BIOCELL

Tech Science Press

http://doi.org/10.32604/biocell.2026.075170

REVIEW

Receptor Reexpression after Hypermethylation: Novel Targets for Inhibitors and Antibody-Drug Conjugates in ALL

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Received: 26 October 2025; Accepted: 21 January 2026; Published: 13 May 2026

ABSTRACT: Despite improved overall prognosis, the treatment of high-risk acute lymphoblastic leukemia (ALL) remains challenging due to the toxicity of intensive polychemotherapy and the limited efficacy of antibody-targeted therapies beyond cluster of differentiation 20 and 22 (CD20 and CD22). ALL is driven not only by genetic alterations but also by profound epigenetic dysregulation, including promoter hypermethylation that also silences surface receptor genes. This epigenetic repression can reduce the efficacy of targeted immunotherapies and contribute to relapse. Epigenetic reprogramming with DNA demethylating agents (e.g., decitabine) has the potential to restore the expression of key B cell receptors such as CD19 or CD20, as well as other therapeutically relevant target antigens on the cell surface, thus enhancing the susceptibility of leukemia cells to antibody-based therapies. In addition to new generations of bispecific antibodies and advanced CAR-T cell constructs, novel antibody-drug conjugates (ADCs) are increasingly coming into focus. The sequential application of DNA methylation inhibitors followed by ADC or inhibitor treatment represents an innovative approach that simultaneously restores tumor suppressor function, enhances leukemia immunogenicity, and expands the therapeutic window of receptor-targeted therapies. We investigated the hypothesis that several hypermethylated genes encoding cell surface proteins accessible to immunotherapy exist in acute lymphoblastic leukemia (ALL). Our review provides a comprehensive analysis of hypermethylated cell surface markers for ALL and the underlying epigenetic reprogramming after demethylation. We propose that the integration of epigenetic therapies into existing immuno-oncology treatment regimens could substantially improve treatment efficacy and open new avenues to overcome resistance mechanisms in ALL.

KEYWORDS: Acute lymphoblastic leukemia; antibody-drug conjugates; DNA methyltransferase inhibitors; hypermethylation; cell surface markers

1 Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood, but it also occurs in adults. Despite an improved overall prognosis, ALL treatment remains a serious clinical challenge, as only 40–90% of patients achieve long-term survival, depending on age and risk group [1,2].

Leukemia arises from the clonal expansion of immature lymphoid progenitor cells, whose differentiation and proliferation are impaired by genetic and epigenetic alterations. While genetic aberrations such as chromosomal translocations have long been studied, the role of epigenetic alterations, particularly DNA methylation, is gaining increasing attention [3–5]. Recently, it has been described that several potential surface targets for immunotherapy are methylated in ALL [6]. Hypermethylation of promoter regions leads

to the silencing of numerous genes, including those encoding receptors or receptor-associated signaling proteins [7–9]. These changes have far-reaching consequences for signal transduction, cell adhesion, the survival of leukemia cells, and their treatment.

Epigenetic reprogramming represents a promising strategy for potentiating targeted treatments in ALL. By restoring receptor gene expression, leukemic cells become more susceptible to inhibitors and antibody-based therapies (e.g., antibody-drug conjugates [ADCs]), offering new opportunities for durable disease control (Fig. 1). The integration of epigenetic priming into treatment protocols could pave the way for more personalized and effective immunotherapies in ALL. This review highlights current strategies and therapeutic approaches using antibody-drug conjugates for the described hypermethylated receptor genes in ALL.

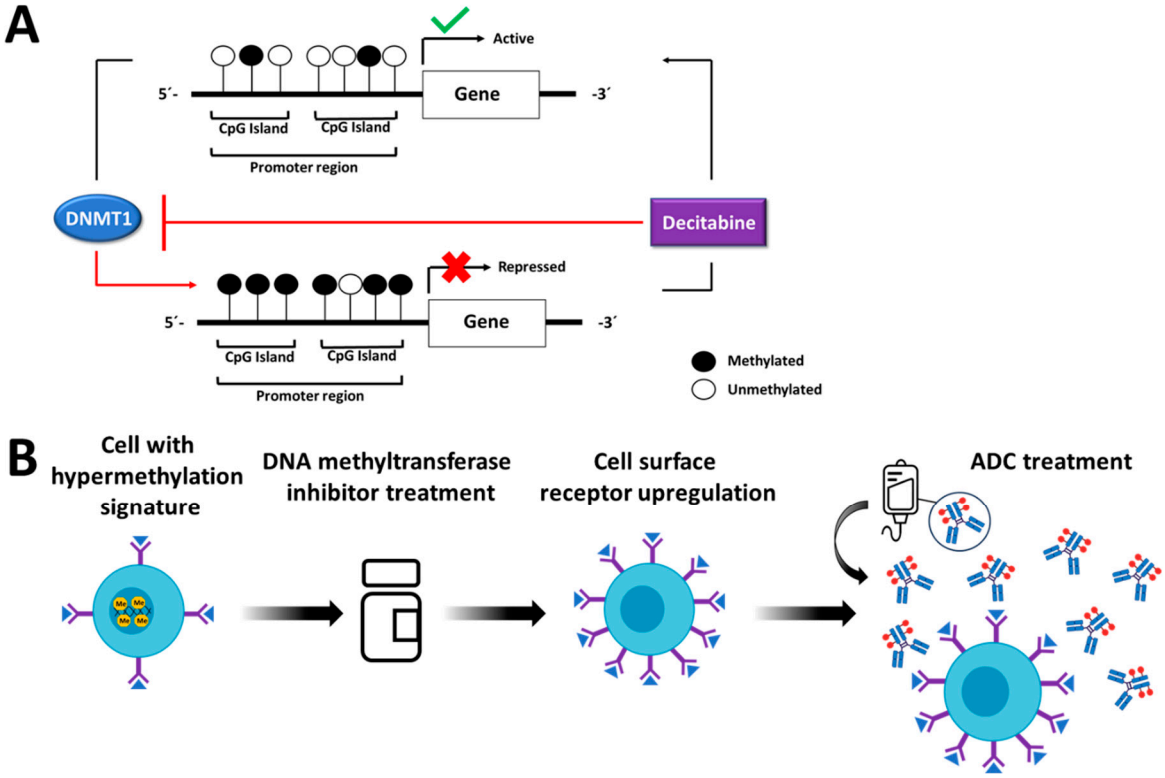

Figure 1: Mode of action of DNA methyltransferase inhibitors and their combination with antibody-drug conjugates for the treatment of acute lymphoblastic leukemia (ALL). (**A**) DNA methyltransferase inhibitors (e.g., decitabine) are epigenetic drugs that block the enzyme DNA methyltransferase (DNMT1), which is responsible for DNA methylation of CpG islands in the DNA. By inhibiting this enzyme, decitabine can cause the reactivation of silenced genes, for example, cell surface receptor genes. (**B**) Schematic representation of the combined therapeutic approach consisting of a DNA-methyltransferase inhibitor that upregulates receptor expression on the cell surface and an antibody-drug conjugate (ADC) that binds to the upregulated receptor and specifically transports the conjugated cytotoxin into the cell by subsequent endocytosis.

2 Current Status of Hypermethylation in Subgroups of ALL

Epigenetic alterations, particularly DNA methylation, play a crucial role in the pathogenesis and progression of ALL. DNA methylation describes the attachment of a methyl group to the cytosine residue in CpG-rich (Cytosine phosphate Guanine) regions, often within promoter regions. Hypermethylated

promoters are associated with transcriptional inactivation. In tumors, this is a common mechanism for inactivating tumor suppressor genes or signaling proteins [10]. In recent years, extensive methylation profiling has been performed in ALL [5,11–13], showing that different ALL subgroups exhibit characteristic methylation patterns with specific genes being affected [14–18]. Hypermethylation, in particular, occurs in specific genetic and epigenetic contexts that are associated with disease development, relapse risk, and prognosis. High-risk groups are of particular interest because these subgroups often respond poorly to standard chemotherapy. While remission can typically be achieved in approximately 75% of cases after induction of chemotherapy, overall survival decreases to 50% in all risk groups across ALL [19]. The identification of genetic subgroups and classification into ALL subtypes is important for risk stratification of patients and has increased the likelihood of response to targeted therapy.

In B cell ALL (B-ALL), various genetically defined subtypes can be distinguished, including ETV6-RUNX1 (ETS variant transcription factor 6/runt-related transcription factor 1), high hyperdiploid (HeH), KMT2A-rearranged (histone-lysine N-methyltransferase 2A), Ph-positive (philadelphia-positive)/BCR-ABL1-positive (breakpoint cluster region/abelson murine leukemia viral oncogene homolog 1), Ph-like/CRLF2-rearranged (philadelphia-like/cytokine receptor like factor 2), dic(9;20), DUX4/ERG-altered (double homeobox 4/ETS transcription factor ERG; ERG-alt) and TCF3-PBX1 (transcription factor 3/pre-B-cell leukemia transcription factor 1). ALL subgroups, such as KMT2A-r and TCF3-HLF (transcription factor 3/hepatic leukemia factor), define rare subgroups with highly drug-resistant disease [20]. These subtypes also exhibit specific hypermethylation patterns and can often be distinguished by this as well.

2.1 KMT2A-r B-ALL Subgroup

One subgroup known for pronounced methylation is the KMT2A-r subgroup [16,21]. KMT2A-rearranged ALL results in rearrangements of the KMT2A gene on chromosome 11q23 with numerous partner genes (e.g., AFF1, MLLT1, or MLLT3), leading to epigenetic alterations and differentiation block. It is very common in infants (<1 year of age) (up to 80%), but also occurs in adults with a very poor prognosis [16,22]. This subgroup exhibits pronounced promoter hypermethylation, particularly in CpG islands, although it lacks the global hypomethylation tendency typical of other tumors [23]. It displays broad epigenetic dysregulation through fusion with epigenetic regulators and therefore exhibits massive hypermethylation with concomitant aberrant histone modification [24,25]. The affected genes include the B cell receptor (BCR)-associated tyrosine kinase BTK (bruton tyrosine kinase), the cell cycle transcription factor FOXN3 (Forkhead Box N3), the serine/threonine kinase DAPK1 (death-associated protein kinase 1), which plays a role in programmed cell apoptosis, and the enzyme FHIT (fragile histidine triad), which promotes apoptosis after DNA damage [13,16,26].

2.2 ETV6-RUNX1 B-ALL Subgroup

The ETV6-RUNX1 translocation t(12;21)(p13;q22) leads to a block in B cell maturation, often acquired prenatally. It represents the most common subtype in children (20–25%) with a favorable prognosis [27]. However, relapse has been observed in up to 20% of patients with ETV6-RUNX1 [28,29]. The ETV6-RUNX1 subtype exhibits hypermethylation in promoter regions of several genes involved in cell cycle regulation or as developmental regulators, controlling embryonic development (CHD5, PAX7, HOXD1, SOX3, SNAI3, NKX2-8, ALX1, or VAX2) or resistance (ASNS; asparagine synthetase) [13,14]. This is likely relevant for the preleukemic stage, which can develop as early as childhood.

2.3 TCF3-PBX1 B-ALL Subgroup

The TCF3-PBX1 translocation t(1;19)(q23;p13) leads to a block in B cell development and frequently activates pre-BCR signaling. Approximately 5–6% of pediatric B-ALL are affected [30]. The prognosis is moderate with usually a good initial response to chemotherapy, but a higher risk of CNS (central nervous system) relapse [30]. In accordance, the TCF3-PBX1 subtype exhibits hypermethylation in genes involved in B cell development (APAF1, FOXM1, CTCF, or MEF2C) and signal transduction (KRAS, DUSP4, or PDK1) [13].

2.4 Ph-Positive B-ALL Subgroup

The t(9;22)(q34;q11) translocation, known as Philadelphia chromosome-positive (Ph-positive, BCR-ABL1) ALL, results in BCR-ABL1 fusion with constitutive tyrosine kinase activity. Approximately 20–30% of adults and 2–3% of children are affected [31]. The prognosis used to be very poor, but is now significantly improved due to TKI (tyrosine kinase inhibitor) treatment [2]. Hypermethylation in the Ph-positive subtype affects genes involved in signal transduction (MAPK14, DUSP5, and GRB7) and may be linked to resistance mechanisms to tyrosine kinase inhibitors [13]. For example, miR-124 is suppressed by promoter methylation in ALL cells with Ph-positive subtype and negatively regulates CDK6 (cyclin-dependent Kinase 6), whose increased expression is associated with TKI resistance [32–34].

2.5 Ph-Like B-ALL Subgroup

The Philadelphia-like (Ph-like) ALL lacks BCR-ABL1 translocation, but displays a similar gene expression signature with frequent alterations in JAK/STAT (janus kinase/signal transducer and activator of transcription) or ABL kinases (e.g., CRLF2 rearrangements, JAK2 mutations). Approximately 10–15% of children and up to 30% of young adults are affected [35]. The prognosis is unfavorable with a high risk of recurrence [36]. The Ph-like/CRLF2-r B-ALL subtype has the fewest differentially methylated regions (DMRs) [13]. However, it is characterized by overexpression of CRLF2 (cytokine receptor-like factor 2), which often arises independently of methylation through translocations. This subtype exhibits hypermethylation in genes involved in cell developmental and differentiation signaling (HOXB2, ZIC5, SIX6, ASXL1) [13].

2.6 High Hyperdiploid B-ALL Subgroup

The high hyperdiploid ALL (HeH) subtype has 51–67 chromosomes and typically results in chromosome gains of 4, 10, and 17. It is very common in children (25–30%) and has a very favorable prognosis with excellent long-term survival rates [37]. The high hyperdiploid subtype has the highest number of differentially methylated regions (DMRs) of all B-ALL subtypes [13]. Many of these DMRs affect genes involved in cell cycle regulation (SETBP1, CDC14B, RAD50, or RMI1) and signal transduction (DUSP15, GLI1, CNKSR2, or INHBE) [13].

2.7 DUX4-r B-ALL Subgroup

The DUX4-rearranged ALL subtype is characterized by rearrangements of the DUX4 gene (usually insertion of the DUX4 gene into the IGH locus). DUX4 is a transcription factor that is normally active during embryonic development [38]. DUX4-r occurs primarily in childhood B-ALL (5–10%), often with concurrent IKZF1 (Ikaros family zinc finger 1) mutations [39,40]. Despite high-risk features, DUX4-ALL is now considered a favorable subtype using modern treatment protocols. Therefore, children with DUX4-ALL

have very good long-term survival rates [39]. This subtype exhibits hypermethylation in genes involved in cell cycle and V(D)J-recombination (CDKN1A, CDKN2C, CDCA3/5 or RAG2) as well as in signal transduction (VAV1, VRK2, and GAB1) [13].

2.8 dic(9;20) B-ALL Subgroup

The dic(9;20)(p11–13;q11) ALL subtype results in a dicentric chromosome rearrangement between chromosomes 9 and 20 and deletions on 9p and 20q. The genes PAX5 (paired-box-protein 5; an important B cell transcription factor) and CDKN2A/CDKN2B tumor suppressors are affected. It is a relatively rare subtype of B-ALL (2% of pediatric cases) with a moderate to poor prognosis and an increased risk of recurrence compared to other childhood ALL subtypes [41,42].

2.9 T-ALL

DNA methylation also plays an important role in T cell ALL (T-ALL). Two phenotypes can be distinguished: CIMP-positive (CpG island methylator phenotype positive) and CIMP-negative. CIMP-positive cases are characterized by high CpG island hypermethylation and are associated with a better prognosis [5]. CIMP-negative cases, on the other hand, exhibit hypomethylated profiles and are associated with a worse clinical course [43,44].

In addition to subtype-specific patterns, constitutive hypermethylation has also been identified, which is common to all subtypes of ALL. In a large-scale study with 764 patients and 435,941 CpG sites examined, 9406 CpGs were identified that were constitutively hypermethylated in ALL cases [45]. In addition, specific hypermethylation has been observed in relapses, which is associated with an increased risk of relapse [22,46].

3 Hypermethylation in ALL Affects the Expression of Certain Receptor Genes

Receptors play a central role in signal transduction in ALL and are therefore potential therapeutic targets. An example is the PDGF receptor (platelet-derived growth factor receptor), which frequently fuses with other genes of the Ph-like B-ALL subgroup, leading to impaired and hyperactivated signal transduction [47]. In addition to genetic alterations, epigenetic regulation, particularly promoter hypermethylation, is also a key feature of ALL [11]. Although hypermethylation typically leads to reduced expression, the pharmacological modulation of these genes and their signaling pathways remains of great interest.

To systematically identify potential immunotherapy targets [11,13,14,48], we first collected genes reported as hypermethylated in primary ALL samples [49–52] across nine molecular subgroups [53–56]. Candidate proteins encoded by these genes were subsequently evaluated for plasma membrane localization using a bioinformatic pipeline. Specifically, we employed the STRING database [57] to retrieve gene annotations for membrane association, using UniProt keywords (KW-0472: membrane; KW-1133: transmembrane helix) and Gene Ontology cellular component terms (GO:0009986: cell surface; GO:0005886: plasma membrane; GO:0071944: cell periphery; GO:0016021: integral component of membrane). In parallel, subcellular localization annotations from the Human Protein Atlas (HPA) [58] were queried, including experimentally determined and predicted plasma membrane or cell junction localizations. Proteins satisfying these criteria were retained as putative cell surface receptors. Using this approach, we identified 156 hypermethylated proteins across the nine ALL subgroups, providing a curated set of candidates for potential immunotherapeutic targeting.

We identified 156 hypermethylated cell surface receptors in 9 different ALL subgroups (TCF3-PBX1, Ph-positive, Ph-like/CRLF2-r, KMT2A-r, HeH, ETV6-RUNX1, DUX4/ERG-alt, dic[9;20], and T-ALL) (Fig. 2). Of these 156 receptor genes, 34 belong to the adhesion receptor type, 1 gene encodes an endothelial

membrane protein, 21 genes encode G-protein-coupled receptors (GPCRs), 31 genes encode immune receptors, 20 genes encode ion channels, 5 genes encode ephrin (receptor) ligands, 8 genes encode protein tyrosine phosphatase receptors (PTP receptors), 15 genes encode receptor tyrosine kinases (RTKs), 2 genes encode toll-like receptors (TLR), 3 genes encode tumor necrosis factor receptors (TNF receptors), 1 gene encodes a transmembrane protein and 15 genes encode other transporter proteins (Table 1).

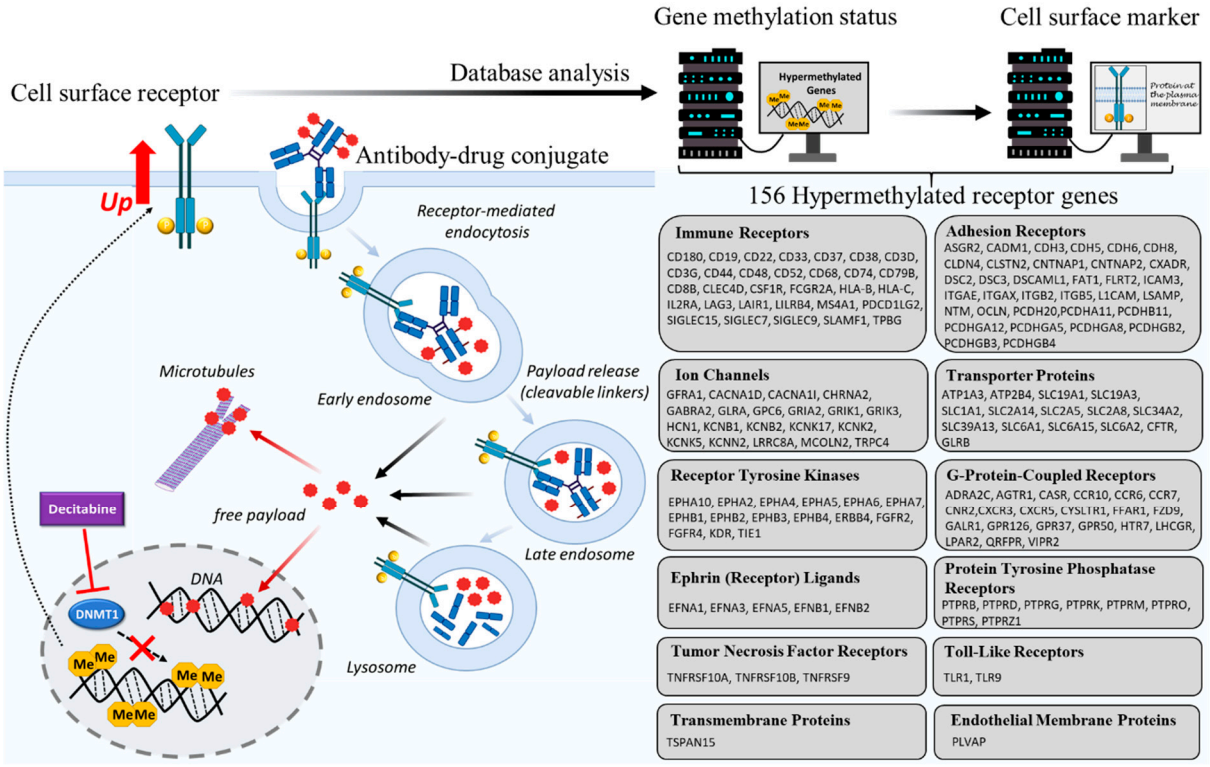

Figure 2: Identification of hypermethylated cell surface receptor genes for the development of antibody-drug conjugates. Hypermethylated cell surface target genes are of interest for the development of therapeutic antibodies and can be treated with decitabine, leading to increased expression. Therefore, the methylation status of several data from different studies was examined. In addition, these genes were analyzed for their localization on the outer cell membrane and thus their accessibility to immunotherapy. We identified 156 hypermethylated cell surface receptors from various receptor subtypes (on the right side). After developing these antibodies (ADCs) against these target genes, the antibody portion of the ADC specifically binds to the target antigen on the surface of the cancer cell (on the left side). The cancer cell takes up the antibody-drug complex via receptor-mediated endocytosis. Within the cell, the drug is cleaved from the linker. The released drug exerts its cytotoxic effect, for example, by inhibiting DNA synthesis, interrupting cell division, or triggering apoptosis. Abb: Up—upregulation; Me—methylated; DNA—deoxyribonucleic acid; DNMT1—DNA methyltransferase 1.

Table 1: Receptor methylation profile of ALL.

Gene ID	Name	Synonym/Protein ID	Receptor type	Reference
ASGR2	Asialoglycoprotein receptor 2	CLEC4H2	Adhesion	[13]
CADM1	Cell adhesion molecule 1	NECL2	Adhesion	[14]
CDH3	Cadherin 15	CDH3	Adhesion	[13]

Table 1: *Cont.*

Gene ID	Name	Synonym/Protein ID	Receptor type	Reference
CDH5	Cadherin 5	CD144	Adhesion	[13]
CDH6	Cadherin 6	CAD6	Adhesion	[14]
CDH8	Cadherin 8	Cadherin-8	Adhesion	[14]
CLDN4	Claudin 4	CPETR	Adhesion	[13]
CLSTN2	Calsyntenin 2	CSTN2	Adhesion	[13]
CNTNAP1	Contactin associated protein 1	CASPR	Adhesion	[13]
CNTNAP2	Contactin associated protein 2	CASPR2	Adhesion	[14]
CXADR	Coxsackie virus and adenovirus receptor	HCAR	Adhesion	[14]
DSC2	Desmocollin 2	DSC2	Adhesion	[13,51]
DSC3	Desmocollin 3	DSC3	Adhesion	[13,14]
DSCAML1	DS cell adhesion molecule like 1	DSCAM2	Adhesion	[14]
FAT1	FAT atypical cadherin 1	CDHF7	Adhesion	[13,53]
FLRT2	Fibronectin leucine rich transmembrane protein 2	FLRT2	Adhesion	[14]
ICAM3	Intercellular adhesion molecule 3	CD50	Adhesion	[13]
ITGAE	Integrin alpha-E	CD103	Adhesion	[13]
ITGAX	Integrin alpha-X	CD11C	Adhesion	[14]
ITGB2	Integrin beta-2	CD18	Adhesion	[13]
ITGB5	Integrin beta-5	ITGB5	Adhesion	[14]
L1CAM	L1 cell adhesion molecule	CD171	Adhesion	[13]
LSAMP	Limbic system associated membrane protein	IGLON3	Adhesion	[14]
NTM	Neurotrimin	IGLON2	Adhesion	[14]
OCLN	Occludin	PTORCH1	Adhesion	[11]
PCDH20	Protocadherin 20	PCDH13	Adhesion	[14]
PCDHA11	Protocadherin alpha 11	CNRN7	Adhesion	[13]
PCDHB11	Protocadherin beta 11	PCDH-BETA11	Adhesion	[13]
PCDHGA12	Protocadherin gamma A12	PCDH-GAMMA-A12	Adhesion	[55]
PCDHGA5	Protocadherin gamma A5	PCDH-GAMMA-A5	Adhesion	[13]
PCDHGA8	Protocadherin gamma A8	PCDH-GAMMA-A8	Adhesion	[13]
PCDHGB2	Protocadherin gamma B2	PCDH-GAMMA-B2	Adhesion	[13]
PCDHGB3	Protocadherin gamma B3	PCDH-GAMMA-B3	Adhesion	[13]
PCDHGB4	Protocadherin gamma B4	PCDH-GAMMA-B4	Adhesion	[13]
PLVAP	Plasmalemma vesicle associated protein	DIAR10	Endothelial membrane protein	[53]
ADRA2C	Adrenergic receptor alpha-2C	ADRARL2	GPCR	[14]
AGTR1	Angiotensin II receptor type 1	AGTR1B	GPCR	[14]
CASR	Calcium-sensing receptor	GPRC2A	GPCR	[14]

Table 1: *Cont.*

Gene ID	Name	Synonym/Protein ID	Receptor type	Reference
CCR10	Chemokine receptor 10	CCR10	GPCR	[13]
CCR6	Chemokine receptor 6	CD196	GPCR	[13,26]
CCR7	Chemokine receptor 7	CD197	GPCR	[13]
CNR2	Cannabinoid receptor 2	CNR2	GPCR	[13]
CXCR3	C-X-C motif chemokine receptor 3	CD182	GPCR	[13]
CXCR5	C-X-C motif chemokine receptor 5	CD185	GPCR	[13]
CYSLTR1	Cysteinyl leukotriene receptor 1	CYSLT1	GPCR	[13]
FFAR1	Free fatty acid receptor 1	GPR40	GPCR	[13]
FZD9	Frizzled family receptor 9	CD349	GPCR	[14]
GALR1	Galanin receptor 1	GALNR1	GPCR	[14]
GPR126	Adhesion G protein-coupled receptor G6	GPR126	GPCR	[14]
GPR37	G protein-coupled receptor 37	EDNRBL	GPCR	[14]
GPR50	G protein-coupled receptor 50	H9	GPCR	[13]
HTR7	5-hydroxytryptamine receptor 7	5-HT7	GPCR	[13]
LHCGR	Luteinizing hormone/choriogonadotropin receptor	LGR2	GPCR	[14]
LPAR2	Lysophosphatidic acid receptor 2	LPA2	GPCR	[13]
QRFPR	Pyroglutamylated RFamide peptide receptor	GPR103	GPCR	[14]
VIPR2	Vasoactive intestinal peptide receptor 2	PACAP-R-3	GPCR	[14]
CD180	CD180 molecule	RP105	Immunoreceptor	[13]
CD19	CD19 molecule	CD19	Immunoreceptor	[50]
CD22	CD22 molecule	SIGLEC2	Immunoreceptor	[13]
CD33	CD33 molecule	SIGLEC3	Immunoreceptor	[13]
CD37	CD37 molecule	TSPAN26	Immunoreceptor	[13]
CD38	CD38 molecule	ADPRC 1	Immunoreceptor	[13]
CD3D	CD3 delta subunit of T-cell receptor complex	CD3-DELTA	Immunoreceptor	[13]
CD3G	CD3 gamma subunit of T-cell receptor complex	CD3-GAMMA	Immunoreceptor	[13]
CD44	CD44 molecule	CSPG8	Immunoreceptor	[14]
CD48	CD48 molecule	SLAMF2	Immunoreceptor	[13]
CD52	CD52 molecule	EDDM5	Immunoreceptor	[13]
CD68	CD68 molecule	LAMP4	Immunoreceptor	[13]
CD74	CD74 molecule	HLADG	Immunoreceptor	[13]
CD79B	CD79b molecule	Igbeta	Immunoreceptor	[13]
CD8B	CD8 subunit beta	LYT3	Immunoreceptor	[14]

Table 1: *Cont.*

Gene ID	Name	Synonym/Protein ID	Receptor type	Reference
CLEC4D	C-type lectin domain family 4 member D	CLEC6	Immunoreceptor	[13]
CSF1R	Colony stimulating factor 1 receptor	CD115	Immunoreceptor	[13]
FCGR2A	Fc gamma receptor IIa	CD32A	Immunoreceptor	[13,14]
HLA-B	Major histocompatibility complex, class I, B	HLAB	Immunoreceptor	[13]
HLA-C	Major histocompatibility complex, class I, C	HLAC	Immunoreceptor	[13]
IL2RA	Interleukin 2 receptor subunit alpha	CD25	Immunoreceptor	[13]
LAG3	Lymphocyte activation gene 3	CD223	Immunoreceptor	[13]
LAIR1	Leukocyte-associated Ig-like receptor 1	CD305	Immunoreceptor	[13]
LILRB4	Leukocyte immunoglobulin-like receptor B4	ILT3	Immunoreceptor	[13]
MS4A1	Membrane spanning 4-domains A1	CD20	Immunoreceptor	[52]
PDCD1LG2	Programmed cell death 1 ligand 2	CD273	Immunoreceptor	[14]
SIGLEC15	Sialic acid-binding Ig-like lectin 15	SIGLEC-15	Immunoreceptor	[13]
SIGLEC7	Sialic acid-binding Ig-like lectin 7	CD328	Immunoreceptor	[13]
SIGLEC9	Sialic acid-binding Ig-like lectin 9	CD329	Immunoreceptor	[13]
SLAMF1	Signaling lymphocytic activation molecule family member 1	CD150	Immunoreceptor	[13]
TPBG	Trophoblast glycoprotein	WAIF1	Immunoreceptor	[14]
GFRA1	GDNF family receptor alpha-1	GDNFR	Ion channel	[13]
CACNA1D	Calcium voltage-gated channel subunit alpha1 D	CACN4	Ion channel	[14]
CACNA1I	Calcium Voltage-Gated Channel Subunit Alpha1 I	CACNA1I	Ion channel	[13]
CHRNA2	Cholinergic receptor nicotinic alpha 2 subunit	CHRNA2	Ion channel	[13]
GABRA2	Gamma-aminobutyric acid type A receptor subunit alpha2	EIEE78	Ion channel	[14]
GLRA2	Glycine receptor alpha 2	MRXSP	Ion channel	[13]
GPC6	Glypican 6	OMIMD1	Ion channel	[14]
GRIA2	Glutamate ionotropic receptor AMPA type subunit 2	HBGR2	Ion channel	[14]
GRIK1	Glutamate ionotropic receptor kainate type subunit 1	GLUR5	Ion channel	[14]
GRIK3	Glutamate ionotropic receptor kainate type subunit 3	GLUR7	Ion channel	[14]
HCN1	Hyperpolarization activated cyclic nucleotide gated potassium channel 1	BCNG-1	Ion channel	[14]

Table 1: *Cont.*

Gene ID	Name	Synonym/Protein ID	Receptor type	Reference
KCNB1	Potassium voltage-gated channel subfamily B member 1	DRK1	Ion channel	[14]
KCNB2	Potassium voltage-gated channel subfamily B member 2	KV2.2	Ion channel	[14]
KCNK17	Potassium two pore domain channel subfamily K member 17	TASK4	Ion channel	[13]
KCNK2	Potassium two pore domain channel subfamily K member 2	TREK1	Ion channel	[55]
KCNK5	Potassium two pore domain channel subfamily K member 5	TASK2	Ion channel	[14]
KCNN2	Potassium calcium-activated channel subfamily N member 2	SKCA2	Ion channel	[13,14]
LRRC8A	Leucine rich repeat containing 8 VRAC subunit A	SWELL1	Ion channel	[13]
MCOLN2	Mucolipin TRP cation channel 2	TRPML2	Ion channel	[48]
TRPC4	Transient receptor potential cation channel subfamily C member 4	HTRP-4	Ion channel	[14]
EFNA1	Ephrin A1	EFL1	Ligand	[49]
EFNA3	Ephrin A3	LERK3	Ligand	[49]
EFNA5	Ephrin A5	EFL5	Ligand	[11,49]
EFNB1	Ephrin B1	EFB1	Ligand	[49]
EFNB2	Ephrin B2	LERK5	Ligand	[49]
PTPRB	Protein tyrosine phosphatase receptor type B	VEPTP	PTP	[13]
PTPRD	Protein tyrosine phosphatase receptor type D	R-PTP-delta	PTP	[14,54]
PTPRG	Protein tyrosine phosphatase receptor type G	R-PTP-gamma	PTP	[14,54]
PTPRK	Protein tyrosine phosphatase receptor type K	R-PTP-kappa	PTP	[14,54]
PTPRM	Protein tyrosine phosphatase receptor type M	R-PTP-mu	PTP	[14,54]
PTPRO	Protein tyrosine phosphatase receptor type O	PTP-PI	PTP	[14]
PTPRS	Protein tyrosine phosphatase receptor type S	R-PTP-sigma	PTP	[48]
PTPRZ1	Protein tyrosine phosphatase receptor type Z1	PTP-ZETA	PTP	[14]
EPHA10	Ephrin receptor A10	DFNA88	RTK	[49]
EPHA2	Ephrin receptor A2	ARCC2	RTK	[49]
EPHA4	Ephrin receptor A4	TYRO1	RTK	[49]
EPHA5	Ephrin receptor A5	HEK7	RTK	[13,14]
EPHA6	Ephrin receptor A6	EHK2	RTK	[49]

Table 1: *Cont.*

Gene ID	Name	Synonym/Protein ID	Receptor type	Reference
EPHA7	Ephrin receptor A7	EHK3	RTK	[49]
EPHB1	Ephrin receptor B1	ELK	RTK	[49]
EPHB2	Ephrin receptor B2	EPHT3	RTK	[49]
EPHB3	Ephrin receptor B3	TYRO6	RTK	[49]
EPHB4	Ephrin receptor B4	MYK1	RTK	[49]
ERBB4	Erb-B2 receptor tyrosine kinase 4	HER4	RTK	[14]
FGFR2	Fibroblast growth factor receptor 2	CD332	RTK	[14]
FGFR4	Fibroblast growth factor receptor 4	CD334	RTK	[13]
KDR	Kinase insert domain receptor	VEGFR2	RTK	[14]
TIE1	Tyrosine kinase with immunoglobulin like and EGF like domains 1	JTK14	RTK	[13]
TLR1	Toll like receptor 1	CD281	TLR	[13]
TLR9	Toll like receptor 9	CD289	TLR	[13]
TNFRSF10A	TNF receptor superfamily member 10a	DR4	TNF receptor	[56]
TNFRSF10B	TNF receptor superfamily member 10b	DR5	TNF receptor	[56]
TNFRSF9	TNF receptor superfamily member 9	CD137	TNF receptor	[13]
TSPAN15	Tetraspanin 15	NET7	Transmembrane protein	[13]
ATP1A3	ATPase Na+/K+ transporting subunit alpha 3	DEE99	Transporter	[13]
ATP2B4	ATPase plasma membrane Ca2+ transporting 4	PMCA4b	Transporter	[13]
SLC19A1	Solute carrier family 19 member 1	CHMD	Transporter	[13]
SLC19A3	Solute carrier family 19 member 3	hTHTR2	Transporter	[14]
SLC1A1	Solute carrier family 1 member 1	hEAAC1	Transporter	[14]
SLC2A14	Solute carrier family 2 member 14	GLUT14	Transporter	[13]
SLC2A5	Solute carrier family 2 member 5	GLUT5	Transporter	[13]
SLC2A8	Solute carrier family 2 member 8	GLUT8	Transporter	[13]
SLC34A2	Solute carrier family 34 member 2	PULAM	Transporter	[14]
SLC39A13	Solute carrier family 39 member 13	ZIP13	Transporter	[13]
SLC6A1	Solute carrier family 6 member 1	hGAT-1	Transporter	[14]
SLC6A15	Solute carrier family 6 member 15	NTT73	Transporter	[14]
SLC6A2	Solute carrier family 6 member 2	NAT1	Transporter	[14]
CFTR	Cystic fibrosis transmembrane conductance regulator	MRP7	Transporter	[14]
GLRB	Glycine receptor beta	HKPX2	Transporter	[14]

3.1 Hypermethylated Genes in the B-Cell Receptor-Dependent Signaling Pathway

In ALL, several components of the B cell receptor signaling pathway exhibit epigenetic alterations. These include CD19 (CD, cluster of differentiation), CD20 (MS4A1), CD22 and CD79B (Ig-beta subunit of the BCR), as well as adaptor proteins such as SYK (spleen associated tyrosine kinase) and BTK [13,50,59]. Inactivation of these genes leads to the loss of physiological BCR signals that normally regulate cell differentiation. Many of these receptors are targets of current clinical trials related to immunotherapies in ALL [e.g., CD19: NCT05535855, CD20: NCT05292898, CD22: NCT03739814].

Several studies have shown that epigenetic modulation by DNA methyltransferase inhibitors (DNMTi) such as decitabine (5-aza-2′-deoxycytidine) leads to the reexpression of B cell receptor genes that are frequently downregulated or lost in ALL. Hypermethylation of the CD19 promoter has been described to enable antigen-negative escape from CART-19 (chimeric antigen receptor T-cell therapy against CD19) *in vitro* and *in vivo* in mature B cells [50]. Furthermore, treatment of B cells with decitabine increased CD19 mRNA expression [60]. Preclinical data are also available for CD20. Treatment with decitabine resulted in a significant induction of CD20 mRNA and protein in B cell models, which previously suggested that CD20-negative cells could be sensitized to rituximab and other CD20-targeted therapies [52]. For example, CD22 was shown to be hypermethylated in the KMT2A-r B-ALL subtype [13]. In addition, chidamide, an HDAC (histone deacetylase) inhibitor, has been shown to increase CD22 surface expression, thereby improving the efficacy of CD22-targeted immunotherapies [61]. Clinical protocols in which patients received decitabine in combination with CD19/CD22 dual targeted CAR-T (chimeric antigen receptor T) cell therapy confirmed these results, demonstrating improved response rates, suggesting an epigenetic enhancement of target antigen availability [62]. Collectively, these data demonstrate that decitabine-induced hypomethylation represents a targeted strategy to restore B cell antigen expression, thereby improving the efficacy of antibody-based or cellular immunotherapies in ALL.

Small molecule inhibitors and humanized monoclonal antibodies against RTKs are among the most effective targeted therapies in the clinic [63]. We analyzed that several RTKs are among the genes hypermethylated in B-ALL. One of the most affected gene families in ALL is the Eph receptor tyrosine kinases (ephrin type-A and B receptors). These receptors (EPHA [Ephrin receptor A]2, EPHA4, EPHA5, EPHA6, EPHA7, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4) regulate cell-cell interactions, migration, and tissue organization [64]. Hypermethylation of these genes has been demonstrated in various cohorts of ALL patients with frequencies ranging from 18% to 96% [49]. Particularly noteworthy is the fact that several Eph receptors are often simultaneously silenced by methylation [49]. Their inactivation could thus contribute to the uncontrolled expansion of leukemic precursor cells. In addition to the receptors mentioned above, large-scale methylation analyses have identified other RTKs, including ERBB4 (Erb-B2 receptor tyrosine kinase 4; HER4), FGFR2 as well as FGFR4 (fibroblast growth factor receptor 2/4), KDR (kinase insert domain receptor; VEGFR2) and TIE1 (tyrosine kinase with immunoglobulin like and EGF like domains 1) [13,14].

In addition to the Eph receptors themselves, their ligands, the ephrins (ephrin A and B receptors), are also affected by promoter hypermethylation in ALL. In particular, the promoter region of EFNA [Ephrin A]1, EFNA3, EFNA5, as well as EFNB1 and EFNB2, was identified as frequently methylated [49]. This demonstrates that not only the receptors but also their ligands are epigenetically regulated.

Moreover, hypermethylation of the death receptors 4 (DR4; TRAIL [Tumor necrosis factor-related apoptosis-inducing ligand]-R1) and 5 (DR5; TRAIL-R2) has been demonstrated. These receptors normally mediate apoptosis signals upon binding by TRAIL. Significant promoter hypermethylation has been demonstrated in B-ALL cells, particularly in KMT2A-rearranged, HeH, and dic(9;20) ALL [56]. This hypermethylation, combined with reduced gene expression, allows cells to evade apoptotic signals, which

may increase their resistance to chemotherapy. Decitabine has been shown to terminate methylation of DR4 gene promoters and restore DR4 gene expression [65]. Moreover, some cells have been shown to be resistant to TRAIL-induced cell death. Decitabine enhances the effect of TRAIL by inducing cell apoptosis. This, in turn, is achieved through epigenetic modification of decitabine, which leads to increased DR4 expression [66].

3.2 Hypermethylated Genes in the KMT2A-r B-ALL Subtype

The hypermethylated genes in the KMT2A-r subtype include CD37, CD52, CD68, SIGLEC15 (sialic acid-binding immunoglobulin-like lectin 15), and CCR6 (C–C chemokine receptor type 6) [13] (Table S1). CD37 and CD52 are primarily expressed as B and T cell surface proteins, while CD68 is primarily a macrophage marker and plays an important role in tumor immunology [67–69]. CD52 is also a target of different clinical trials with immunotherapeutics in ALL [NCT00983528 and NCT00089349]. SIGLEC15 is an interesting immune checkpoint molecule and a potential target for cancer therapy [70]. The chemokine receptor CCR6 (CD196) is a G protein-coupled receptor on leukocytes that is responsible for signaling upon binding of the chemokine CCL20 (C–C motif chemokine ligand 20) and plays a role in the immune response and cell migration [71]. Specifically, it is silenced in KMT2A-rearranged infantile ALL by promoter hypermethylation. This inactivation is reversible by treatment with hypomethylating agents such as decitabine [26]. Other chemokine receptors, such as CCR7 (DUX4/ERG-alt and Ph-positive) and CCR10 (DUX4/ERG-alt), are also methylated in ALL [13].

3.3 Hypermethylated Genes in the ETV6-RUNX1 B-ALL Subtype

The ETV6-RUNX1 subtype shows hypermethylation of interesting therapeutic genes such as CD44, SIGLEC9 (sialic acid-binding Ig-like lectin 9), TSPAN15 (tetraspanin 15), SLC2A5 (solute carrier family 2 member 5), and some members of the PCDH-gamma family (PCDH-gamma A5, A8, B2, B3, and B4) [13,14] (Table S2). CD44 regulates cell adhesion, migration, and lymphocyte homing and is therefore an important marker for cancer stem cells [72]. Its overexpression is associated with metastasis and chemoresistance [73]. SIGLEC9 binds sialylated glycans on cell surfaces and inhibits immune activation via ITIM motifs (inhibitory tyrosine-based motifs). Tumor cells utilize SIGLEC9 ligands to evade immune escape [74]. TSPAN15 organizes tetraspanin-enriched microdomains (TEMs) that can modulate signaling pathways such as integrin signaling and ADAM10 activity (protease for the Notch signaling pathway) [75]. SLC2A5 (GLUT5) is an important transporter of fructose, which serves as an important energy source for tumor cells [76]. The Protocadherin-gamma family has been suggested to play a potential role as tumor suppressors in some cancers [77].

3.4 Hypermethylated Genes in the TCF3-PBX1 B-ALL Subtype

The Ig-beta receptor (CD79B), CLEC4D (C-type lectin domain family 4 member D), and the FCGR2A (Fc gamma receptor IIa) receptor are affected by hypermethylation in the TCF3-PBX1 subtype [13] (Table S3). CD79B, together with CD79A (Igα), forms the signal transduction module of the BCR. It contains ITAM motifs (immunoreceptor tyrosine-based activation motifs) that are phosphorylated upon antigen binding to the membrane-bound immunoglobulin chain. Moreover, it recruits SYK kinase for B cell activation, proliferation, and differentiation [78]. Furthermore, a CD79b CAR-T cell therapy is being investigated in clinical trials for patients with relapsed and/or refractory acute lymphoblastic leukemia [NCT04609241]. CLEC4D (C-type lectin domain family 4, member D) primarily recognizes mycobacteria and binds to specific microbial structures via the C-type lectin domain. It forms heterodimers with CLEC4E and

activates the Syk-CARD9-NF-κB signaling pathway, leading to the induction of proinflammatory cytokines (TNFα, Interleukin-6, IL-23) [79]. FCGR2A is an activating Fcγ receptor (ITAM motif) on monocytes and macrophages that mediates phagocytosis of opsonized pathogens [80].

3.5 Hypermethylated Genes in the High Hyperdiploid B-ALL Subtype

CLSTN2 (calsyntenin 2) was found to be hypermethylated in the HeH subtype of pediatric B-ALL cases [13] (Table S4). FAT1 (FAT atypical cadherin 1) is also highly methylated in the HeH subtype, leading to reduced expression. Knockdown of FAT1 in cells with high FAT1 expression inhibits cell growth and triggers apoptosis [53].

Hypermethylation also affects the family of transmembrane tyrosine phosphatases (PTPR [Protein tyrosine phosphatase receptor] G, PTPRK, PTPRM, PTPRO). These receptors act as negative regulators of signal transduction. In ALL, they are hypermethylated in 47–64% of cases, with methylation of PTPRK (protein tyrosine phosphatase receptor type K) in particular being associated with a worse prognosis [54]. PTPRK acts as a negative regulator of EGFR (epidermal growth factor receptor) signaling [81], and methylation of the PTPRK promoter is associated with increased cell proliferation, decreased apoptosis, and reduced overall survival [54]. Methylation was shown to be reversible with DNMTi and histone deacetylase inhibitors [54].

The cell surface receptor DSC3 (desmocollin 3) is hypomethylated in patients with the ETV6-RUNX1 subtype compared to other B-ALL subtypes [82]. However, in the HeH, KMT2A-r, Ph-positive, Ph-like/CRLF2-r and TCF3-PBX1 B-ALL subtype, DSC3 was hypermethylated and downregulated compared to non-leukemic controls [13,14]. High hypomethylation and strong overexpression of IL2RA (interleukin 2 receptor subunit alpha; CD25) have been demonstrated in Ph-positive ALL cells [12], while hypermethylation of IL2RA has been shown in KMT2A-r and TCF3-PBX1 cells [13]. This suggests that different methylations states can be observed for some genes in different ALL subtypes. Consequently, this also means that a gene can be hypermethylated in multiple ALL subtypes. CD25 is also the subject of clinical investigations for high-risk ALL cases treated with immunotherapies [NCT05139004].

3.6 Hypermethylated Genes in the Ph-Positive B-ALL Subtype

Hypermethylated and downregulated genes of the Ph-positive subtype include CD38, CSF1R (colony-stimulating factor 1 receptor), LPAR2 (lysophosphatidic acid receptor 2), and LILRB4 (leukocyte immunoglobulin-like receptor B4) [13] (Table S5). CD38 possesses enzymatic activity as an NADase/cyclase, producing cADPR and ADPR (adenosine diphosphate-ribose) as important second messengers for Ca^{2+} signaling pathways. It is highly expressed in multiple myeloma cells and treated with daratumumab [83]. It also appears to be relevant in CLL (chronic lymphocytic leukemia) [84]. CD38 is currently being investigated in several clinical trials as part of immunotherapeutic treatment for B- and T-cell acute lymphoblastic leukemia [NCT05038644 and NCT03860844]. CSF1R (CD115) regulates the survival, proliferation, and differentiation of monocytes/macrophages after M-CSF stimulation and drives tumor-associated macrophages in tumors [85]. LPAR2 regulates Rho, PLC, MAPK, and PI3K signaling pathways after Lysophosphatidic acid (LPA) stimulation [86]. LILRB4 (CD85k, ILT3) belongs to the inhibitory immune checkpoint receptor family (ITIM motif), which is mainly expressed on monocytic cells, dendritic cells, and myeloid-derived suppressor cells, and is upregulated in AML (acute myeloid leukemia) [87]. It is an interesting target for immunotherapy, as blocking LILRB4 could enhance T cell activity against tumors.

3.7 Hypermethylated Genes in the DUX4-r B-ALL Subtype

Large-scale methylation analyses have also identified other receptor- or signaling-related genes as methylated. Interesting genes of the DUX4/ERG-alt subtype are ICAM3 (intercellular adhesion molecule 3), L1CAM (L1 cell adhesion molecule), CD33, CD48, CNR2 (cannabinoid receptor 2), and CXCR3 (C–X–C motif chemokine receptor 3) [13] (Table S6). ICAM3 binds to LFA-1 (integrin CD11a and CD18) and is important for the initial contact between immune cells (e.g., T cells and APCs) [88]. L1CAM is frequently overexpressed in many solid tumors and promotes invasion, metastasis, and chemoresistance [89]. CD33 (Siglec-3) is an inhibitory receptor that regulates the cell activation of myeloid cells. It is an important target molecule in AML, and the CD33-directed ADC Gemtuzumab ozogamicin is approved for AML therapy [90]. CD33 is also being investigated in clinical trials for high-risk ALL cases being treated with immunotherapies [NCT00038805]. CD48 exerts a ligand function for the natural killer (NK) cell receptor CD244, thereby regulating the activity of NK cells and T cells. Therefore, the CD48-CD244 axis is relevant for infections, autoimmunity, and tumor defense [91]. CNR2 (CB2) binds endogenous cannabinoids and exerts immunomodulatory and anti-inflammatory effects, which are also required for the energy metabolism of leukemia cells [92]. CXCR3 mediates the migration of immune cells into inflamed or tumor tissue [93].

3.8 Hypermethylated Genes in T-ALL

In T-ALL, components of the T cell receptor (TCR) signaling pathway are affected. These include the CD3 subunits CD3G and CD3D, as well as the associated kinases LCK (lymphocyte cell-specific protein-tyrosine kinase), LAT (linker for activation of T cells), and ZAP70 (zeta-chain-associated protein kinase 70) [13,94]. Methylation leads to the silencing of these important signaling axes, which blocks T cell differentiation and contributes to leukemogenesis [95,96].

In addition to gene promoter methylation and its effects on ALL subgroups described above, it should be mentioned that important transcription factors can also influence receptor expression in ALL, as described for the FLT3 (FMS-like tyrosine kinase 3) gene [97].

Despite the molecular and genetic differences in the subgroups of ALL, there are commonalities in epigenetic reprogramming and in the molecular mechanism of action through demethylation.

4 Epigenetic Reprogramming and Molecular Mechanism of Action through Demethylation

The identification of methylated receptor genes has several clinical implications. They can serve as diagnostic and prognostic markers, and epigenetic drugs such as DNMTi could restore the expression of silenced receptors [98,99]. Decitabine is a nucleoside analogue and belongs to the so-called DNA methyltransferase inhibitors. It is used clinically in myelodysplastic syndromes, AML, and in other malignancies [100]. Its mechanism of action is based on the irreversible inhibition of DNA methyltransferases, with far-reaching consequences for signal transduction and gene expression. Decitabine is incorporated into DNA during DNA replication in proliferating cells. DNA methyltransferase 1 (DNMT1) binds covalently to the incorporated decitabine nucleotide. This leads to an irreversible block of enzymatic activity and the degradation of DNMTs [101]. The consequence is global hypomethylation of DNA.

The pharmacological reversal of aberrant DNA methylation represents a central mechanism of epigenetic therapies. The use of DNMTi, such as decitabine, leads to the reactivation of previously silenced genes. This particularly affects tumor suppressor genes such as p15/CDKN2B (cyclin dependent kinase inhibitor 2B) and p16/CDKN2A (cyclin dependent kinase inhibitor 2A), as well as genes involved in apoptosis induction (BCL2 Associated X [BAX], BCL2 Antagonist/Killer 1 [BAK]) [101,102]. In this way, DNMTi-treatment leads to epigenetic reprogramming of malignant cells and creates a functional basis

for improved therapeutic susceptibility (Fig. 3). Hypomethylation-induced reexpression of key regulatory genes triggers a variety of changes in the intracellular signaling pathway:

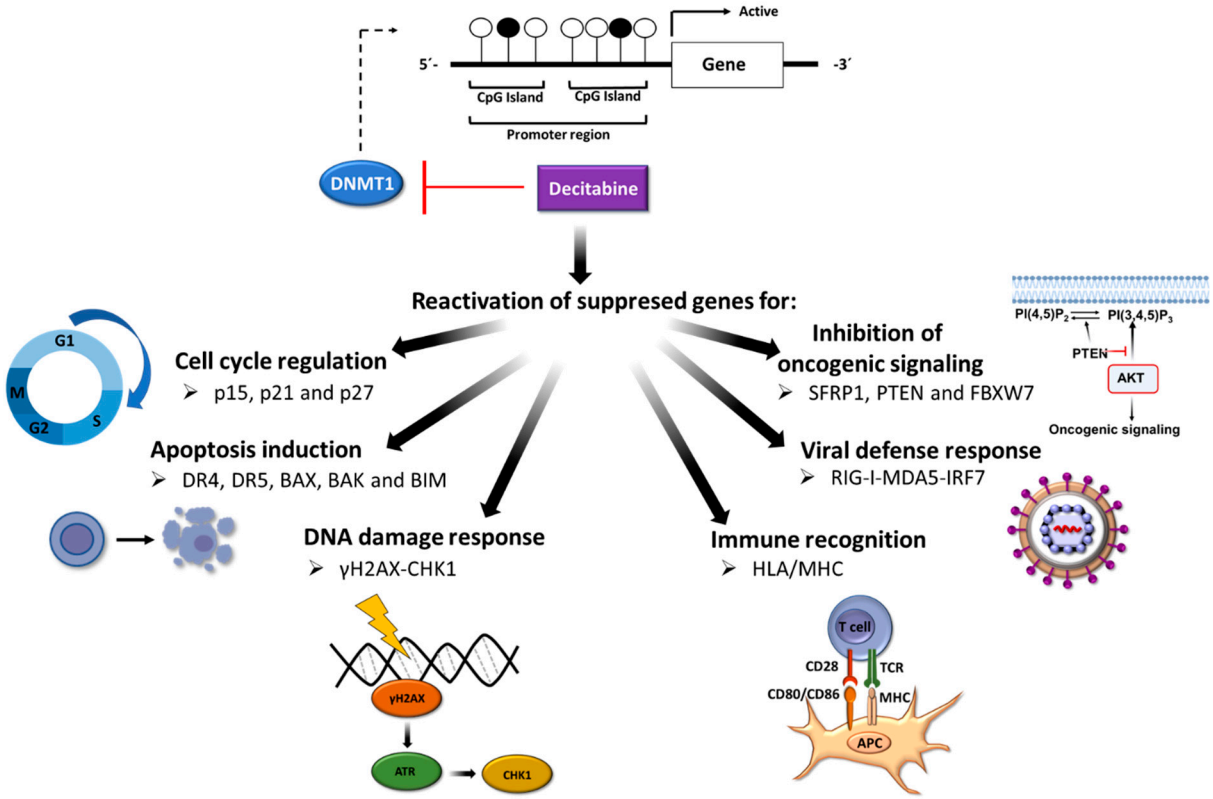

Figure 3: Schematic representation of the central signal transduction mechanisms of decitabine in tumor cells. Decitabine induces far-reaching signal transduction changes via epigenetic reprogramming. These include both direct tumor suppressive effects (cell cycle arrest, apoptosis, DNA damage response) and immunomodulatory mechanisms (viral mimicry, reexpression of HLA and other antigens). This results in a multifaceted therapeutic potential that addresses both cell-intrinsic and immunological targets. Abb: APC—antigen-presenting cells; TCR—T cell receptor; MHC—major histocompatibility complex; HLA—human leukocyte antigen; AKT—protein kinase B; PTEN—phosphatase and tensin homolog; H2AX—H2A.X variant histone; ATR—ataxia telangiectasia and rad3-related; CHK1—checkpoint kinase 1; RIG-I—retinoic acid inducible gene I; MDA5—melanoma differentiation-associated protein 5; IRF7—interferon regulatory factor 7; BAX—BCL2 associated X; BAK—BCL2 antagonist/killer 1; BIM—Bcl-2 interacting mediator of cell death.

1. Cell cycle regulation: The reexpression of CDK inhibitors such as p15, p21 (CDKN1A), and p27 (CDKN1B) leads to stable cell cycle arrest in the G1 phase [103,104].
2. Apoptosis induction: Upregulation of death receptors (DR4, DR5) and pro-apoptotic factors (BAX, BAK, Bcl-2 Interacting Mediator of cell death [BIM]) promotes the activation of extrinsic and intrinsic apoptosis pathways [56,102,105], resulting in the activation of apoptosis [106].
3. DNA damage response: DNMTi-induced hypomethylation activates markers of the DNA damage response, such as γH2AX (phosphorylated form of the H2AX histone protein) and signaling axes via ATR (ataxia telangiectasia and rad3 related)/ATM (ataxia telangiectasia mutated)—Chk1/Chk2 (checkpoint kinase 1/2) [101,107].

4. Viral defense response: Demethylation of genes of endogenous retroviruses (ERVs) leads to the accumulation of double-stranded RNA (dsRNA), which activates the immune signaling in cancer through the type I interferon signaling pathways via RIG-I (retinoic acid inducible gene I)/MDA5 (melanoma differentiation-associated protein 5) and IRF7 (interferon regulatory factor 7) [108] and makes the patient more subsceptible to immune therapy.
5. Immune recognition: Reexpression of HLA (human leukocyte antigen)/MHC (major histocompatibility complex) molecules and cancer testis antigens improves tumor recognition by cytotoxic T lymphocytes and enhances immune surveillance [13,109–112].
6. Oncogenic signaling pathways: Oncogenic signaling pathways such as WNT/β-catenin, PI3K/AKT (phosphoinositide 3-kinase/protein kinase B), and NOTCH (neurogenic locus notch homolog protein) can be indirectly inhibited by reactivating epigenetically silenced tumor suppressors (e.g., SFRP1, PTEN, FBXW7) [113–115].

Many of the molecular mechanisms of action following demethylation involve intracellular signaling molecules. These are often more difficult to target therapeutically, as suitable inhibitors for kinases must be found. A corresponding or specific inhibitor does not exist for every kinase. Therefore, immunological targets on the cell surface often represent an easier target, since the development of suitable antibodies has made great progress in recent years.

5 Immunotherapeutic Approach for the Treatment of Hypermethylated Receptor Genes in ALL

ADCs combine the high targeting accuracy of monoclonal antibodies with the efficacy of cytotoxic agents. They consist of a monoclonal antibody and a chemical linker that delivers a cytotoxic drug (payload) specifically to cancer cells. Since the first FDA approval in 2000 (gemtuzumab ozogamicin), the field of research has developed rapidly. To date, 12 ADCs (tisotumab vedotin, loncastuximab tesirine, belantamab mafodotin, sacituzumab govitecan, trastuzumab deruxtecan, enfortumab vedotin, polatuzumab vedotin, inotuzumab ozogamicin, trastuzumab emtasine, brentuximab vedotin, and gemtuzumab ozogamicin) have been approved for the treatment of hematological and solid tumors, and over 400 novel ADCs are in various stages of development worldwide, including over 200 in clinical trials [116]. The CD22-targeted ADC inotuzumab ozogamicin (InO) received approval for relapsed/refractory (r/r) B-ALL [117]. New approaches, such as computational and AI-based (artificial intelligence) tools (e.g., ADCNet) [118], are improving the design and prediction of ADC activity. New payload classes such as immunoagonists, RNA inhibitors, and protein degraders are also being developed [119]. Advances in linker technologies, payload stability, and antibody engineering are driving further development.

Clinical therapies with antibody-drug conjugates and combination therapies with these are increasing rapidly and improving patient prognosis. Datopotamab deruxtecan (anti-TROP2) for HR-positive/HER2-negative breast cancer was approved in early 2025 [120]. Telisotuzumab vedotin, a c-MET-targeted ADC for non-small-cell lung cancer (NSCLC), received FDA approval in May 2025 [121]. Sacituzumab govitecan (anti-TROP2) in combination with pembrolizumab (PD-1 inhibitor) is showing progress in patients with metastatic urothelial cancer [122]. Trastuzumab deruxtecan (anti-HER2) is currently being investigated in combination with pertuzumab (anti-HER2) as a potential first-line therapy for HER2+ metastatic breast cancer [123]. Enfortumab vedotin (anti-NECTIN4) in combination with pembrolizumab (PD-1 inhibitor) doubles overall survival in bladder cancer [124]. Tisotumab vedotin, directed against tissue factor (F3), is approved for recurrent/refractory cervical cancer [125]. Sigvotatug vedotin, an ADC targeting integrin β-6 in NSCLC, is making promising progress [126].

In the treatment of B-ALL, standard chemotherapy leads to significantly worse outcomes than new immunotherapies and combinations. This has been demonstrated by international, randomized trials [127,128]. Tumor heterogeneity and early payload release remain major obstacles and require new targets in ALL. The optimal target for ADC development should exhibit both high and uniform expression in tumor cells while simultaneously preventing expression in normal and healthy cells [129]. However, ADC targets currently under development exhibit a broad expression profile in both tumor and normal cells. Toxicity, such as hematological side effects, hepatotoxic effects, and pulmonary damage, also limits their use. Some studies have already very successfully identified ADC targets for solid tumors [129–131]. The lack of validated suitable secondary target antigens for ALL is also a key reason for the failure of treatment of resistant cells. The future lies in personalized approaches, AI-assisted predictions, and new ADC formats (such as bispecific or immunostimulatory ADCs). Therefore, the identification of a broad repertoire of diverse target antigens is essential.

In addition to the known B-cell markers CD19, CD20, and CD22, which would benefit from decitabine-dependent expression enhancement, there are further candidates (e.g., CD33, CD38, KDR, or IL2RA) that should be investigated with priority and for which therapeutic antibodies already exist, as described in the following chapter.

6 Therapeutic Perspectives: Combinations of Epigenetics and Targeted Therapy of Surface Molecules

6.1 Immunotherapy and Epigenetic Priming for ALL

Immunotherapy has fundamentally changed the treatment of B-cell acute lymphoblastic leukemia (B-ALL) over the past decade, going far beyond traditional chemotherapy. Bispecific T-cell engagers (BiTEs), antibody-drug conjugates (ADCs), and CAR T-cell therapies frequently achieve deep remissions in relapsed/refractory cases. Classic targets (CD19, CD22, CD20) are clinically validated, while a new generation of bispecific antibodies and advanced CAR T-cell constructs is being developed to address antigen loss, heterogeneity, and persistence issues. In parallel, novel, epigenetically modulated combination strategies (e.g., epigenetic priming) are driving clinical development. Furthermore, allogeneic CAR T cells, CAR NK cells, CAR NKT, and other alternative platforms are currently under development [132,133].

Combinations of DNMT inhibitors (e.g., decitabine/azacitidine) with immunotherapies aim to increase antigen density, enhance the immune response, and make tumor cells more visible to immune mechanisms [134]. Initial data show that epigenetic priming can increase the expression of antigens such as CD22/CD38 [61,135]. While direct combination therapies for ALL are currently being investigated primarily in phase I/II trials and exploratory studies, there are already registered studies investigating such a priming effect through epigenetic modulation prior to CAR-T cell or BiTE therapies, particularly in myelodysplastic syndromes, AML, or lymphoma [60,136,137]. These could potentially be applied to future treatment approaches for ALL. However, the potential risks of treatment (e.g., induction of oncogenes, upregulation of checkpoints) necessitate close monitoring and the use of rational combination therapies (e.g., with checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4). Decitabine is currently being investigated as part of a priming strategy prior to tandem CAR (CD19/CD20) infusion in aggressive, relapsed/refractory B-cell non-Hodgkin lymphoma with high tumor burden [NCT04553393]. Furthermore, a combination of decitabine, venetoclax, and blinatumomab is being tested as maintenance therapy after hematopoietic stem cell transplantation (HSCT) [NCT06393985]. This is an interesting example of epigenetic priming strategies in combination with BiTE and BCL2 inhibition in follow-up studies.

6.2 CAR-T Cell Therapy for ALL

The first generation of CAR-T cell therapies has fundamentally changed the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL) [138]. These CD19-targeted products have enabled deep remissions in previously difficult-to-treat cases and are now standard therapy for eligible patient populations. Tisagenlecleucel, for example, demonstrates groundbreaking data with high initial remission rates and sustained remissions in children and young adults with ALL [NCT02435849] [139]. Obecabtagene autoleucel, an anti-CD19 CAR-T product approved in the US in November 2024 and receiving positive EMA assessments in 2025, shows high response rates and a favorable safety profile in adults with r/r B-ALL [NCT04404660] [140]. Relapses due to antigen loss or insufficient CAR persistence remain a challenge.

Therefore, an important trend is the development of dual- or multi-directed CAR T-cell constructs to overcome antigen loss and tumor heterogeneity. Tandem CARs, or bispecific CARs that simultaneously target multiple surface antigens, are being evaluated preclinically and in early clinical trials [141]. These designs aim to improve the duration of remissions and reduce resistance. Numerous early phase I/II trials are already underway for dual/tandem CARs, such as the CD19/CD22 combination. Initial clinical results show reduced antigen escape rates [NCT05442515, NCT03233854, and NCT04499573].

6.3 Bispecific Antibodies for ALL

Bispecific antibodies typically bind a tumor antigen and CD3 on T cells, thereby mediating the direct recruitment and activation of cytotoxic T cells against malignant cells. The original BiTE format is clinically established in ALL and is increasingly being used in MRD (minimal residual disease) settings. Blinatumab (anti-CD19 x anti-CD3) connects CD3-positive T cells with CD19-positive B-ALL cells, leading to direct T-cell-mediated lysis of B-ALL cells. Blinatumomab is used not only in refractory cases but also increasingly in MRD-positive cases, where high MRD negativity rates can be achieved [142]. Several preclinical and early clinical programs for CD22-targeted BiTE candidates (CD22 × CD3) are currently active. Initial results show activity in CD19-negative or CD19-relapsed cases and could potentially act synergistically with blinatumomab in the future [143]. CD38-targeted therapies (CD38 × CD3; XmAb18968) are in early stages of research for acute leukemias, particularly acute lymphoblastic T-cell leukemia (T-ALL) [NCT05038644] [144]. This approach targets CD38-positive blasts and could be of particular interest in CD19/CD22 relapses. Furthermore, numerous new candidates outside of ALL are currently being investigated in clinical trials [145]. In the future, these concepts could be adapted for ALL if they demonstrate sufficiently positive results for this target.

6.4 Established ADCs and Therapeutic Antibodies for ALL

A particularly promising strategy for ALL involves combining epigenetic therapies with targeted inhibitors or ADCs. Hypomethylating agents can restore receptor expression, thus making them accessible to ADCs or inhibitors. This combination could achieve synergistic effects and overcome treatment resistance in ALL. However, treatment with DNMTi alone could lead, at least partially, to a complex reactivation of gene expression. This could be particularly true for receptors that enhance proliferative signaling pathways. Subsequent intervention, for example, with kinase inhibitors, could be promising in many cases. However, receptors in the ALL are often constitutively activated, and attempts to inhibit individual molecules frequently lead to complex feedback mechanisms that result in reciprocal influences of the signaling pathways [63,146]. For example, inhibition of HER2 (human epidermal growth factor receptor 2) activates FOXO3A (forkhead box class O 3A)-mediated ERBB3 transcription as a compensatory cell survival

mechanism [147]. In addition, inhibition of EGFR has been described to upregulate the expression of PDGFRB, MET (hepatocyte growth factor receptor), and AXL [148–150]. A more advanced approach involves the targeted delivery of cytotoxins into ALL cells with high antigen expression, which can be achieved via antibodies (e.g., ADCs). Table 2 provides a current overview of the currently approved antibodies for different clinical therapies. Internalization of the antibody-cytotoxin complex into the target cell circumvents the aforementioned compensatory signaling processes.

The B cell receptor signaling pathway plays a central role in B-ALL and includes receptors such as CD19 and CD79B, and the downstream kinase SYK. Inhibitors of this pathway have proven effective in other B cell malignancies, particularly SYK inhibitors such as fostamatinib [151].

Loncastuximab tesirine is a CD19-targeted ADC consisting of a humanised immunoglobulin G1 (IgG1) kappa monoclonal antibody and conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent. It is approved for adult patients with relapsed or refractory large B cell lymphoma [152]. Polatuzumab vedotin is a CD79B-targeted ADC consisting of a humanized IgG1 monoclonal antibody conjugated to MMAE (monomethyl auristatin E) via a cleavable linker. It is approved for various forms of diffuse large B cell lymphoma (DLBCL) [153]. These agents are not yet established in ALL, but represent a promising concept, especially in combination with epigenetic modulators. The CD22-targeted ADC inotuzumab ozogamicin is used in relapsed/refractory (r/r) B-ALL patients [117], and recent large phase III data demonstrate remission benefits [NCT03150693]. Gemtuzumab ozogamicin (anti-CD33) targets CD33 on myeloid blasts and is therefore approved for treatment of AML [154], but is also an interesting ADC for high-risk B-ALL [NCT00038805].

Rituximab, Ofatumumab, and Obinutuzumab (anti-CD20) are classic B-cell-targeted antibodies that induce ADCC (antibody-dependent cell-mediated cytotoxicity), CDC (complement-dependent cytotoxicity), and apoptosis of the cell. They are used in non-Hodgkin lymphoma (NHL), CLL, and autoimmune diseases [155].

Table 2: Approved therapeutic antibodies against methylated receptors in ALL.

Gene ID	Synonym	Approved Therapeutic Antibody
CD52	EDDM5	Alemtuzumab
IL2RA	CD25	Basiliximab
CD38	ADPRC 1	Daratumumab, Isatuximab
CD33	SIGLEC3	Gemtuzumab Ozogamicin (ADC)
CD22	SIGLEC2	Inotuzumab Ozogamicin (ADC)
CD19	CD19	Loncastuximab Tesirine (ADC), Blinatumomab
CD79B	Igbeta	Polatuzumab Vedotin (ADC)
KDR	VEGFR2	Ramucirumab
LAG3	CD223	Relatlimab
MS4A1	CD20	Rituximab, Ofatumumab, Obinutuzumab

6.5 New Putative Targets for Antibody Treatment of ALL with Approved Therapeutic Antibodies

The death receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2) belong to the TNF receptor family and are frequently hypermethylated in ALL, limiting their pro-apoptotic function [56]. Agonistic antibodies induce apoptosis via an extrinsic signaling pathway. They are currently in clinical trials but show limited efficacy in phase II/III studies [156]. Although clinical trials have so far been limited by resistance mechanisms, combination with hypomethylating agents could increase efficacy.

The Eph receptors, particularly EPHA2, EPHA4-7, EPHA10, and EPHB1-4, are frequently hypermethylated in ALL [11]. Despite epigenetic silencing, they play a key role in tumor biology. Specific

inhibitors and antibodies have been developed for EPHA2. These include the ADC MEDI-547, which has been tested preclinically in solid tumors [157], and the humanized antibody DS-8895a, which demonstrated safety and limited efficacy in a phase I trial [158]. Preclinical data show that reexpression by DNA methyltransferase inhibitors could enhance the effects of these targeted therapies [49]. Furthermore, tyrosine kinase inhibitors such as dasatinib and nilotinib possess off-target activity against Eph receptors, supporting their potential use in ALL.

Gemcitabine shares structural similarities with the DNMTi decitabine, but was originally developed as a pyrimidine cytosine analogue, which acts as an antimetabolite [159]. Gemcitabine has previously been shown to reactivate epigenetically silenced genes such as ERBB2 (HER2). For example, treatment of breast cancer cells with low HER2-expression with gemcitabine leads to increased HER2 expression and enhanced antitumor effects of trastuzumab emtansine [160]. HER2 is expressed in approximately 30% of B-ALL cases, and 56% of Ph (philadelphia)-positive ALL cases show increased HER2 activity [161]. Two HER2-targeted ADCs, trastuzumab emtansine and trastuzumab deruxtecan, are approved as second-line therapy after trastuzumab taxane-based therapy in patients with HER2-positive breast cancer [162,163].

Alemtuzumab (anti-CD52) binds CD52 on T and B cells and leads to severe cell depletion. It is used for CLL and transplantation [164]. Basiliximab (anti-IL2RA/CD25) inhibits CD25 and blocks T cell activation. It is primarily used in kidney transplantation [165]. Daratumumab and isatuximab (anti-CD38) are used to treat multiple myeloma and lead to the induction of ADCC, CDC, and cell apoptosis. Daratumumab also has an additional immunomodulatory effect (elimination of suppressive Tregs/MDSCs) [166]. Milatuzumab targets CD74, an invariant chain of MHC II. It has been clinically tested in CLL and NHL (Phase I/II) but is not yet approved [167]. Bemarituzumab targets FGFR2b, specifically in gastric cancer with FGFR2b overexpression. It exerts its effect by blocking ligand binding. It is not currently approved, but has a breakthrough therapy designation [168]. Emactuzumab targets CSF1R on tumor-associated macrophages and reduces immunosuppressive microenvironmental components. It is not currently approved but has received fast-track designation status [169]. Ramucirumab is approved for the treatment of gastric and colon cancer because it targets VEGFR2 (vascular endothelial growth factor receptor 2) and angiogenesis [170]. LAG3 inhibitors show promising effects in overcoming resistance mechanisms that cannot be overcome by PD-1 inhibitors [171]. Relatlimab blocks the LAG3 (lymphocyte-activation gene 3) checkpoint. In combination with nivolumab (anti-PD-1), it is approved for the treatment of melanoma [172]. CD137 is a costimulatory molecule on the surface of activated T cells and other immune cells that enhances the anti-tumor response by increasing their activation, survival, and function [173]. Urelumab and utomilumab target this receptor, with utomilumab being the weaker but safer agonist. They are in clinical development, but not approved [174].

The transmembrane tyrosine phosphatases PTPRG, PTPRK, PTPRM, and PTPRO are hypermethylated in a significant proportion of ALL cases [54]. Specific inhibitors or ADCs do not yet exist. Therefore, the therapeutic strategy focuses on reactivating expression using hypomethylating agents such as azacytidine or decitabine [54]. Preclinical studies show that restoring PTPR expression can lead to a reduction in proliferative signaling pathways (ERK, STAT3/5, and PI3K/AKT) [54,175]. The chemokine receptor CCR6 is hypermethylated and thus inactivated, particularly in KMT2A-rearranged infantile ALL [26]. Although no approved ADCs against CCR6 exist to date, antagonists and blockade strategies have been investigated in preclinical models. Experiences with CCR4, for which mogamulizumab is established as a therapeutic antibody [176], suggest that similar approaches could be developed for CCR6 in the future.

The T cell receptor signaling pathway includes the CD3 complex and the tyrosine kinases LCK and ZAP70. Inhibitors such as dasatinib can block this pathway and are being tested preclinically in the treatment

of T-ALL [177]. Muromonab (OKT3, anti-CD3) was the first approved mAb (1986) and leads to T cell depletion by binding to CD3. It was withdrawn from the market due to severe side effects (cytokine storm).

In summary, in addition to the classic B-ALL targets CD19, CD20, and CD22, which are increasingly being incorporated into various immunotherapy strategies and techniques, current data show that there is a significant need for further target structures for the treatment of B- and T-ALL, particularly for high-risk groups (KMT2A-r B-ALL, Ph-positive B-ALL, and T-ALL) and r/r cases. Surface receptors such as CD33 (DUX4), CD38 (Ph-positive), CD52 (KMT2A-r), CD79B (KMT2A-r and TCF3-BPX), or IL2RA (KMT2A-r and TCF3-BPX) could represent a further solution for these cases in the future. Due to the existence, at least in part, of established antibodies, we hereby suggest that these therapies, also in combination with epigenetic priming, be applied to ALL.

7 Summary

ALL is characterized by genetic and epigenetic dysregulation. Receptor genes and their signaling pathways are frequently affected by promoter hypermethylation. The inactivation of Eph receptors, BCR and TCR components, and death receptors such as DR4/DR5 underscores the central role of epigenetic mechanisms [13,49,50,56,178]. These findings open new perspectives for diagnostics, prognosis, and therapy. Analysis of DNA methylation patterns has shown that certain subgroups of ALL are particularly frequently affected by hypermethylation and could therefore benefit most from improved therapy. This is particularly true for KMT2A-rearranged infantile ALL and T-ALL with a CIMP-positive phenotype [5,13,16]. Both KMT2A-rearranged ALL and T-ALL, along with Ph-positive ALL cases, are among the high-risk subgroups within ALL [179,180], and patients in these groups could significantly benefit from improved treatment strategies. Furthermore, a cross-subtype pattern of constitutive hypermethylation exists [45]. These epigenetic alterations are not only relevant for understanding disease pathogenesis but also offer potential targets for personalized therapeutic approaches in the form of antibody immunotherapies.

The targeted increase in gene expression of receptor genes prior to immunotherapy is a promising approach to optimize the efficacy and durability of modern ALL treatments. It improves binding efficiency, reduces the risk of antigen loss, and enhances immune-mediated cytotoxicity. In the long term, this strategy could significantly contribute to reducing relapse rates and improving the prognosis of ALL patients [181].

However, caution is advised, as gene demethylation does not always lead to direct re-expression of surface proteins. Post-transcriptional regulation, for example by miRNAs, and post-translational regulation (folding, transport, cleavage) can modulate protein levels or influence the cell surface localization of proteins [182,183]. Therefore, protein expression must be carefully reviewed for each protein under investigation.

Importantly, not all cells uniformly re-express receptors after DNMTi treatment. Both interpatient heterogeneity and intraclonal variability significantly influence treatment success [184]. This carries the risk that cells with low receptor expression may survive and potentially lead to relapse. Some promoters of the same gene may be highly methylated, while others may be less so [185]. Histone modifications and three-dimensional chromatin structure can influence how efficiently DNMTi can reactivate genes [186]. Furthermore, cytokines, stromal signaling, and metabolic status can modulate gene expression. It has also been shown that some CD19-negative clones exhibited unmethylated promoters due to alternative splicing or deletion [50]. Furthermore, decitabine treatment led to upregulation of CD38 in most AML blasts, but the fraction of cells remained low-expressing [187]. Additionally, DNA methylation in promoters is well known to silence genes and is the presumed therapeutic target of methylation inhibitors. However, it must be considered that gene body methylation correlates positively with expression [188]. In these

cases, it was shown that treatment with DNMT inhibitors not only reactivates genes but also reduces their overexpression [188]. The timing also plays an important role, as protein expression at the cell surface often peaks only days after maximum mRNA induction, resulting in a time lag between RNA and detectable protein expression at the cell surface [65,189]. Furthermore, it should be considered that DNMT inhibitors are incorporated during DNA replication, so quiescent cells may express receptors more slowly or not at all [107].

However, global demethylation carries further risks. Besides its primary target, it can also activate oncogenes or upregulate immune checkpoints. Examples include the HOXA cluster genes in myeloid leukemia and KMT2A-r B-ALL. DNMTi-induced overexpression of HOXA9/HOXA10 promotes self-renewal and proliferation [190,191]. DNMTi can temporarily increase their transcription, potentially leading to the expansion of leukemic clones. DNMTi can also increase the transcription of immune checkpoint genes (e.g., PD-L1, PD-L2, CTLA-4) [192]. As a result, tumor cells can become more resistant to T-cell attacks, potentially weakening the efficacy of CAR-T cell or BiTE therapies if they are not combined with checkpoint blockade. The risks associated with this treatment, therefore, necessitate close monitoring and rational combination therapies. The combination of DNMTi and checkpoint blockade could counteract immune escape mechanisms. Furthermore, low-dose or short-term DNMTi treatment can promote antigen expression without causing excessive global demethylation [193].

Research on ADCs targeting hypermethylated receptor genes in ALL is at an early but dynamic stage of development. While specific drugs targeting CD19, CD22, CD38, CD33, and Eph receptors are already in clinical trials, approaches targeting CCR6 or the PTPR family are largely preclinical. The combination of epigenetic reactivation with targeted inhibitors and especially ADCs is likely to play an important role in new, modern therapeutic approaches for ALL. Accordingly, the further development of new ADCs targeting corresponding targets is of great importance for the future of (high-risk) ALL therapy.

Acknowledgement: None.

Funding Statement: The authors received no specific funding for this study.

Author Contributions: Conceptualization, Patrick A. H. Ehm; methodology, Patrick A. H. Ehm, Christoph Rehbach; software, Patrick A. H. Ehm; formal analysis, Patrick A. H. Ehm, Christoph Rehbach; investigation, Patrick A. H. Ehm, Christoph Rehbach; data curation, Patrick A. H. Ehm; writing—original draft preparation, Patrick A. H. Ehm, Christoph Rehbach; writing—review & editing, Patrick A. H. Ehm, Christoph Rehbach; visualization, Patrick A. H. Ehm; supervision, Patrick A. H. Ehm; project administration, Patrick A. H. Ehm. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The author declares no conflicts of interest.

Supplementary Materials: The supplementary material is available online at https://www.techscience.com/doi/10.32604/biocell.2026.075170/s1. Table S1: Receptor methylation profile of the KMT2A-r subtype of ALL; Table S2: Receptor methylation profile of the ETV6-RUNX1 subtype of ALL; Table S3: Receptor methylation profile of the TCF3-PBX1 subtype of ALL; Table S4: Receptor methylation profile of the HeH subtype of ALL; Table S5: Receptor methylation profile of the Ph-positive subtype of ALL; Table S6: Receptor methylation profile of the DUX4 (ERG-alt) subtype of ALL.

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