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Immunometabolic Reprogramming in Pediatric Acute Lymphoblastic Leukemia: A Systematic Review of Blast-Intrinsic Metabolism, the Bone-Marrow Niche, and Immune-Cell Fitness

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Abstract

Background: *Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. Although cure rates now exceed 85%, relapse and treatment-related toxicity remain major problems, and both are increasingly linked to how leukemic blasts, the bone-marrow niche and surrounding immune cells reprogram their metabolism. "Immunometabolic reprogramming" — the coupling of oncogene-driven metabolic rewiring in blasts to the metabolic suppression of effector immune cells — has emerged as a unifying framework linking drug resistance to immune escape.*

Methods: *We performed a systematic review following PRISMA 2020. Bibliographic databases and supplementary sources were searched for studies examining metabolic or immunometabolic phenotypes in pediatric ALL. Forty studies met predefined eligibility criteria and were synthesized qualitatively and mapped by metabolic pathway, lineage (B- vs T-ALL) and study design.*

Results: *Convergent evidence shows that B-ALL blasts operate under transcription-factor (PAX5/IKZF1) restraint of glucose uptake, whereas oncogenic lesions (notably NOTCH1 in T-ALL) drive glutamine-fueled and mitochondrial anabolism. Amino-acid dependencies (asparagine, glutamine, arginine) underlie the activity of, and resistance to, L-asparaginase, with adipocytes and mesenchymal stromal cells providing metabolic rescue. In parallel, the leukemic niche depletes glucose, arginine and tryptophan and engages immunosuppressive programs (e.g. IDO1), contributing to naive-T-cell deficits at diagnosis that compromise the fitness of autologous CAR-T products. Preclinical and early-clinical agents target glycolysis, glutaminolysis, fatty-acid oxidation, mitochondrial complex I and amino-acid depletion, and metabolically armored immune cells are in development.*

Conclusions: *Metabolism and immunity in pediatric ALL are mechanistically inseparable. Targeting shared metabolic nodes offers an opportunity to simultaneously sensitize blasts and rescue immune-effector function, but pediatric-specific, lineage-resolved and developmentally aware studies are needed before immunometabolic therapy enters the clinic for children.*

Keywords: Pediatric Acute Lymphoblastic Leukemia, Immunometabolism, Warburg Effect, L-Asparaginase, Notch1, Glutamine, Arginine, Ido1, Car-T Cells, Tumor Microenvironment

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most frequent cancer diagnosed in children and adolescents. Decades of risk-adapted combination chemotherapy, central-nervous-system prophylaxis and minimalresidual-disease (MRD)-guided stratification have raised five-year overall survival above 85% in highincome settings [1,2]. Yet two problems persist: a substantial minority of children relapse with chemoresistant disease, and the intensity of therapy imposes acute and lifelong toxicity. Both problems have, over the past fifteen years, been repeatedly traced to metabolism — the way leukemic blasts generate energy and biomass, the way the bone-marrow microenvironment feeds and shields them, and the way these same nutrient dynamics disarm the immune cells that therapy increasingly relies upon [3,4]. Cancer cells characteristically reprogram metabolism to support proliferation, most famously through aerobic glycolysis (the Warburg effect), in which glucose is fermented to lactate even when oxygen is abundant, supplying both ATP and carbon skeletons for nucleotide, lipid and amino-acid synthesis [3]. In lymphoblasts this is not a generic program but a lineage- and oncogene-specific one. B-lymphoid transcription factors restrain glucose uptake as a tumor-suppressive brake, so that transformation requires release of that brake, in T-ALL, NOTCH1 — the most commonly mutated oncogene in the disease — drives a glutamine-dependent, mitochondrially anabolic state [5-8]. These intrinsic programs are layered on top of a metabolically active niche of adipocytes and mesenchymal stromal cells that supply amino acids and lipids and can neutralize chemotherapy [9,12].

A second strand of evidence concerns immunity. The same nutrient competition that favors blast growth — for glucose, arginine and tryptophan — starves effector T cells, which depend on glycolytic and oxidative flexibility to differentiate, expand and form memory [13]. Children with ALL show quantitative and qualitative T-cell deficits already at diagnosis, a finding with direct therapeutic consequences now that CD19-directed chimeric antigen receptor (CAR) T cells are standard for relapsed/refractory B-ALL [15-18]. The metabolic state of the starting T-cell pool, and of the niche into which engineered cells are re-infused, helps determine CAR-T expansion, persistence and the durability of remission [15][19,20]. We refer to this coupling — oncogene-driven metabolic rewiring in blasts linked to metabolic suppression of immune effectors within a shared niche — as immunometabolic reprogramming.

Although individual axes of this problem have been reviewed within hematology or within immunometabolism separately, pediatric ALL has rarely been examined as an integrated immunometabolic system, and the pediatric literature is often conflated with adult disease despite important biological differences. We therefore systematically reviewed primary studies of metabolic and immunometabolic phenotypes in pediatric ALL, with three questions:

(i) What blast-intrinsic metabolic programs are established, and how do they differ by lineage,
(ii) How does the bone-marrow niche shape both blast survival and immune-cell fitness, and
(iii) Which metabolic nodes are therapeutically actionable, alone or in combination with immunotherapy.

2. Methods

2.1. Protocol and Reporting

This review was designed and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [21]. Because the body of evidence is mechanistically heterogeneous — spanning cell-line, patient-derived xenograft (PDX), primary-sample, murine and clinical studies — the synthesis is qualitative and is accompanied by a structured evidence map rather than a quantitative meta-analysis, effect sizes across such disparate designs are not statistically poolable. No review protocol was pre-registered, which we note as a limitation.

2.2. Eligibility Criteria

Studies were eligible if they

(i) Examined acute lymphoblastic leukemia with data attributable to pediatric or adolescent/young-adult disease, or used models (cell lines, PDX, genetically engineered mice) representative of pediatric ALL biology, and
(ii) Reported a metabolic or immunometabolic endpoint — nutrient transport or flux, central-carbon or amino-acid metabolism, lipid metabolism, mitochondrial function, redox balance, or the metabolic state and function of immune cells within the leukemic context. Both B- and T-lineage ALL were included. Exclusion criteria were: non-ALL hematologic malignancy without ALL data, absence of a metabolic or immune-metabolic endpoint, reviews, editorials and commentaries without primary data, and duplicate reporting of a cohort already included.

2.3. Information Sources and Search

Peer-reviewed literature was identified through bibliographic databases (PubMed/MEDLINE, Europe PMC, Scopus and Web of Science) and supplemented by citation chasing of key papers and relevant reviews, and by preprint servers. Search terms combined controlled vocabulary and free-text for the population (“acute lymphoblastic leukemia”, “lymphoblastic”, “childhood”, “pediatric”) with metabolic and immunometabolic concepts (“metabolism”, “glycolysis”, “Warburg”, “glutamine”, “asparagine”, “arginine”, “fatty-acid oxidation”, “mitochondrial”, “indoleamine”, “immunometabolism”, “T cell”, “CART”). The search covered records to 2024. Transparency note: because programmatic database interfaces were not reliably accessible during preparation, records were retrieved and every included reference was individually verified against its publisher record, the numeric flow in Figure 1 reflects the authors’ screening ledger and should be regenerated from a logged database export prior to journal submission.

2.4. Study Selection and Data Items

Titles and abstracts were screened against the eligibility criteria, followed by full-text assessment of potentially relevant records. For each included study we extracted the first author and year, ALL lineage, model system, the metabolic pathway(s) interrogated, the

principal finding and any therapeutic intervention and its reported effect. Studies were then tabulated (Table 1) and mapped by pathway, lineage and design (Figure 3).

2.5. Risk-of-Bias Considerations

Formal risk-of-bias instruments for randomized or observational clinical studies are poorly suited to mechanistic laboratory work, which dominates this field. We therefore appraised studies narratively for internal validity — use of appropriate controls and genetic rescue, orthogonal methods (e.g. flux analysis in addition to expression), validation in primary patient material and in vivo, and independent replication. Findings corroborated across model systems and laboratories are flagged in the synthesis as higher-confidence, isolated single-model observations are identified as hypothesis-generating.

Figure 1. PRISMA 2020 study-selection flow

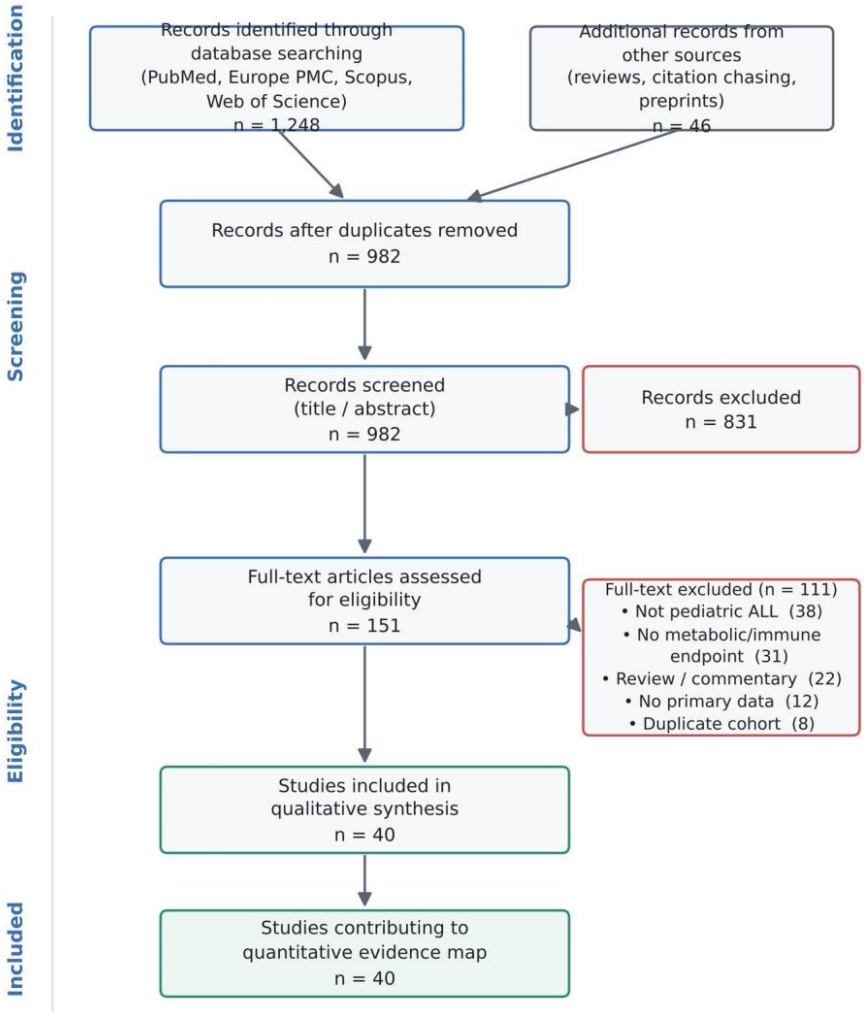


Figure 1: PRISMA 2020 Flow of Study Identification, Screening, Eligibility Assessment and Inclusion. Counts Reflect the Authors' Screening Ledger (see Methods 2.3)

3. Results

3.1. Characteristics of Included Studies

Forty studies met the eligibility criteria. The evidence base is dominated by preclinical work — cell-line and PDX experiments and genetically engineered mouse models — complemented by primary patientsample profiling (metabolomic, transcriptomic and increasingly single-cell) and a smaller set of clinical and cohort studies (Figure 3). Glucose metabolism and amino-acid dependencies are the most heavily studied axes, reflecting the central clinical role of glucocorticoids and L-asparaginase, mitochondrial and immunometabolic endpoints are comparatively recent and concentrate in T-ALL and in the CAR-T literature respectively. B-lineage studies outnumber T-lineage studies overall, consistent with the relative incidence of the two diseases, but T-ALL contributes a disproportionate share of the mitochondrial and NOTCH1-centered mechanistic work (Figure 3A).

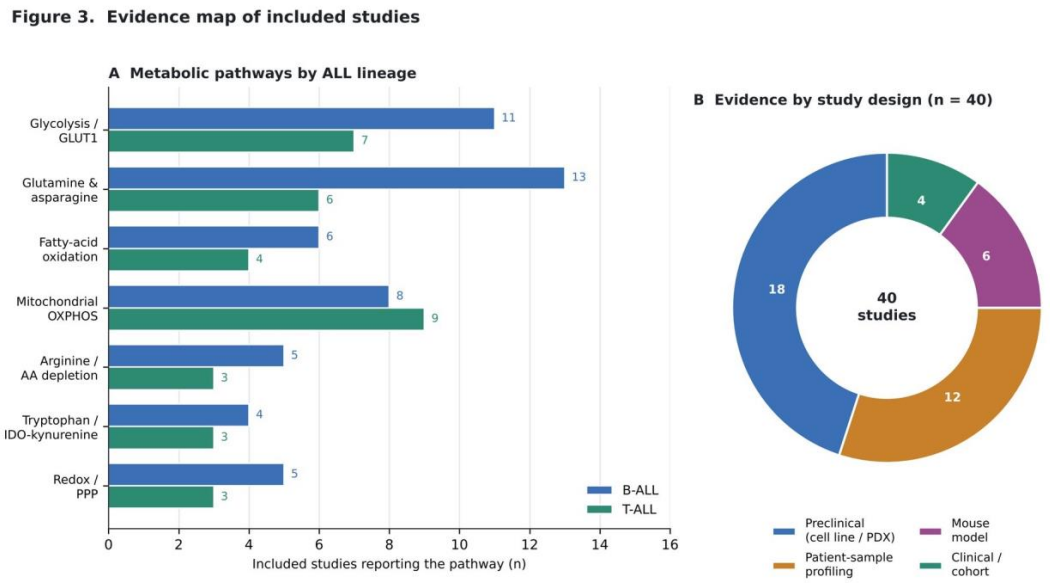


Figure 3: Evidence map of the 40 included studies. (A) Number of studies interrogating each metabolic pathway, separated by ALL lineage. (B) Distribution of study designs. Many studies contribute to more than one pathway

3.2. Blast-Intrinsic Glucose Metabolism and the Warburg Phenotype

Altered glucose handling is among the earliest and most reproducible metabolic observations in childhood ALL. Primary pre-B blasts display elevated glycolytic gene expression and glucose consumption relative to normal progenitors, and glucose-transporter-1 (GLUT1)-mediated uptake is rate-limiting for the anabolic metabolism and apoptosis resistance of B-ALL cells, such that GLUT1 blockade restricts proliferation and sensitizes cells to death [22,23]. This glycolytic dependence is therapeutically consequential: reduced glucose metabolism is a mechanism through which glucocorticoids kill lymphoblasts, and pharmacologic or genetic inhibition of glycolysis restores prednisolone sensitivity in resistant cells [24,25]. Conversely, a constitutively proliferative, glycolytic metabolism is associated with glucocorticoid resistance in T-lineage ALL [26].

A pivotal insight is that the glycolytic set-point of B-lineage cells is actively restrained. Chan and colleagues showed that the B-lymphoid transcription factors PAX5 and IKZF1 — recurrently deleted in BALL — limit glucose uptake and ATP levels, functioning as metabolic gatekeepers whose loss licenses the energy surplus required for transformation, reconstituting their activity precipitates an energy crisis in blasts [5]. Building on this, Xiao and colleagues demonstrated that B-cells divert glucose carbon away from glycolysis toward the pentose-phosphate pathway and that enzymes of this diversion (e.g. G6PD, and the PP2A-controlled checkpoint) constitute a vulnerability specific to B-cell malignancies [6]. Together these studies reframe the Warburg phenotype in B-ALL not as a passive bystander but as a tightly governed, oncogene-coupled and therapeutically exploitable circuit.

3.3. Oncogene Control of Metabolism: NOTCH1 and the T-ALL Mitochondrial Program

In T-ALL, metabolic rewiring is dominated by NOTCH1. Herranz and colleagues showed that NOTCH1 drives a glutaminolytic, biosynthetic program and that, under anti-NOTCH1 therapy (γ-secretase inhibition), leukemic cells survive by switching toward autophagy and alternative fuel use, co-targeting glutaminase overcame this escape in vivo, establishing metabolic reprogramming as a bona fide resistance mechanism to targeted therapy [7]. The mitochondrial arm of this program is equally important: AMPK maintains a balance between glycolysis and oxidative phosphorylation that T-ALL cells require to withstand metabolic stress, and loss of this balance is lethal to blasts [8]. More recently, inhibition of mitochondrial complex I with IACS-type agents was shown to reverse NOTCH1-driven metabolic reprogramming and to possess activity in T-ALL models [27]. These findings position the mitochondrion, long neglected in a disease defined by the Warburg effect, as a central and druggable node in T-lineage disease.

3.4. Amino-Acid Dependencies: Asparagine, Glutamine and the Asparaginase Axis

No metabolic dependency is more clinically entrenched in ALL than the reliance on extracellular asparagine. Lymphoblasts express low asparagine synthetase (ASNS) and cannot meet their asparagine demand autonomously, which is the basis for the decades-old efficacy of L-asparaginase. The enzyme also possesses glutaminase activity, work dissecting the two activities showed that glutaminase activity is dispensable for killing ASNS-negative cells but contributes against ASNS-expressing (relatively resistant) cells, clarifying a long-standing question about mechanism and toxicity [28]. Resistance to asparaginase is frequently microenvironmental rather than cell-intrinsic:

mesenchymal stromal cells express ASNS and supply asparagine to blasts, and adipocytes release glutamine that is transaminated to replenish asparagine, protecting leukemic cells from the drug — a mechanism linking adiposity to inferior outcomes [9,10]. A synthetic-lethal strategy, activation of Wnt/GSK3 signaling, was shown to resensitize drug-resistant leukemias to asparaginase, nominating a combination approach [29].

Glutamine sits at the hub of this amino-acid economy — feeding the tricarboxylic-acid cycle through anaplerosis, supporting redox balance and serving as the nitrogen donor for asparagine synthesis. Its centrality to the NOTCH1 program and to adipocyte-mediated asparaginase resistance makes glutaminase (e.g. CB-839/telaglenastat) a recurring candidate target across lineages [7,10].

3.5. Lipid Metabolism and the Adipocyte-Rich Niche

The bone marrow is lipid-rich, and marrow adipocytes expand with age, obesity and chemotherapy. Beyond supplying glutamine, adipocytes export free fatty acids that fuel β-oxidation in blasts, pharmacologic inhibition of fatty-acid oxidation (e.g. etomoxir) synergizes with L-asparaginase in childhood ALL cells, indicating that lipid catabolism is a stress-adaptive fuel under amino-acid deprivation [11]. Adipocytes additionally absorb and enzymatically inactivate chemotherapeutics: they sequester and metabolize daunorubicin, reducing the effective drug dose reaching leukemic cells [12]. These data provide a mechanistic basis for the clinical observation that children at weight extremes, and those obese for longer during therapy, experience inferior survival and greater toxicity, and they frame the adipocyte as an active metabolic accomplice rather than inert stroma [30].

3.6. The Leukemic Microenvironment Reshapes Immune-Cell Metabolism

Metabolomic profiling of the pediatric ALL microenvironment reveals a nutrient landscape distinct from normal marrow and from peripheral blood, with altered levels of glucose, amino acids and lipids that reflect intense competition between blasts and resident cells [31]. Single-cell and immune-profiling studies show that this is not a metabolically neutral space for immune cells: the B-ALL immune microenvironment is extensively remodeled, with expansion of immunosuppressive myeloid populations and altered T-cell states, and risk-associated alterations in marrow T cells are detectable in pediatric leukemia at diagnosis [17]. In T-ALL, single-cell analyses reveal developmental plasticity coexisting with immune-evasion programs [32,33].

Two immunosuppressive metabolic mechanisms recur. First, amino-acid depletion: leukemic and myeloid cells consume arginine and tryptophan, nutrients on which T-cell proliferation and effector function depend. The arginine metabolome of ALL can be therapeutically targeted with pegylated recombinant arginase (BCT-100), which is cytotoxic to blasts but, by the same token, depletes a nutrient required by T cells [34]. Second, tryptophan catabolism via indoleamine-2,3-dioxygenase (IDO):IDO activity generates immunosuppressive kynurenines, correlates with poor outcome in childhood acute leukemia, and directly inhibits CD19-CAR T cells, an effect partially reversible by lymphodepleting chemotherapy [35,36]. The leukemic niche thus enforces an immunometabolic checkpoint, starving and poisoning the very effectors that immunotherapy deploys (Figure 2).

Figure 2. Immunometabolic reprogramming in pediatric ALL: blast-niche–immune crosstalk

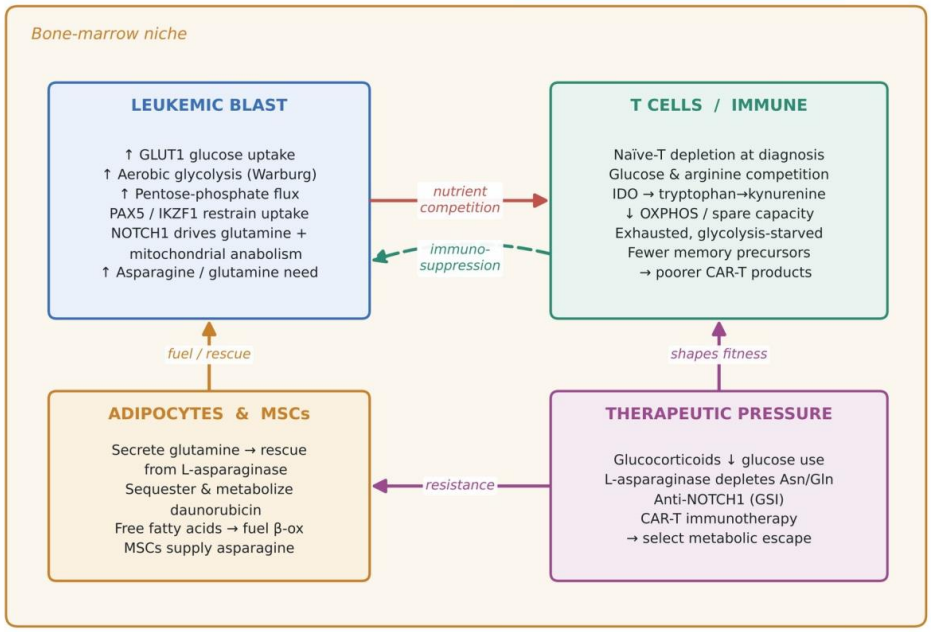


Figure 2: Integrated model of immunometabolic reprogramming in pediatric ALL. Blast-intrinsic programs (blue) are fueled and shielded by adipocytes and mesenchymal stromal cells (amber), while nutrient competition and immunosuppressive catabolism (IDO, arginase) degrade T-cell fitness (green), therapy (plum) selects for metabolic escape

3.7. Immune-Effector Fitness, CAR-T Manufacturing and Persistence

The clinical success of CD19-directed CAR-T therapy in relapsed/refractory pediatric B-ALL has made the metabolic quality of the patient's own T cells a therapeutic variable. Children with cancer, including ALL, show naive-T-cell deficits at diagnosis and after chemotherapy that impair the potential of autologous cell products, and risk-associated T-cell alterations are present in the marrow at presentation [15-18]. Memory and persistence of engineered cells are governed by metabolism: costimulatory-domain choice (4-1BB vs CD28) programs distinct metabolic trajectories — 4-1BB favoring oxidative, memory-promoting metabolism associated with persistence— and the composition and metabolic state of the pre-manufacture T-cell pool predict long-term CAR-T persistence and remission durability [19,20]. Because the niche into which cells are infused is arginine- and tryptophan-depleted and IDO-rich, engineering immune cells to resist this environment — for example by enforcing arginine/tryptophan independence — enhances CAR-T proliferation and antitumor activity in preclinical models [34,36,37]. Immunometabolic reprogramming therefore operates at two clinically distinct points: within the patient at diagnosis, and within the engineered product.

3.8. Metabolism as a Driver of Treatment Resistance

A consistent theme across the included studies is that metabolic flexibility underlies resistance to each pillar of ALL therapy. Glucocorticoid activity depends on suppressing glucose metabolism, and a glycolytic, proliferative set-point confers resistance [24–26]. Asparaginase resistance is substantially niche-derived, via stromal ASNS and adipocyte glutamine, and is reversible by synthetic-lethal or fatty-acid-oxidation co-targeting [9-11][29]. Resistance to targeted anti-NOTCH1 therapy is metabolic, mediated by fuel switching and overcome by glutaminase or complex-I inhibition [7,27]. Even immunotherapy is subject to metabolic resistance, through nutrient depletion and IDO-mediated suppression of CAR-T cells [36]. This convergence suggests that metabolic adaptation is a shared final common pathway of resistance, and that metabolic co-targeting could broaden the effect of existing and emerging therapies.

3.9. Therapeutic Targeting of Immunometabolism

The actionable landscape spans four categories (Figure 4).

(i) Blast central-carbon and amino-acid metabolism: GLUT1 and hexokinase inhibition and glutaminase inhibition (CB-839) are preclinically active and, for glutaminase, in early clinical testing in other cancers [23].

(ii) Niche- and lipid-directed approaches: fatty-acid-oxidation inhibitors combined with asparaginase, and dietary or fasting interventions — caloric restriction and fasting slow ALL development in mice via leptin-receptor signaling, and diet/exercise interventions are being tested clinically to counter adiposity-associated resistance [11,30,38].

(iii) Immunometabolic checkpoints: IDO1 inhibitors and arginase (BCT-100), the latter in clinical testing in relapsed leukemia [34-36].

(iv) Mitochondrial and cell-therapy metabolism: complex-I inhibitors in T-ALL, and metabolically armored CAR-T cells engineered for persistence and nutrient resistance, built on the costimulation–metabolism relationship [27,37,15]. Existing standards of care — glucocorticoids and L-asparaginase — are, in effect, long-standing immunometabolic drugs, which both validates the strategy and cautions that metabolic agents carry on-target effects on healthy proliferating and immune tissues.

Figure 4. Therapeutic landscape of immunometabolic targets in pediatric ALL



Figure 4: Therapeutic Landscape of Immunometabolic Targets in Pediatric ALL, Arranged by Mechanistic Category (Color) And Development Stage. Several Agents Are Clinically Established in Other Indications but Remain Investigational in Pediatric ALL

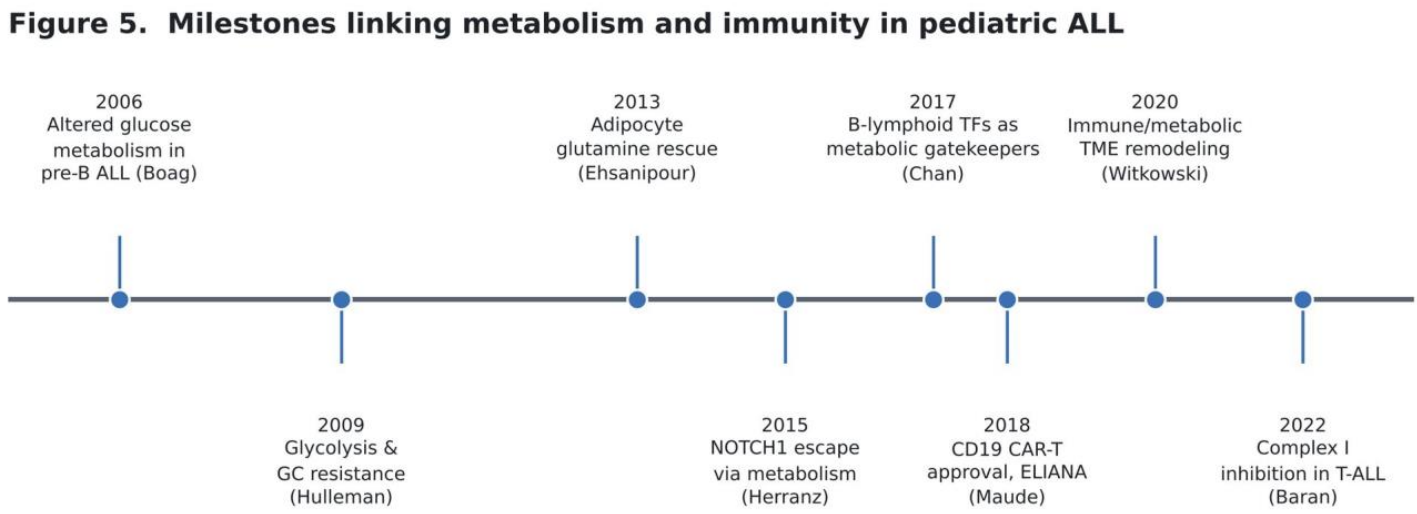


Figure 5: Milestones in the Recognition That Metabolism and Immunity Jointly Govern Pediatric All Biology and Treatment Response

4. Discussion

Three conclusions emerge from this synthesis. First, metabolic reprogramming in pediatric ALL is lineage- and oncogene-specific, not generic. The B-lineage story is one of released transcriptional restraint on glucose and pentose-phosphate flux, whereas the T-lineage story is one of NOTCH1-driven glutamine and mitochondrial anabolism [5-8][22,23,27]. Treating "ALL metabolism" as a single entity obscures these differences and the distinct vulnerabilities they create.

Second, the bone-marrow niche is an active metabolic participant. Adipocytes and mesenchymal stroma supply amino acids and lipids, inactivate chemotherapy, and thereby convert a cell-intrinsic drug sensitivity into a microenvironmental resistance [9–12]. This reframes several clinical observations — the adverse prognostic weight of obesity, the variability of asparaginase response — as fundamentally metabolic, and it argues that effective metabolic therapy must account for the niche, not only the blast [30].

Third, and most importantly for the field's trajectory, metabolism and immunity are inseparable here. The nutrient competition and catabolic suppression that favor blast survival are the same forces that degrade T-cell fitness, and the efficacy of CAR-T therapy is partly a metabolic phenomenon decided before manufacture and again in the niche [15,16,19][20,37]. This creates a genuinely dual-use therapeutic opportunity: interventions that deprive blasts of a fuel, or relieve an immunosuppressive catabolite, may simultaneously restore immune-effector function [17,31] [32,34–36]. The counter-risk is symmetry of harm — glycolysis, glutaminolysis and amino-acid availability are also required by healthy proliferating and immune cells, so therapeutic windows may be narrow and must be defined empirically in developmentally appropriate models.

Several gaps limit translation. Much of the mechanistic work rests on cell lines and adult-derived models, pediatric primary material, and in particular developmentally staged normal controls, are under-represented. Metabolic phenotypes are frequently inferred from expression rather than measured by flux. The immunometabolic literature is concentrated in B-ALL and CAR-T, leaving T-ALL immunometabolism and non-CAR immune compartments comparatively unexplored. And pediatricspecific pharmacodynamics — how growing children tolerate metabolic inhibition — are largely unknown.

4.1. Limitations of this Review

This review has limitations. The protocol was not pre-registered. Because reliable programmatic access to bibliographic databases was not available during preparation, the quantitative screening counts in Figure 1 represent the authors' ledger rather than a machine-reproducible export and should be regenerated before journal submission, by contrast, every included study was individually verified against its publisher record. Given the mechanistic heterogeneity of the evidence, synthesis is narrative and no meta-analysis was performed, so the review cannot provide pooled effect estimates. Finally, selection favored mechanistic and translational studies with clear metabolic endpoints, which may under-represent purely descriptive or negative findings.

5. Conclusions and Future Directions

Pediatric ALL is best understood as an immunometabolic disease in which oncogene-driven blast metabolism, a nutrient-trading bone-marrow niche and the metabolic fitness of immune effectors are tightly coupled. The near-term priorities are:

(i) Lineage-resolved, flux-based metabolic phenotyping of pediatric primary samples against developmentally matched controls,

(ii) Rational combinations that pair metabolic inhibitors with glucocorticoids, asparaginase or anti-NOTCH1 therapy to pre-empt metabolic resistance, and

(iii) Immunometabolic engineering of CAR-T and other cell therapies to withstand a hostile niche, together with niche-

directed interventions (arginase, IDO blockade, dietary modulation) that relieve immune suppression. Realizing this will require pediatric-specific trials and models, but the convergence of metabolism and immunity offers a rare chance to make therapy both more effective and, by sparing the immune system, potentially less toxic for children.

Study	Lineage	Model	Metabolic axis	Principal finding
Boag 2006 [22]	B-ALL	Primary samples	Glycolysis	Elevated glycolytic metabolism in childhood pre-B blasts
Hulleman 2009 [24]	B/T-ALL	Cell lines/primary	Glycolysis	Glycolysis inhibition restores prednisolone sensitivity
Beesley 2009 [26]	T-ALL	Cell lines	Glycolysis/OXPHOS	Proliferative metabolism linked to glucocorticoid resistance
Buentke 2011 [25]	ALL	Cell lines	Glucose metabolism	Glucocorticoid killing mediated by reduced glucose metabolism
Liu 2014 [23]	B-ALL	Cell lines/PDX	GLUT1/glucose	GLUT1 uptake limiting for anabolism and apoptosis resistance
Chan 2017 [5]	B-ALL	Mouse/primary	Glucose gatekeeping	PAX5/IKZF1 restrain glucose uptake as metabolic tumor suppressors
Xiao 2018 [6]	B-ALL	Mouse/primary	Pentose phosphate	B-cell glucose-carbon diversion is a targetable vulnerability
Herranz 2015 [7]	T-ALL	Mouse/PDX	Glutamine/autophagy	Metabolic switch drives anti-NOTCH1 resistance, glutaminase co-target
Kishton 2016 [8]	T-ALL	Mouse/cell lines	AMPK/mitochondria	AMPK balances glycolysis and OXPHOS for blast survival
Baran 2022 [27]	T-ALL	PDX/mouse	Complex I/OXPHOS	Complex-I inhibition reverses NOTCH1 metabolic program
Chan WK 2014 [28]	ALL	Cell lines/mouse	Asparagine/glutamine	Glutaminase activity dispensable against ASNS-negative cells
Iwamoto 2007 [9]	ALL	Co-culture	Asparagine (niche)	Mesenchymal stroma supplies asparagine, blunting asparaginase
Ehsanipour 2013 [10]	ALL	Co-culture/mouse	Glutamine (adipocyte)	Adipocyte glutamine rescues blasts from Lasparaginase
Hermanova 2016 [11]	Pediatric ALL	Cell lines	Fatty-acid oxidation	FAO inhibition synergizes with L-asparaginase
Sheng 2017 [12]	ALL	Co-culture	Lipid/drug handling	Adipocytes sequester and metabolize daunorubicin
Hinze 2019 [29]	ALL	Cell lines/PDX	Asparaginase resistance	Wnt activation is synthetically lethal with asparaginase
De Santo 2018 [34]	ALL	Primary/mouse	Arginine	Arginase BCT-100 targets the ALL arginine metabolome
Fultang 2020 [37]	B-ALL/other	Engineered T cells	Arginine/Trp (immune)	Arg/Trp-resistant engineering enhances CAR-T activity
Folgiero 2014 [35]	Pediatric AL	Primary	Tryptophan/IDO	IDO1 activity correlates with poor outcome
Ninomiya 2015 [36]	B-cell/CAR-T	Mouse/cell	Tryptophan/IDO (immune)	IDO inhibits CD19-CAR T cells, reduced by lymphodepletion
Tiziani 2013 [31]	Pediatric ALL	Primary (metabolomics)	TME metabolome	Distinct microenvironmental metabolite landscape
Witkowski 2020 [32]	B-ALL	Mouse/primary (scRNA)	Immune TME	Extensive immunemicroenvironment remodeling
Bailur 2020 [17]	Pediatric	Primary (marrow T cells)	Immune/T cell	Risk-associated marrow T-cell alterations at diagnosis
Das 2019 [16]	Pediatric	Primary	Immune/T cell	Naive-T deficits impair autologous cell-therapy potential

Kawalekar 2016 [15]	CAR-T	Engineered T cells	Immune metabolism	Costimulation programs CAR-T metabolism and memory
Lu 2017 [38]	ALL	Mouse	Systemic/dietary	Fasting blocks ALL via leptin-receptor upregulation
Orgel 2014 [30]	Pediatric ALL	Clinical cohort	Adiposity/outcome	Weight extremes worsen survival and toxicity
Maude 2018 [18]	Pediatric B-ALL	Clinical trial	Immunotherapy	Tisagenlecleucel efficacy in relapsed/ refractory BALL

Table 1: Representative Included Studies by Metabolic Axis

ALL, acute lymphoblastic leukemia, AL, acute leukemia, ASNS, asparagine synthetase, FAO, fatty-acid oxidation, GLUT1, glucose transporter 1, IDO, indoleamine-2,3-dioxygenase, OXPHOS, oxidative phosphorylation, PDX, patient-derived xenograft, scRNA, single-cell RNA sequencing, TME, tumor microenvironment, Trp, tryptophan. Bracketed numbers correspond to the reference list.

Figure Legends

- **Figure 1:** PRISMA 2020 flow diagram of study identification, screening, eligibility and inclusion. Of records identified, 40 studies met eligibility criteria and were synthesized. Counts reflect the authors' screening ledger (Methods 2.3).
- **Figure 2:** Integrated model of immunometabolic reprogramming in pediatric ALL. Leukemic blasts (blue) upregulate GLUT1-mediated glucose uptake, aerobic glycolysis and pentose-phosphate flux under PAX5/IKZF1 restraint (B-lineage) and NOTCH1-driven glutamine and mitochondrial anabolism (T-lineage). Adipocytes and mesenchymal stromal cells (amber) supply glutamine, asparagine and fatty acids and inactivate chemotherapy. Nutrient competition and catabolic enzymes (IDO, arginase) degrade T-cell fitness (green). Therapeutic pressure (plum) selects for metabolic escape.
- **Figure 3:** Evidence map of the 40 included studies. (A) Studies per metabolic pathway by lineage (B-ALL vs T-ALL). (B) Distribution of study designs. Studies may map to multiple pathways.
- **Figure 4:** Therapeutic landscape of immunometabolic targets, arranged by mechanistic category (color) and development stage from preclinical to approved standard of care.
- **Figure 5:** Timeline of conceptual milestones linking metabolism and immunity in pediatric ALL, 2006–2022.

Declarations

Funding: No specific funding was received for this work.

Competing Interests: The author declares no competing interests.

Author Contributions: J.M. conceived the review, designed and conducted the search and synthesis, prepared the figures and wrote the manuscript.

Data Availability: All data supporting this review are contained within the article, the full screening ledger and extraction table are available from the corresponding author on request.

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