electron transport chain (ETC), indicating that *ZBTB7A* loss enables leukemic cells to thrive under hypoxic conditions characteristic of the bone marrow microenvironment[16]. This phenotype aligns with biochemical evidence showing that ZBTB7A heterodimerizes with ZBTB2 to inhibit ZBTB2 homodimerization, a step required for full hypoxia-inducible factor 1 (HIF-1) transcriptional activation[36]. Consequently, loss of ZBTB7A relieves inhibition of the ZBTB2–HIF-1 axis, reinforcing glycolytic adaptation and leukemic survival under hypoxia.

Interestingly, when subjected to acute glucose deprivation, *ZBTB7A* KO K562 cells exhibited an approximately 1.5-fold higher oxygen consumption rate (OCR) than ZBTB7A-WT control cells[16,17]. This observation suggests that *ZBTB7A*-deficient cells retain the capacity to rewire their energy metabolism toward alternative mitochondrial substrates—such as fatty acids (FAs) or glutamine/glutamate—when extracellular glucose becomes limiting. Nevertheless, treatment with the glycolytic inhibitor 2-DG significantly suppressed the long-term proliferation of ZBTB7A-mutant and *ZBTB7A*-KO cells relative to controls[16,18]. Arfelli et al. (2023) similarly noted transcriptional upregulation of both glycolysis and the PPP in *ZBTB7A*-KO K562 cells[20]. Collectively, despite cell line-specific variations in individual target gene expression, current evidence establishes transcriptional repression of glycolysis as a central mechanism underlying the tumor suppressor activity of ZBTB7A in t(8;21) AML.

ZBTB7A and Lipid Metabolism in t(8;21) AML

Although fewer studies have examined the role of ZBTB7A in lipid homeostasis, emerging evidence

indicates that *ZBTB7A* loss substantially remodels leukemic lipid metabolism. Redondo Monte et al. (2019) reported that ZBTB7A KO in K562 cells upregulates multiple genes governing FA metabolism and mitochondrial beta-oxidation[17]. Chromatin immunoprecipitation sequencing (ChIP-Seq) and transcriptomic profiling identified *ACAA2*, *ACOX1*, *ACADVL*, and *CPT1A* as direct ZBTB7A target genes, alongside elevated expression of *ACSL1* and *CPT1B*[17]. Pharmacological inhibition of carnitine palmitoyltransferase 1 (CPT1A and CPT1B)—the rate-limiting step in mitochondrial fatty acid oxidation (FAO)—using etomoxir revealed that *ZBTB7A*-KO cells were significantly more sensitive to FAO blockade, exhibiting a 50% reduction in the half-maximal inhibitory concentration (IC_{50}) compared with WT controls[17,37]. Consistent with these *in vitro* findings, RNA sequencing (RNA-Seq) of primary t(8;21) AML patient samples harboring *ZBTB7A* mutations demonstrated significant overexpression of unsaturated FA metabolism genes, including *EPHX2*, *FADS2*, and *FADS1*[17]; notably, elevated *FADS1* expression independently correlates with inferior overall survival in AML[38]. Furthermore, under combined glucose- and glutamate-deprived conditions, ZBTB7A-KO cells displayed elevated mitochondrial oxygen consumption, supporting an increased reliance on endogenous FAO under nutrient stress[17].

Conversely, Arfelli et al. (2023) reported divergent findings regarding FAO dependency in ZBTB7A-KO K562 cells, despite employing the same cellular model[20]. First, stable isotope-resolved palmitate oxidation assays indicated that ZBTB7A-KO cells did not preferentially oxidize exogenous palmitate, even under glutamate-depleted conditions, and did not exhibit heightened sensitivity to etomoxir treatment compared with WT controls[20]. Second, transcriptomic and flux analyses suggested that ZBTB7A-KO cells are largely independent of mitochondrial oxidative phosphorylation (OXPHOS), as multiple ETC subunit genes were downregulated[20]. Instead, excess glycolytic acetyl-CoA generated by *ZBTB7A*-deficient cells was channeled into de novo lipogenesis—specifically palmitate synthesis—driven by marked upregulation of fatty acid synthase (FASN), a signature also confirmed in CBF AML patients harboring ZBTB7A mutations[20]. Third, *ZBTB7A*-KO cells diverted surplus glycolytic acetyl-CoA toward ketogenesis, accumulating and secreting acetoacetate into the extracellular medium without utilizing ketone bodies for intracellular ATP production or lipid synthesis, consistent with the concurrent downregulation of *HMGCS1* and *ACAT1*[20].

Taken together, while Redondo Monte et al. (2019) observed transcriptional de-repression of beta-oxidation enzymes and increased sensitivity to etomoxir under nutrient stress[17], Arfelli et al. (2023) demonstrated a metabolic shift toward aerobic glycolysis, de novo palmitate synthesis, and ketogenesis independent of FAO and OXPHOS under standard culture conditions[20]. These apparent discrepancies likely reflect differences in extracellular nutrient availability, passage conditions, or assay readouts (endogenous vs. exogenous palmitate oxidation). Crucially, however, both studies converge on the finding that ZBTB7A loss upregulates de novo lipid biosynthesis, a process essential for membrane biogenesis, signaling, and leukemic proliferation[17,20,39]. It should be noted that the studies by Redondo Monte et al. (2018, 2019), Arfelli et al. (2023), and Liu et al. (2024) were published as conference abstracts rather than full peer-reviewed articles[16,17,20,27]; their mechanistic conclusions should therefore be interpreted as preliminary pending full peer-reviewed publication. Future targeted lipidomic and fluxomic investigations across primary t(8;21) AML blasts are warranted to delineate how microenvironmental nutrient gradients shape lipid metabolic dependencies in ZBTB7A-mutant leukemia.

ZBTB7A MUTATIONS WITHIN THE BROADER MUTATIONAL AND METABOLIC LANDSCAPE OF t(8;21) AML

In clinical cohorts of t(8;21) AML, somatic mutations in signaling pathway genes—most notably *KIT*, *NRAS*, *KRAS*, *FLT3*, and *JAK2*—represent the most frequent co-occurring genetic lesions alongside RUNX1::ETO[40,41]. Just as RUNX1::ETO requires cooperating mutations to induce overt leukemia[2,3], ZBTB7A inactivation likely interacts with co-occurring signaling and epigenetic mutations to orchestrate global metabolic reprogramming in t(8;21) AML. For example, KIT mutations are the most prevalent secondary alterations in both adult and pediatric t(8;21) AML and are strongly associated with higher relapse rates and inferior overall and progression-free survival[42,43]. Beyond proliferative signaling, aberrant KIT activation promotes glutaminolysis, which depletes microenvironmental glutamine to suppress anti-tumor T-cell proliferation and enhance the immunosuppressive activity of

myeloid-derived suppressor cells[44]. Similarly, recurrent mutations in *EZH2*, *NRAS*, *TET2*, and *JAK3* identified in relapsed or refractory RUNX1::RUNX1T1 AML have been linked to distinct alterations in lipid metabolism and glycolytic flux[45]. Elucidating the combinatorial metabolic effects of ZBTB7A loss alongside co-occurring KIT, RAS, or epigenetic mutations represents a priority for future multi-omics research in t(8;21) AML.

CONCLUSION

Somatic loss-of-function mutations in ZBTB7A represent a recurrent, subtype-enriched genetic lesion in t(8;21) AML that disrupts the transcriptional repression of key enzymes governing glycolysis and lipid metabolism. By de-repressing glycolytic regulators (SLC2A3, PFKP, and *PKM*) and upregulating de novo lipogenesis, beta-oxidation, and ketogenesis, ZBTB7A inactivation confers metabolic flexibility and a survival advantage to leukemic stem and progenitor cells within the hypoxic bone marrow microenvironment. Acting in concert with the *RUNX1::ETO* fusion oncoprotein, loss of ZBTB7A reinforces myeloid differentiation arrest and accelerates clonal expansion. Importantly, this metabolic rewiring creates actionable therapeutic vulnerabilities, rendering *ZBTB7A*-deficient leukemic cells hypersensitive to pharmacological inhibitors of glycolysis (such as 2-deoxy-D-glucose) and lipid metabolism (such as etomoxir). Targeted inhibition of these dysregulated metabolic nodes holds considerable promise for improving therapeutic outcomes in patients with *ZBTB7A*-mutant t(8;21) AML.

DECLARATIONS

Abbreviations

- **2-DG:** 2-deoxy-D-glucose
- **AML:** Acute myeloid leukemia
- **BTB:** Broad-complex, tramtrack, and bric-à-brac
- **CBF:** Core-binding factor
- **CFC:** Colony-forming cell
- **ChIP:** Chromatin immunoprecipitation
- **ChIP-Seq:** Chromatin immunoprecipitation sequencing
- **CI:** Confidence interval
- **CML:** Chronic myeloid leukemia
- **CN-AML:** Cytogenetically normal acute myeloid leukemia
- **CPT1:** Carnitine palmitoyltransferase 1
- **ECAR:** Extracellular acidification rate
- **ETC:** Electron transport chain
- **FA:** Fatty acid
- **FAO:** Fatty acid oxidation
- **FASN:** Fatty acid synthase
- **fs:** Frameshift mutation
- **GLUT3:** Glucose transporter 3
- **hCD34$^+$:** Human CD34-positive hematopoietic stem and progenitor cells
- **HIF-1:** Hypoxia-inducible factor 1
- **HSPC:** Hematopoietic stem and progenitor cell
- **IBS:** Illustrator of Biological Sequences
- **IC_{50}:** Half-maximal inhibitory concentration
- **KD:** Knockdown
- **KO:** Knockout
- **LC-MS/MS:** Liquid chromatography–tandem mass spectrometry
- **LOF:** Loss-of-function
- **LRF:** Leukemia/lymphoma-related factor
- **MEF:** Mouse embryonic fibroblast
- **NLS:** Nuclear localization signal
- **OCR:** Oxygen consumption rate
- **OXPHOS:** Oxidative phosphorylation
- **PDX:** Patient-derived xenograft
- **PFKP:** Platelet-type phosphofructokinase
- **PKM:** Pyruvate kinase M1/2
- **POK:** BTB/POZ and Krüppel-type
- **POZ:** Poxvirus and zinc finger
- **PPP:** Pentose phosphate pathway
- **RNA-Seq:** RNA sequencing
- **shRNA:** Short hairpin RNA
- **siRNA:** Small interfering RNA
- **SLC2A3:** Solute carrier family 2 member 3
- **UCEC:** Uterine corpus endometrial carcinoma
- **WT:** Wild type
- **X:** Nonsense (stop-gain) mutation
- **ZBTB7A:** Zinc finger and BTB domain-containing protein 7A
- **ZF:** Zinc finger

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Author's contributions

Zainul Abeden: Conceptualization, Methodology, Literature search, Data curation, Visualization, Writing – original draft. Muhamad Amir Azizan, Mohammad Syamsul Reza Harun, Mohd Nazri Ismail, and Fadly Ahid: Literature analysis, Validation, Writing – review and editing. Asmida Isa: Conceptualization, Supervision, Funding acquisition, Project administration, Writing – review and editing. All authors read and approved the final manuscript.

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