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Review

Recent Advances in Chronic Myeloid Leukaemia (CML): Emerging Molecular and Immunotherapeutic Targets

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Abstract

Chronic myeloid leukaemia (CML), a distinct myeloproliferative neoplasm, results from the malignant reprogramming of haematopoietic stem cells (HSCs) into leukaemia stem cells (LSCs), primarily driven by breakpoint cluster region and Abelson (*BCR-ABL1*) fusion oncogene. Although the advent of tyrosine kinase inhibitors (TKIs) has significantly transformed clinical management, leading to improved patient survival and quality of life, sustained treatment-free remission (TFR) remains achievable in only a minority of patients. This limitation is largely attributable to the persistence of LSCs and the development of resistance mechanisms. Emerging evidence indicates that LSCs evade TKI-induced apoptosis through aberrant expression of specific cell-surface markers, dysregulated intracellular signalling pathways, and extensive epigenetic alterations. This review examines recent advancements in CML therapy, with a focus on these novel therapeutic targets. It highlights the pivotal role of LSCs in disease progression and relapse, evaluates potential molecular and epigenetic regulators as new targets for intervention, and supports the development of combination treatment strategies to improve TFR rates and move towards curative outcomes.

Keywords: chronic myeloid leukaemia; leukaemia stem cell; signal transduction; epigenomics; tyrosine kinase inhibitor; molecular targeted therapy; treatment-free remission

1. Introduction

Chronic myeloid leukaemia (CML) is a relatively slow-progressing myeloproliferative malignancy, characterised by the aberrant transformation of normal haematopoietic stem cells (HSCs) into self-renewing leukaemia stem cells (LSCs) that sustain the malignant clone. This conversion is driven by the formation of the Philadelphia (Ph) chromosome within HSCs, resulting from a reciprocal translocation t(9;22)(q34;q11). The consequent breakpoint cluster region and Abelson (*BCR-ABL1*) fusion oncogene encodes a constitutively active tyrosine kinase, triggering dysregulated cell proliferation, conferring growth factor independence, and inhibiting apoptosis through activation of downstream signalling pathways [1,2,3].

Global epidemiological data from 1990 to 2021 show a decline in both age-standardized incidence rates (ASIR) and death (ASDR) of CML (per 100,000 patient-years), although the incidence remains consistently higher in males than females [4,5]. Despite improvements in treatment reducing both incidence and mortality, the increasing global population is expected to amplify the disease burden by 2050 due to the growing absolute number of CML cases [6,7].

CML typically progresses through three phases: chronic (CP), accelerated (AP), and blast (BP), defined by haematological, cytogenetic, and clinical parameters. The majority of cases are diagnosed in CP, while progression to AP or BP is associated with poor therapeutic response, rapid clinical deterioration, and significantly reduced survival, often limited to around 12 months due to infections or disease-related complications. Current treatment options include radiotherapy, chemotherapy, HSC transplantation, and chimeric antigen receptor T-cell (CAR-T) immunotherapy, guided by peripheral blood and bone marrow morphology, immunophenotypic profiling, chromosomal analysis, and molecular diagnostics [8].

The introduction of BCR-ABL1-targeted tyrosine kinase inhibitors (TKIs) such as imatinib and subsequent generations of TKIs has revolutionised CML treatment. These therapies have substantially improved remission rates, overall survival, and quality of life, transforming CML from a fatal disease into a manageable chronic condition with life expectancy approaching that of the general population. However, durable therapy-free remission (TFR) remains achievable only for a subset of patients. Patients with CP-CML who have undergone long-term (≥3 years) TKI therapy and maintained sustained deep molec-

ular response (MR) (e.g., sustained MR4 for $\geq$3 years or MR4.5 for $\geq$2 years) can attempt TFR. Approximately 40–60% of these patients maintain remission without therapy. Most relapses occur within the first 6–12 months due to the loss of major MR (MMR), with remission being rapidly restored upon reinitiation of TKI treatment [9,10,11,12,13,14]. Even under deep molecular remission (DMR), residual disease often persists, and relapse may occur, a phenomenon attributed to LSC persistence. CML remains clinically challenging due to its prolonged chronic phase and the unpredictable response to treatment, with issues such as LSC persistence, TKI resistance, intolerance, and blast crisis (BC). Therefore, curative strategies must focus on selectively eradicating LSCs without damaging normal haematopoiesis. This review consolidates current insights into LSC-specific surface markers and their associated signalling pathways, as well as the role of epigenetic regulators in haematological malignancies. It explores the therapeutic potential of these mechanisms in CML management and highlights their translational implications.

2. Cell Surface Markers

LSCs were initially conceptualized following the observation that only a small subset of leukaemia cells with the $CD34^{+}CD38^{-}$ immunophenotype could induce disease in a xenograft model of acute myeloid leukaemia (AML), a concept later extended to CML [15]. These cells possess several defining characteristics, including quiescence, self-renewal, differentiation potential, the capacity to regenerate disease upon transplantation, and the ability to evade TKI-mediated apoptosis, making them challenging therapeutic targets [16]. A variety of distinct cell surface markers are differentially expressed between normal HSCs and LSCs, presenting both diagnostic and therapeutic opportunities (Table 1, Ref. [17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48]). Notably, CD25, CD26, and interleukin-1-receptor accessory protein (IL-1RAP) show relative specificity for CML LSCs.

Beyond their biological relevance, LSC-associated surface markers have practical diagnostic and therapeutic implications. Of particular note, CD26, due to its characteristic expression pattern, can serve as a specific marker to differentiate LSCs from normal HSCs using multicolour flow cytometry [49,50]. CD26 is generally absent on normal HSCs but is consistently expressed on CML LSCs, facilitating the accurate quantification of the LSC compartment. This enables refined assessments of LSC burden and minimal residual disease (MRD), particularly in patients who have achieved deep MRs under TKI therapy, where conventional BCR-ABL1 transcript measurements may underestimate residual LSCs [49,51,52,53]. Although fluorescence *in situ* hybridization and reverse transcription polymerase chain reaction (PCR) for BCR-ABL remain the gold-standard assays for diagnosing CML, the detection of CD26 represents a novel, non-invasive, rapid, and accurate method for this purpose. Additionally, IL-1RAP further enhances the specificity of LSC detection and is increasingly incorporated into advanced flow-based MRD platforms for monitoring disease and stratifying relapse risk [54].

Notably, several of these surface markers are being explored as potential therapeutic targets. IL-1RAP CAR T-cells have shown selective elimination of CML LSCs while sparing normal HSCs in both *in vitro* and xenograft models, highlighting their potential as highly specific immunotherapeutic targets [55]. Similarly, CD26 presents an attractive therapeutic target, with approaches such as antibody-mediated or enzymatic inhibition shown to disrupt LSC-niche interactions and enhance LSC eradication when combined with TKIs [17,53,56,57,58]. These studies position CML LSC surface markers not only as biomarkers but also as mechanistically informed targets for overcoming LSC persistence.

While some markers listed in Table 1, including CD33 and CD123, are well-established in AML biology and therapy, their functional roles in CML LSCs remain less comprehensively validated [18]. Evidence supporting CD33 and CD123 expression in CML LSCs is limited, primarily derived from patient data and experimental studies, and often extrapolated from AML. Therefore, these markers are discussed here as potentially targetable myeloid antigens rather than as specific identifiers of CML LSCs. In contrast, CD25, CD26, and IL-1RAP are supported by extensive functional and clinical evidence directly obtained from CML models and patient samples, highlighting their particular relevance to CML LSC biology and their potential for translational targeting.

3. Signalling Pathways

LSCs rely on several critical signalling pathways, including Hedgehog (Hh), Notch, and Wnt/β-catenin, which are central to leukaemia pathogenesis and essential for maintaining self-renewal, survival, quiescence, and resistance to therapy (Table 2). Consequently, targeting these signalling pathways in combination with TKIs has emerged as a significant therapeutic strategy.

3.1 Hedgehog (Hh) Pathway

The Hh pathway is well-established for its critical role in embryogenesis, tissue regeneration, and repair [59,60]. Hh proteins bind to their receptor, Patched (PTC), thereby relieving its inhibition of the transmembrane protein Smoothened (Smo) and activating glioma-linked oncogenes (GLI1 and GLI2), which in turn suppress apoptosis [59,60,61,62,63].

Emerging evidence indicates that the Hh pathway plays a significant role in disease progression, HSC proliferation, and LSC maintenance. Glycogen synthase kinase 3 beta (GSK3β), an enzyme implicated in advanced CML, modulates Hh signalling [64,65]. The expression of Hh

Table 1. Cell surface markers in CML.

Markers	HSC	LSC	Function	Reference
CD25 (IL-2RA)	–	+	CD25 mediates IL-2 signalling to regulate cellular survival and proliferation through the JAK/STAT pathways. It acts as a STAT5-dependent growth regulator of LSCs, and at high expression levels, it reduces their proliferative capacity. In addition to serving as a phenotypic marker, CD25 is also implicated as a key growth-regulatory node in the biology of CML LSCs.	[19,20,21]
CD26 (DPPIV)	–	+	CD26 is a multifunctional type II transmembrane glycoprotein that facilitates the niche escape of LSCs by cleaving the stromal derived factor-1/C-X-C chemokine receptor type 4 (SDF1/CXCR4) axis. This action may contribute to extramedullary myeloproliferation in patients with CML.	[17]
CD33 (Siglec-3)	±	+	CD33, a membrane-bound protein of the Siglec family, plays a pivotal role in modulating inflammatory responses. It is expressed on AML blasts as well as normal myeloid cells. Notably, primary CML studies have shown elevated CD33 expression on stem cell-enriched $CD34^{+}CD38^{-}$ leukemic fractions, particularly in CP, positioning CD33 as a potential therapeutic target in CML, though it is not specific to CML LSCs.	[22,23,24]
CD34	+	+	CD34, a transmembrane protein, plays a role in inhibiting differentiation, expansion, signal transduction, and anti-adhesion of HSCs. It is widely used as a marker for HSCs and is associated with therapeutic responses and MRD levels in LSCs. However, CD34 expression is not specific to LSCs and should not be regarded as a discriminatory LSC antigen.	[25,26,27]
CD38	–	–	A type II glycoprotein with dual enzymatic and signal-transducing surface receptor functions, it is dynamically regulated during differentiation and is best considered a negative gate rather than a positive marker for CML LSCs.	[27,28]
CD44 (Pgp1)	+	+	CD44, a non-kinase transmembrane glycoprotein, is involved in haematopoiesis, microenvironmental communication, and the transmission of intracellular signalling related to cell proliferation, differentiation, and metastasis through its interactions with various extracellular matrix components. In CML, CD44-mediated interactions with the vascular niche (including E-selectin-linked mechanisms) have been implicated in LSC engraftment and treatment response. However, CD44 is not selective for CML LSCs.	[29,30,31,32,33,34,35]
CD123 (IL-3RA)	±	+	CD123, a cytokine receptor expressed on LSCs, enhances proliferative responses to IL-3 at high levels, while simultaneously impairing chemotactic activity through the down-regulation of CXCR4. CD123 is a well-established antigen and therapeutic target in AML LSCs. In CML, CD123 is also found on BCR-$ABL1^{+}$ primitive $CD34^{+}CD38^{-}$ fractions and tends to be more highly expressed in advanced phases, supporting IL-3R-directed strategies. However, its value as a selective marker for CML LSC enrichment is less consistent than CD25, CD26, or IL-1RAP.	[24,36,37,38,39,40]
IL-1RAP	–	+	IL-1RAP functions as a co-receptor for IL-1 in association with CD25, promoting LSC proliferation by activating the nuclear factor kappa light chain enhancer of activated B cells (NF-Kb) and protein kinase B (AKT) pathways. IL-1RAP is upregulated on candidate CML stem cells compared to normal counterparts. Along with CD25 and CD26, IL-1RAP is commonly used to phenotype primitive CML cells and is being explored as a potential target for immunotherapy.	[41,42,43,44,45]
ROBO4	+	+	ROBO4, a mesenchymal-associated antigen, plays a role in regulating cytokine-dependent growth of endothelial cells and in specifying HSC localization to bone marrow niches. Since ROBO4 is also present on HSCs, its use is more appropriately framed within the context of niche biology rather than as a selective marker for CML LSCs.	[18,46,47,48]

CML LSCs aberrantly express certain cell surface markers, such as CD25 and CD26, which can be used to distinguish between HSCs and LSCs [17,18,21,41]. The following abbreviations are used throughout: DPPIV, dipeptidyl peptidase; IL-1, Interleukin-1; IL-1RAP, interleukin-1-receptor accessory protein; IL-2, interleukin-2; IL-2RA, the α-chain of the interleukin-2 receptor; IL-3RA, the α chain of the interleukin 3 receptor; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MRD, minimal residual disease; ROBO4, roundabout 4; STAT5, signal transducer and activator of transcription 5; CML, Chronic myeloid leukaemia; HSC, haematopoietic stem cell; LSC, leukaemia stem cell; AML, acute myeloid leukaemia; CP, chronic.

Table 2. Important signalling pathways in LSC.

Pathway	Apoptosis	Proliferation	Resistance	Stemness	Self-renewal
Notch	+/–	+/–	+	+/–	+/–
Hh	–	+	+	+	+
Wnt/β-catenin	–	+	+	+	+

Multiple signalling pathways are involved in LSCs, mainly including Hedgehog (Hh), Notch, Wnt/β-catenin. +: indicate a promoting effect; –: indicate an inhibitory effect; +/–: indicate that both promoting and inhibitory effects have been reported, depending on the context.

components, including the ligand Sonic Hedgehog (Shh), transducer Smo, and effector GLI1, is markedly elevated in LSCs, with further upregulation observed in higher-risk or late-stage disease [60]. In a CML murine model, depleting Smo led to the selective exhaustion of LSCs without compromising normal HSC function [59]. Aberrant activation of the Hh pathway in LSCs contributes to the maintenance of stem cell properties and survival in AML, potentially promoting drug resistance [66,67,68,69]. Furthermore, the Hh pathway regulates LSC frequency and is essential for maintaining BC [59,61]. Combining chemotherapy with Hh pathway antagonists has been shown to decrease LSC dormancy and promote their differentiation. Blocking the Hh pathway forces LSCs into the cell cycle, enhancing their sensitivity to chemotherapy and reducing LSC persistence [68,70,71]. The Hh pathway has been suggested to be BCR-ABL1-independent, given its persistence despite TKI treatment. LSCs can use the Hh pathway in conjunction with arachidonate 5-lipoxygenase (*ALOX5*) to achieve survival and TKI resistance [61,63,72]. *ALOX5* encodes a member of the lipoxygenase gene family, such as 5-lipoxygenase (5-LOX), which plays a critical role in the arachidonic acid metabolism pathway. *ALOX5* is upregulated in mouse LSCs and is not inhibited by imatinib [72]. Although *ALOX5* is a key LSC dependency in mouse models, its role in human CML may vary depending on disease stage, therapy, or the microenvironment [73]. Notably, these two pathways are often co-upregulated. Shh can also drive a Gli-independent response that induces cytoskeletal rearrangement and migration, requiring arachidonic acid metabolism *via* the 5-LOX pathway [74]. Moreover, research has shown that imatinib has minimal impact on the expression of various Hh-related proteins [60].

Smo, a key transmembrane protein in the Hh pathway, can enhance the chemosensitivity of AML-LSCs but also accelerate drug resistance [75]. Knockdown of Smo has been reported to decrease the pathogenesis of LSCs [61]. Inhibition of Smo with compounds like Glasdegib and cyclopamine, or Smo antagonists such as LDE225, has shown promise in eradicating LSCs in combination with TKIs like nilotinib in murine models [71,76,77]. Compared to nilotinib monotherapy, the addition of cyclopamine significantly reduced the number of human and murine LSCs, prolonging relapse-free intervals by nearly threefold, suggesting that Smo inhibition can reduce LSCs [59,61]. Glasdegib has also been shown to reduce cell survival in non-responding patients and increase the sensitivity of TKI-resistant stem and progenitor cells to bosutinib, a second-generation TKI [78].

3.2 Notch Pathway

Notch receptors, expressed on and activated in HSCs, are a family of evolutionarily conserved transmembrane receptors that regulate normal T cell development. Consequently, the Notch pathway is essential for HSC niche expansion, which relies on specific direct interactions between Notch and its ligands [79]. Ligand binding induces sequential cleavage of Notch receptors, with S2 cleavage mediated by ADAM/TACE (a disintegrin and metalloprotease/tumor necrosis factor-α converting enzyme) enzymes and S3 cleavage by γ-secretase. This process releases the Notch intracellular domain (NICD), which translocates to the nucleus and interacts with transcriptional regulators to activate target genes involved in cell differentiation, proliferation, and survival [80].

Notch signalling plays a key role in restricting differentiation and supporting self-renewal, partly through its cooperation with Wnt signalling to maintain undifferentiated HSCs [81]. The Notch pathway also regulates LSC activity by stimulating LSC differentiation, apoptosis, cell-cycle arrest, and maintenance in collaboration with the Wnt pathway. Dysregulation of Notch signalling has been implicated in the pathogenesis of various leukaemias, including AML, CML, T-acute lymphoblastic leukaemia (T-ALL), and B-chronic lymphocytic leukaemia (B-CLL) [79,82,83]. The components of the Notch family, particularly in T-ALL, remain promising therapeutic targets due to their roles in LSC proliferation and metastasis [84]. Targeting Musashi2-Numb through modulation of the Hh and Notch pathways may offer an effective strategy for curing chronic LSCs [85]. Hairy enhancer of split 1 (Hes1), a downstream target of Notch signalling, is significantly upregulated in CML-BC. Co-expression of Hes1 with BCR-ABL in a retroviral model induces an aggressive acute leukaemic phenotype, highlighting the critical role of Hes1 in the transition to BC [86].

3.3 Wnt/β-Catenin Pathway

The Wnt/β-catenin pathway, a key branch of Wnt signalling, plays a pivotal role in maintaining the self-renewal capacity and developmental regulation of LSCs, but it is relatively less active in normal HSCs [87]. Wnt, a secreted glycoprotein, activates signalling cascades that regulate cell differentiation and proliferation [88]. Wnt ligands initiate signalling through lipoprotein receptor-related protein (LRP) and frizzled (FZD) receptors, stabilising β-catenin in the nucleus. This allows β-catenin to interact with transcription factors such as Forkhead box O (FOXO), constitutively activating Wnt target genes and associated stemness markers like *c-MYC* (*MYC*) and cyclin D1 (*CCND1*), thus promoting HSC expansion [89,90,91,92,93].

Wnt signalling is tightly regulated, as low activity supports HSC maintenance and hematopoietic reconstitution, while excessive activity impairs HSC self-renewal and differentiation. Elevated expression of Wnt inhibitors, such as Dickkopf1 (Dkk1) or Wnt inhibitory factor 1 (Wif1), has been shown to disrupt HSC quiescence and self-renewal potential. In CML, Wnt signalling is suggested to play a role in maintaining LSCs [94]. β-catenin signalling is constitutively activated through GSK3β mis-splicing, β-catenin phosphorylation, or aberrant Mnk signalling in patients with CML in the AP and BC, as well as in imatinib-resistant CML [90,95]. Blockade of β-catenin disrupts LSC self-renewal and engraftment while increasing their sensitivity to TKIs, indicating that β-catenin antagonists, such as axin, could be potential treatments for CML [96]. WNT974, a selective Porcupine (PORCN) inhibitor that blocks Wnt ligand palmitoylation, potently and selectively suppresses Wnt signalling and enhances targeting of CML-LSCs [91,97,98]. However, further studies are needed to clarify the role of the Wnt/β-catenin pathway in eliminating LSCs, as it has been suggested that β-catenin does not influence LSC self-renewal and is dispensable for T cells and LSCs in AML [99].

3.4 Crosstalk Among Different Pathways

Collectively, these pathways act as interdependent regulators of LSC biology. The Wnt/β-catenin pathway is essential for maintaining LSC self-renewal, the Hh pathway promotes stemness and survival, and Notch activation enhances Wnt/β-catenin transcriptional activity in various stem systems, while also modulating Hh components, thereby reinforcing self-renewal programs [100]. NICD can potentiate β-catenin transcriptional output, and in some contexts, β-catenin cooperates with Notch targets, synergistically enhancing self-renewal [101]. Hh activation can indirectly reinforce Wnt signalling, as GLI activity can increase the expression of Wnt ligands and targets, and GLI and β-catenin share downstream targets such as *c-MYC* and *BCL2* [59]. Additionally, Phosphoinositide 3-kinase/AKT (PI3K/AKT) and signal transducer and activator of transcription 3 (STAT3) signalling are often activated downstream or in parallel with Wnt/Notch/Hh pathways, stabilising β-catenin and anti-apoptotic factors, which helps maintain LSC survival and quiescence [102].

4. Epigenetic Regulators

As our understanding of LSC biology advances—from cell surface markers and signalling pathways to epigenetic regulators such as B cell lymphoma 6 (BCL6) and enhancer of zeste homologue 2 (EZH2)—it provides a multidimensional roadmap for eradicating LSCs and potentially curing CML.

4.1 B Cell Lymphoma 6 (BCL6)

BCL6, a transcriptional repressor frequently associated with BCL6-immunoglobulin heavy chain (*BCL6-IGH*) translocations, was first identified as a protooncogene in diffuse large B-cell lymphoma (DLBCL) due to its high expression levels and oncogenic effects [103]. Its transcriptional repressive activity depends on the recruitment of class I or II histone deacetylases (HDACs) to specific recognition sites, mediated by either its zinc finger domain or interactions with co-inhibitory factors [104,105].

Beyond its oncogenic roles, BCL6 orchestrates immune cell development and differentiation, influencing genes associated with apoptosis and cell cycle arrest. By suppressing tumour suppressors and genes involved in cell cycle arrest, BCL6 facilitates cell-cycle progression even in the presence of DNA damage [106,107]. In the immune system, BCL6 is predominantly expressed in germinal centre (GC) B cells and is essential for the development, differentiation, and survival of GC B cells, as well as several T-cell subsets, including follicular helper T (Tfh) cells and $CD4^+$ and $CD8^+$ T cells [108,109,110,111,112,113,114,115,116].

Additionally, BCL6 impacts other transcriptional regulators and networks, acting both as an oncoprotein and tumour suppressor in various malignancies and their resistance to therapy [117]. In CML, BCL6 has been shown to promote colony formation, leukaemia initiation, and self-renewal by repressing alternative reading frame (Arf) and p53, suggesting that inhibiting BCL6 could disrupt the quiescent state of LSCs and sensitize them to drug therapy. This would involve releasing *MYC* suppression and reactivating the Arf/p53 pathway [118].

FOXO factors are essential for maintaining initiating cells, while BCL6 functions downstream of FOXO, preserving self-renewal potential and preventing LSC depletion by blocking the transcription of *Arf/p53* in CP, but not in BC of CML [102,111,118]. TKI therapy induces the relocation of Forkhead box protein O3 (FOXO3a) to the nuclei of LSCs, upregulating BCL6, which in turn helps maintain CML-LSC survival by inhibiting p53-mediated apoptosis [118]. Moreover, the expression levels of FOXO3a and BCL6 correlate strongly in the progression from CP to BC in CML [118]. Peptide inhibitors, such as *retro-inverso*

BCL6 peptide-inhibitor (RI-BPI), have shown promise in reducing colony formation and impairing leukaemia initiation in transplant recipients, while selectively eradicating $CD34^{+}CD38^{-}$ LSCs. Combining TKIs with BCL6 inhibition might more effectively target quiescent LSCs and enhance TKI efficacy [118,119,120]. Another small molecule inhibitor, FX1, combined with imatinib, is also believed to significantly reduce colony formation [121]. Thus, a promising new strategy for curing CML by eradicating LSCs may involve the combined use of BCL6 inhibitors and TKIs. Despite encouraging preclinical data, clinical evaluation of BCL6 inhibitors in CML remains limited, as most studies have focused on lymphoid malignancies. Therefore, further clinical validation is needed to assess the therapeutic value of combining BCL6 inhibition with TKI therapy in CML.

4.2 Enhancer of Zeste Homologue 2 (EZH2)

EZH2, a catalytic subunit of the polycomb repressive complex 2 (PRC2), catalyzes the tri-methylation of histone H3 at lysine 27 (H3K27me3), a modification traditionally linked to transcriptional repression [122,123]. Its expression is regulated by a variety of factors, including transcription factors and microRNAs (miRNAs). EZH2 plays a critical role in cell-cycle regulation and apoptosis, acting as both an oncogene and a tumour suppressor, reflecting the complexity of epigenetic regulation [124]. In various malignancies, including AML, CML, breast cancer, glioblastoma multiforme (GBM), and melanoma, aberrantly elevated EZH2 expression has been associated with increased disease progression and poorer clinical outcomes [125,126,127,128].

In contrast, EZH2 may function as a tumour suppressor in certain myeloid malignancies, such as myelodysplastic syndromes (MDS), where loss of H3K27 trimethylation due to EZH2 inactivating mutations or other alterations has been observed [129,130]. However, further research is needed to clarify this role. BCR-ABL1 transduction has been shown to increase STAT5 phosphorylation, which in turn upregulates EZH2 expression in Ba/F3 CML cell lines [131]. In LSCs, the levels of H3K27me3 are also reprogrammed compared to HSCs, with LSCs becoming more reliant on H3K27me3-mediated gene repression. Approximately 8% of patients with myeloid malignancies harbour inactivating mutations in *EZH2*, while mutations in spliceosomal genes such as *U2AF1* and *SRSF2* can disrupt pre-mRNA splicing, leading to aberrant splicing of *EZH2* transcripts and reduced EZH2 expression in some cases [132]. Among EZH2's downstream targets, the *HOX* gene family is associated with stem cell self-renewal. *EZH2*-mediated self-renewal of myeloid progenitor populations *via HOXA9* may contribute to the formation of cancer stem cells (CSCs) [132]. Therefore, EZH2 inhibitors could promote the exhaustion of CSCs, offering potential therapeutic benefits [133]. The first drug recommended for EZH2 inhibition was 3-Deazaneplanocin (DZNep), but it is not highly selective, as it also inhibits other protein methyltransferases besides EZH2 [134]. DZNep inhibits S-adenosyl-homocysteine hydrolase competitively, leading to the accumulation of its substrate adenosylhomocysteine, which suppresses methyltransferase activity, induces degradation of the PRC2 complex, and reduces EZH2 levels [134,135]. Other S-adenosyl-methionine-competitive (SAM-competitive) inhibitors targeting H3K27me3 include EPZ005687, EPZ6438, GSK126, GSK343, UNC1999, and JQEZ5, among others [136,137,138,139,140,141,142].

Multiple studies indicate that inhibiting EZH2 holds potential in treating myeloid malignancies, though caution is required due to EZH2's dual roles [132,143,144]. For instance, genetic knockout of *EZH2* leads to the elimination of CML LSCs, making them more susceptible to TKI treatment such as imatinib mesylate [145,146]. Preliminary findings from a prospective clinical trial (NCT02435550) suggest that *EZH2* mutation status may serve as a predictor of response to hypomethylating agents (HMAs) in patients with AML [147]. Given the challenges of LSC persistence, TKI resistance, and intolerance, combining TKIs with EZH2 inhibitors could offer a promising therapeutic approach, particularly in relapsed CML. Therefore, further research and clinical trials are essential to elucidate the impact of loss-of-function mutations in CML and develop novel agents that selectively target oncogenic EZH2.

Additionally, studies show that BCL6 and EZH2 can physically cooperate by recruiting chromobox 8-BCL6 corepressor (CBX8-BCOR)-containing noncanonical polycomb repressive complex 1 (PRC1) complexes to common genomic targets, establishing a multilayered chromatin repression architecture that supports LSC survival [123]. Notably, pharmacologic inhibition of either BCL6 (e.g., RI-BPI or FX1) or EZH2 (e.g., tazemetostat) partially restores p53 pathway activity. However, dual inhibition or combination with TKIs more effectively reactivates Arf/p53 signalling, induces BIM-dependent apoptosis, and depletes functional LSCs in xenograft models [118,145]. This mechanism has been primarily validated in preclinical models, with limited validation in large randomized clinical trials for CML.

In summary, it is proposed that EZH2- and BCL6-mediated epigenetic programs cooperate to silence tumour-suppressor loci in TKI-persistent LSCs. Dual pharmacologic inhibition of these regulators can reactivate the Arf/TP53 axis and trigger p53-dependent apoptosis.

5. Conclusion and Prospects

The therapeutic landscape of CML has undergone a profound transformation with the introduction of TKIs, turning what was once a fatal disease into a chronic, manageable condition for the majority of patients. However, the persistent challenges of therapy resistance, disease re-

lapse, and the inability to completely eliminate LSCs highlight the need for a deeper understanding and more effective treatment strategies. LSCs are central to disease maintenance and therapeutic failure, characterized by unique surface markers, drug-resistance-conferring signalling pathways, and complex epigenetic regulation. Targeting these mechanisms presents a promising avenue for achieving curative outcomes. Approaches aimed at disrupting key signalling pathways, modulating epigenetic regulators, or specifically targeting LSC-associated surface markers have shown promise in preclinical studies and early clinical trials. A multi-pronged therapeutic strategy combining TKIs with agents targeting LSC biology could increase the likelihood of achieving sustained TFR. Ongoing research into the molecular mechanisms governing LSC biology, including the epigenetic and transcriptional regulators discussed, will be critical for advancing therapeutic strategies and ultimately achieving LSC eradication and long-term TFR.

In addition, emerging technologies, such as single-cell sequencing, offer unprecedented opportunities to reveal cellular heterogeneity, dissect cell-cell interactions, reconstruct dynamic processes, identify precision medicine targets, and infer differentiation trajectories or disease progression stages. Concurrently, research on the immune microenvironment (IME) has advanced from basic mechanisms to clinical applications, with a focus on disease diagnosis, treatment optimization, and prognosis assessment, including biomarker screening and combination therapy design. Among these, the tumour IME (TIME) has been the most extensively studied, characterized by immune suppression that enables tumours to evade immune detection and presents targets for immunotherapy. These studies highlight the potential of the IME in treating other diseases.

Single-cell transcriptomic profiling has revealed that residual LSCs in patients who achieve durable TFR differ fundamentally from those driving molecular relapse after TKI cessation. TFR-associated LSCs typically exhibit reduced BCR-ABL-driven proliferative signalling, lower oxidative phosphorylation (OXPHOS) activity, and anti-apoptotic gene signatures, along with upregulation of early myeloid differentiation programs, reduced expression of canonical stemness regulators, and higher expression of antigen-presentation and co-stimulatory modules, rendering them susceptible to natural killer (NK) or T cell-mediated killing [148,149,150,151]. In contrast, relapse-associated LSCs display aberrant transcriptional profiles with coordinated expression of stemness and myeloid priming genes, elevated OXPHOS activity, upregulated immune-evasion and checkpoint molecules (e.g., programmed death-ligand 1 (PD-L1), CD47), and increased CXCR4/C-X-C Motif chemokine ligand 12 (CXCR4/CXCL12) signalling [148,149,152,153]. These findings strongly suggest that future eradication strategies targeting residual LSCs must extend beyond the continued use of TKIs alone, focusing instead on state conversion or immune re-engagement. One approach involves combining baseline single-cell profiling of LSC transcriptional states with functional immune competence assays to develop algorithms that can stratify patients into direct discontinuation, immune priming, or metabolic debulking pathways. Such adaptive discontinuation frameworks could transform TFR from a probabilistic outcome into a controllable therapeutic endpoint. Ultimately, overcoming LSC persistence is not only essential for improving patient outcomes but also represents the next frontier in the long-standing goal of curing CML.

Author Contributions

JYD and PPZ designed the research study and wrote the initial draft. JL, LYC, XZ and LJC performed the research, created figures and tables and collected references. JTJ and ZJZ designed the research study, created figures and tables, collected references, reviewed the draft, acquired financial support, and managed and supervised the project. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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