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Review

Epigenetic dysregulation in chronic myeloid leukaemia: A myriad of mechanisms and therapeutic options

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ABSTRACT

The onset of global epigenetic changes in chromatin that drive tumor proliferation and heterogeneity is a hallmark of many forms of cancer. Identifying the epigenetic mechanisms that govern these changes and developing therapeutic approaches to modulate them, is a well-established avenue pursued in translational cancer medicine. Chronic myeloid leukemia (CML) arises clonally when a hematopoietic stem cell (HSC) acquires the capacity to produce the constitutively active tyrosine kinase BCR-ABL1 fusion protein which drives tumor development. Treatment with tyrosine kinase inhibitors (TKI) that target BCR-ABL1 has been transformative in CML management but it does not lead to cure in the vast majority of patients. Thus novel therapeutic approaches are required and these must target changes to biological pathways that are aberrant in CML − including those that occur when epigenetic mechanisms are altered. These changes may be due to alterations in DNA or histones, their biochemical modifications and requisite 'writer' proteins, or to dysregulation of various types of non-coding RNAs that collectively function as modulators of transcriptional control and DNA integrity. Here, we review the evidence for subverted epigenetic mechanisms in CML and how these impact on a diverse set of biological pathways, on disease progression, prognosis and drug resistance. We will also discuss recent progress towards developing epigenetic therapies that show promise to improve CML patient care and may lead to improved cure rates.

1. Introduction

Chronic myeloid leukemia (CML) arises when the t9;22 translocation (the Philadelphia chromosome) [1,2] occurs in a hematopoietic stem cell (HSC), resulting in constitutive expression of the fusion tyrosine kinase BCR-ABL1 [3], and transformation of the HSC into a leukemic stem cell (LSC). The clonal myeloproliferative neoplasm that follows is driven by BCR-ABL1 expression and subversion of normal signalling pathways. CML is rare with an annual incidence of ≈1–2 cases per 100,000 individuals and a peak incidence in the sixth to seventh decade of life [4]. The vast majority (85–90%) of patients present in chronic phase (CP) and then, if untreated, progress to advanced phase (AP) and blast phase (BP) within five years [5] resembling an acute leukemia with poor prognosis. The development of potent tyrosine kinase inhibitors (TKI), such as imatinib, which target BCR-ABL1 is arguably the best example of a targeted cancer therapy. TKI were introduced into the clinic almost two decades ago and have transformed the management of CML [6,7]. However, they have not cured CML for the vast majority of patients as only 10–20% of them can discontinue therapy and achieve long-term treatment-free remission (TFR) [8–10]. More recent evidence suggests that the proportion achieving TFR will increase, with as many as 46% of patients on longer term therapy (> 8 years) or 2nd generation TKI (2G-TKI) qualifying for TKI discontinuation [11], with half of these likely to achieve TFR [12]. A quarter of patients will fail TKI therapy [13], most often due to the acquisition of BCR-ABL1 kinase domain or other mutations [14,15] and in a minority of cases as a result of progression to AP/BP [16]. For the remaining ≈50–60% of patients on life-long TKI, minimal residual disease is maintained by a sub-population of LSC[17] in the bone marrow (referred to as LSC persistence) [18–21] which are TKI-resistant [22–24] and can serve as a reservoir for disease relapse if TKI therapy is discontinued. Thus, in order to improve cure rates for CML, there is still a significant clinical need to develop novel therapeutic approaches that target LSCs and are effective for patients who fail TKI therapy. Many of the pathways subverted by BCR-ABL1 have been studied intensively as a means of identifying dysregulated components that can be selectively targeted to eradicate the disease when used in combination with, or as an alternative to, TKI (reviewed in detail in

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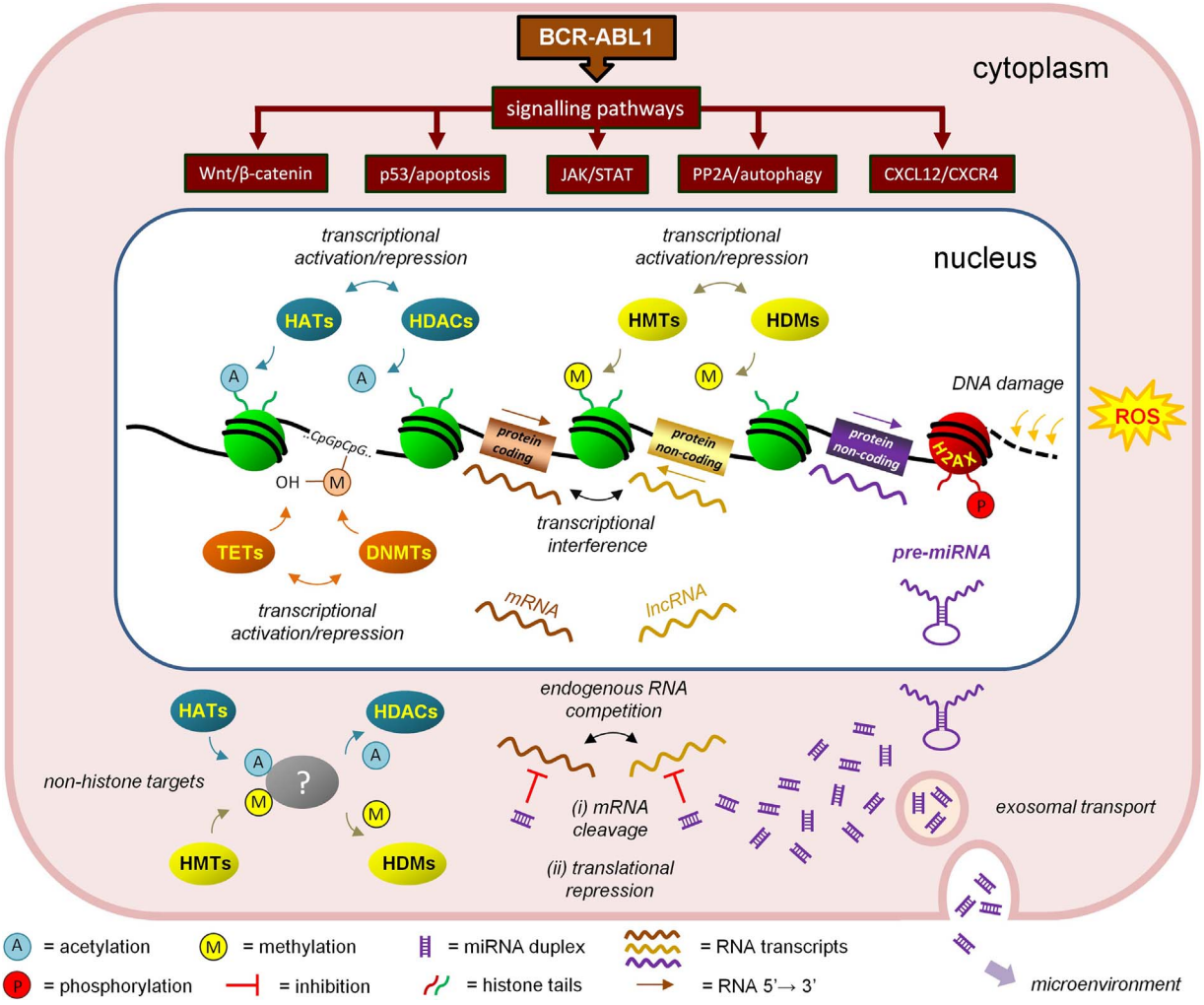

Fig. 1. Layers of epigenetic regulation in CML. Expression of BCR-ABL1 subverts a number of signalling pathways (examples shown) which contribute to, or result from, epigenetic dysregulation in CML cells. The schematic diagram illustrates the three classes of epigenetic processes that have been widely studied and regulate transcription and DNA damage/repair in CML (DNA methylation, histone modifications and non-coding RNAs). Nucleosomes are composed of 2 molecules of histones H2B, H2A, H3 and H4 and are shown here for simplicity as spheres around which the DNA double helix is entwined. Protein-coding or non-coding genes are shown as the coloured rectangles between nucleosomes. DNA methylation is shown at CpG sequences and the process of demethylation is represented by the addition of −OH. HATs = histone acetyltransferases. HDACs = histone deacetylases. HMTs = histone methyltransferases. HDMs = histone demethylases. DNMTs = DNA methyltransferases. TETs = Ten-eleven translocation enzymes. lncRNA = long non-coding RNA. ROS = reactive oxygen species which contributes to DNA damage. All other symbols are described in the legend at the bottom of the schematic.

[16]).

It is now widely acknowledged that cancers are, in part, epigenetically-driven diseases, where epigenetic dysregulation acts in concert with genetic abnormalities to provide an environment to facilitate tumor formation, maintenance and progression. Indeed, in a stem cell disease such as CML, the consequences of such dysregulation may have heightened importance as epigenetic processes are known to be critical for stem cell maintenance and development [25–27]. Epigenetic processes are typically defined within three broad categories: histones and histone modifications, DNA methylation, and non-coding RNAs. Collectively, these can exert their effects to (i) directly regulate transcription, DNA damage/repair and DNA replication, (ii) regulate RNA levels and stability post-transcriptionally, and (iii) regulate protein translation or post-translational protein modifications (Fig. 1). Mutations in components of these pathways are relatively rare in CP CML (Table 1), pointing to epigenetic dysregulation via other ways. Such mutations are detected, however, at higher frequency during disease progression and the proportions of leukemic cells which carry mutation (s) can change in response to TKI therapy. For the purposes of this review we will present examples of how each of these three categories of epigenetic processes is dysregulated in CML, how they impact on critical pathways, and how they may provide new therapeutic opportunities to overcome the current clinical bottlenecks and improve cure rates for CML.

2. Histone modifiers and modifications

Biochemical post-translational modifications of histone tails within nucleosomes of chromatin [28], such as methylation or acetylation, can alter chromatin condensation and topology or provide sites of recruitment for other factors. Such modifications or marks are regulated by 'writer' proteins with opposing enzymatic activities; for example, histone acetyl- or methyl- transferases (HATs and HMTs) or histone deacetylase or demethylases (HDACs and HDMs) that can add or remove modifications, respectively, at specific amino acid residues. Further levels of complexity are contributed by histone variants [29] and the ability of 'writer' proteins to target the post-translational modification of non-histone proteins (Fig. 1). In CML, a number of these histone marking systems are dysregulated, the consequences of which affect numerous pathways that leukemic cells utilise for survival (Table 2).

Table 1
DNA mutations/SNPs in epigenetic regulators or miRNA targets. Column one: Gene name. Column two: encoded protein and function (if known). Column three: epigenetic class. Column four: the type (in *italics*) and frequency of DNA changes are shown as actual number of cases (i) in CP/AP/BP CML or (ii) in TKI-responder, resistant or progressed patients [183]. Column five: clinical significance as described in the cited reference(s). Column six: cited reference(s). Abbreviations: CP = chronic phase; AP = advanced phase; BP = blast phase.

Gene	Protein/Function	Epigenetic class	Type/Frequency	Clinical significance	Reference
DNMT3A	DNA methyltransferase	DNA methylation	*mutation* 3 of 29 CP 2 of 74 TKI responders	pre-leukaemic lesion; CP-CML; TKI treatment	[183,184]
IDH1	isocitrate dehydrogenase		*mutation* 4 of 194 BP	BP-CML	[15,185–188]
IDH2	isocitrate dehydrogenase		*mutation* 5 of 194 BP	BP-CML	[15,185–188]
TET2	methylcytosine dioxygenase 2		*mutation* 3 of 138 CP 2 of 14 AP 9 of 79 BP 2 of 74 TKI responders *3* of 18 TKI resistant *1 of 8 progressed*	CP-CML; AP-CML; BP-CML; TKI treatment	[15,183–187,189,190]
TET3	methylcytosine dioxygenase 3		*mutation* *1 of 24 CP*	CP-CML	[189,190]
MSH6	G/T Mismatch-Binding Protein	DNA repair/ replication	*mutation* 1 of 24 CP	CP-CML	[189,190]
ASXL1	Polycomb Repressive Complex 2; H3K27 methylation	histone modification	*mutation* 12 of 139 CP 12 of 80 BP 3 of 74 TKI responders 3 of 18 TKI resistant 2 of 8 progressed	CP-CML; BP-CML; TKI treatment	[15,183–187,189–191]
EZH2	Polycomb Repressive Complex 2; histone methyltransferase; H3K27 methylation		*mutation* 1 of 29 CP	CP-CML	[15,184]
KDM1A	HMT activity; H3K4 and H3K9 methylation		*mutation* 1 of 24 CP	CP-CML	[189,190]
KMT2A	MLL1; HMT activity; H3K4 methylation		*mutation* 1 of 74 TKI responders	CP-CML; TKI treatment	[183]
KMT2D	MLL2; HMT activity; H3K4 methylation		*mutation* 1 of 74 TKI responders 2 of 18 TKI resistant	CP-CML; TKI treatment	[183]
ARHGAP26	RhoGTPase; target of miR-18a-3p	miRNA	*SNP 3′ UTR* *rs187729 T > C* 30 of 140 CP	increased risk of CP-CML	[192]
IRF8	interferon regulatory factor 8; target of miR-330-3p		*SNP 3′ UTR* *rs10514611 C > T* 84 of 140 CP	increased risk of CP-CML	[192]

2.1. DNA damage, H2AX and histone acetylation

Histone variant H2AX is incorporated into chromatin at varying frequencies [30] and is a known tumor suppressor – haplo-insufficiency of which can facilitate progression to BP in a CP-CML murine model [31]. It is widely known that the phosphorylated form of H2AX, known as γ-H2AX, found at sites of DNA damage in chromatin, is a critical mediator in the cellular decisions that lead to DNA repair or apoptosis [32,33]. Several lines of evidence point to dysregulation of this response in CML. Higher basal levels of γ-H2AX are found in CML cells compared to normal [34,35], consistent with the findings that cells expressing BCR-ABL1 show enhanced levels of oxidative DNA damage, including point mutations and double-stranded breaks (DSBs) induced by endogenous reactive oxygen species (ROS) [36,37]. Inducing additional DSBs in CML and non-CML $CD34^+$ cells results in further increases in γ-H2AX that persist longer in CML. Earlier reports in cell line models suggested the CML response was of a short duration – in keeping with a more rapid response to DNA damage [38] via the error-prone DNA repair mechanisms known to be active in CML cells [39–41]. CML cells also show increased levels of H3 and H4 acetylation which co-localizes with γ-H2AX at sites of DNA damage [34]. These acetylation changes are likely to reflect a more generalised increase in histone H3 and H4 acetylation and HAT activity and a reduced HDAC activity in CML – all of which are dependent on BCR-ABL1 kinase activity [34,42]. Altering the balance of HAT/HDAC activity in CML cells may also lead to increased TP53 acetylation at residues that can block the translocation of TP53 from the nucleus to the cytoplasm and prevent mitochondrial-dependent apoptosis in response to DNA damage [43]. One possible mechanism for this imbalance in acetylation/deacetylation is the ability of BCR-ABL1 to sequester HDAC1 in the cytoplasm [42], which has the additional effect of promoting expression of BCR-ABL1 through increased nuclear H4 acetylation in a positive feedback loop (Fig. 2a).

2.2. SUV39H1 loss of function and lysine methylation

Histone H3 lysine 9 trimethylation (H3K9me3) is a hallmark of heterochromatin with the methyltransferases SETDB1, SUV39H1 and SUV39H2 responsible for its deposition. However, it also plays roles in the cell-type repression of lineage-inappropriate genes during development [44] and is dysregulated across cancer types [45,46]. CP CML $CD34^+$ cells and granulocytes show significantly reduced levels of

Table 2
Proteins implicated in histone dysregulation in CML. Column one: gene/protein name. Column two: complex in which the protein is normally found and its function (if known). Column three: CML cell type studied (primary patient material or cell lines; human unless stated). Column four: clinical significance as described in the cited reference(s). Column five: cited reference(s). Abbreviations: PB = peripheral blood; BM = bone marrow; MNC = mononuclear cells; LSC = leukemic stem cell; CP = chronic phase; BP = blast phase; ND = not determined.

Protein/Protein Family	Complex/Function	CML Cell type	Clinical significance	Reference
AURKB	serine/threonine kinase; H3S10 phosphorylation	K562; Ba/F3-BCR-ABL1 (murine);	mode of action of aurora kinase (AK) inhibitors; TKI resistance	[50]
BMI1	Polycomb Repressive Complex 1; H2AK119 ubiquitinylation	PB MNC; BM MNC; BM $CD34^+$; K562; JURL-MK1; LAMA-84	CP-CML; disease progression; imatinib response	[68,69,73,158,193]
CBX6	Polycomb Repressive Complex 1; H2AK119 ubiquitinylation	BM MNC	imatinib response	[158]
CBX7	Polycomb Repressive Complex 1; H2AK119 ubiquitinylation	BM MNC	imatinib response	[158]
EED	Polycomb Repressive Complex 2; H3K27 methylation	K562; K562-IMA3	imatinib resistance	[65]
EZH1	Polycomb Repressive Complex 2; HMT activity; H3K27 methylation	PB $CD34^+CD38^{+/-}$	CP-CML LSC	[64]
EZH2	Polycomb Repressive Complex 2; HMT activity; H3K27 methylation	K562; PB $CD34^+CD38^{+/-}$; K562-IMA3	down-regulation (PL3); inhibition (EZH2i); CP-CML LSC; imatinib resistance; disease progression via β-arrestin 1	[61–65,67,194]
H2AX	recruitment to sites of DNA damage as γ-H2AX; apoptosis	K562	imatinib response; zerumbone response; resveratrol response; disease progression	[31,35,195–198]
HATs	H3 and H4 acetylation; DNA damage; $TP53^{K317/K320ac}$	BCR-ABL1 − 32Dcl3 (murine)	ND	[34,43]
HDAC1	HAT activity; H4ac	PB $CD34^+$	CP-CML; BP-CML	[42]
HDACs	H3 and H4 deacetylation	BCR-ABL1 − 32Dcl3 (murine)	ND	[34]
HP1	H3K9 methylation	PB $CD34^+$; PB MNC; PB granulocytes	disease progression	[48]
JARID2	Polycomb Repressive Complex 2; H3K27 methylation	PB $CD34^+CD38^{+/-}$	CP-CML/LSC	[64]
PHC3	Polycomb Repressive Complex 1; H2AK119 ubiquitinylation	BM MNC	imatinib response	[158]
PHF19	Polycomb Repressive Complex 2; H3K27 methylation	PB $CD34^+CD38^{+/-}$	CP-CML/LSC	[64]
PRMT5	HMT activity; histone and protein arginine methylation	PB $CD34^+$; BM $CD34^+$	all phases of CML	[54]
RBBP7	Polycomb Repressive Complex 2; H3K27 methylation	PB $CD34^+CD38^{+/-}$	CP-CML/LSC	[64]
SIRT1	HDAC; histone/protein lysine deacetylation ($TP53^{K382}$)	PB $CD34^+CD38^{+/-}$; K562; K562-IMA3	CP-CML/LSC; imatinib resistance	[65,78–80]
SUV39H1	H3K9 methylation	32D clone 8 B (murine); PB $CD34^+$	CP-CML; response to imatinib	[47]
SUZ12	Polycomb Repressive Complex 2; H3K27 methylation	K562; PB $CD34^+CD38^{+/-}$; K562-IMA3	down-regulation by PL3; CP-CML/LSC; BP-CML; imatinib resistance	[64–66,194]

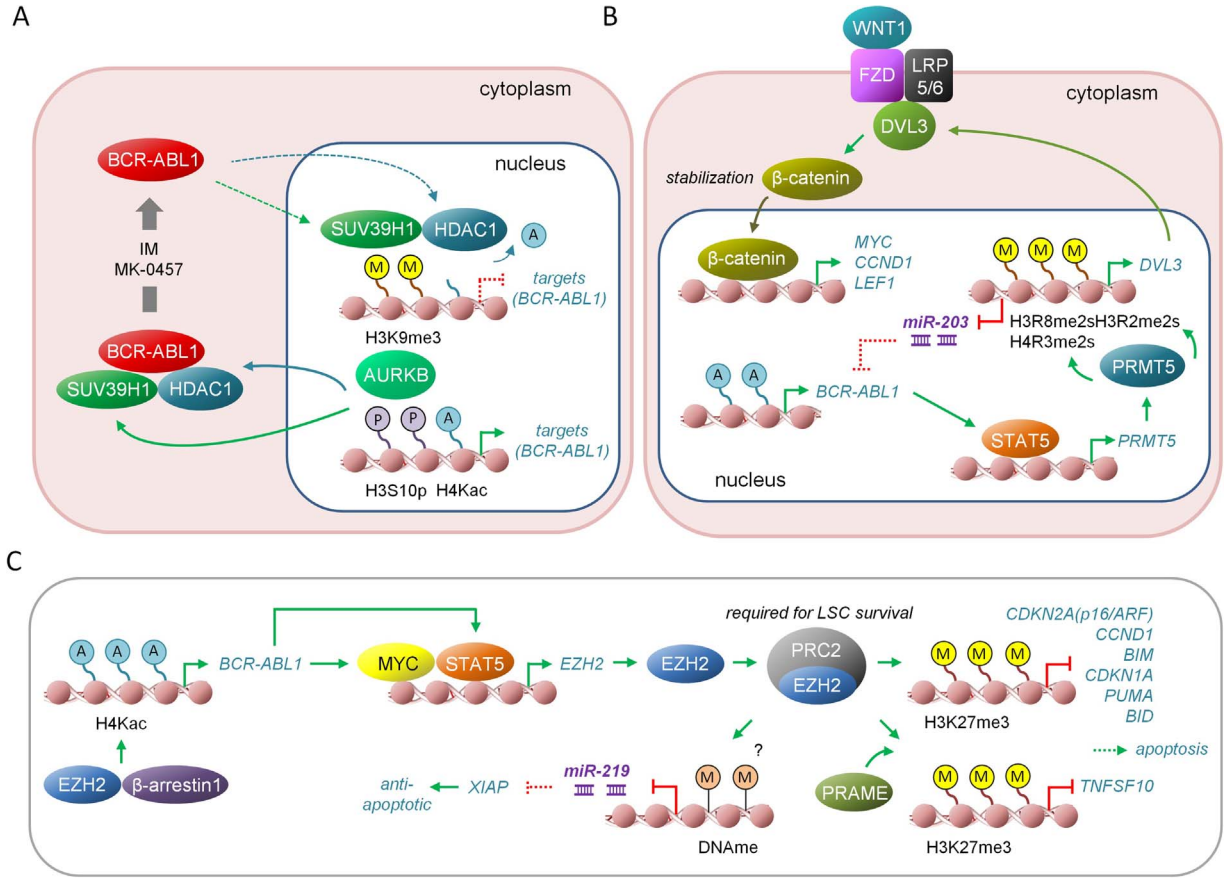

Fig. 2. Dysregulation of histone methylation in CML. **A**. Lower levels of histone H3 lysine 9 trimethylation are found in CML cells and this is linked to the direct interaction of BCR-ABL1 with SUV39H1 (and also HDAC1) in the cytoplasm. This creates transcriptionally permissive chromatin associated with H3 serine 10 phosphorylation (H3S10p) and H4 acetylation at target genes, including BCR-ABL1, in the nucleus − thus allowing their expression [47,48,50]. **B.** A positive feedback loop between BCR-ABL1 and the methyltransferase PRMT5 results in increased levels of histone H3 arginine 2 symmetric demethylation which in turn activates Wnt signalling and its transcriptional targets [54]. **C.** In CML, re-programming of Polycomb Repressive Complex 2 and its methyltransferase subunit EZH2 alters the balance between pro- and anti-apoptotic responses via altered dependencies on histone H3 lysine 27 tri-methylation [61–64,67]. This may also involve a positive feedback loop involving BCR-ABL1 which reinforces EZH2 expression via MYC (public ENCODE datasets) and STAT [62]. Gene transcription is denoted by the blue text in italics. Steps in pathways/processes that are active in CML cells are shown with solid lines; steps that are blocked in CML are shown with dotted lines. All other symbols are as described in Fig. 1. MK–0457 = Aurora kinase inhibitor; IM = imatinib. s = symmetrical histone arginine methylation.

H3K9me3 [47,48] compared to normal, although appreciable levels of both H3K9me2 and H3K9me1 (associated with less repressive chromatin states) are evident in granulocytes [48]. Mechanistically, reductions of H3K9me3 levels in CP CML CD34$^+$ cells are linked to cytoplasmic co-localisation of SUV39H1 by BCR-ABL1 and support a model whereby normal nuclear activity of SUV39H1 [47] and also HDAC1 [42] (see section above) are subverted. This would create a more permissive transcriptional chromatin environment and facilitate expression of genes normally repressed by the SUV39H1/HDAC1 complex [49]. Later work has shown the opposing effects of H3K9me3 and histone H3 serine 10 phosphorylation (H3S10p) in CML cells. Inhibition of the kinase activities of either BCR-ABL1 or the 'writer' protein Aurora kinase B (AURK) results in loss of H3S10p and increases H3K9me3 levels, thus repressing BCR-ABL1 expression [50]. Collectively these results are compatible with the model proposed in Fig. 2a.

2.3. PRMT5 and arginine methylation in LSC survival

Histone arginine methylation, laid down by the PRMT family of HMTs, can activate or repress transcription depending on the histone residues and the dimethyl isomers (a = asymmetrical or s = symmetrical) involved [51]. Early work on one family member, PRMT5, showed it to interact strongly with the V617F mutant form of JAK2 found in BCR-ABL1-negative myeloproliferative neoplasm [52]. Later, PRMT5 was shown to be a critical regulator in neuronal stem cell renewal [53] and, more recently, in CML LSC survival [54]. PRMT5 is upregulated by STAT5 in CML CD34$^+$ cells where it is associated with increased histone arginine methylation compared to normal CD34$^+$ cells. Genetic or pharmacological inhibition of PRMT5 enzymatic activity in CML CD34$^+$ cells diminished this methylation and significantly reduced LSC numbers *in vitro* and reduced long-term engraftment potential in murine xenografts. The critical role for PRMT5 in CML is thought to be centred on the epigenetic regulation of canonical Wnt signalling − a pathway known to be essential for LSC function [55,56] (Fig. 2b). In LSC, elevated PRMT5 activity triggers up-regulation of DVL3, an upstream positive regulator of β-catenin, as a consequence of elevated H3 arginine 2 dimethylation (H3R2me2) at the DVL3 promoter. Intriguingly, elevated PRMT5 activity also leads to down-regulation of the microRNA (miRNA; miR) miR-203, a negative regulator of BCR-ABL1, through H3 arginine 8 and H4 arginine 3 dimethylation (H3R8me2s and H4R3me2 s respectively) at the miR-203 promoter. Reduction of miR-203 creates a scenario where BCR-ABL1 and downstream PRMT5 expression are reinforced in a positive feedback loop.

2.4. The polycomb group proteins

The polycomb group proteins found in either polycomb repressive complex 1 (PRC1) or complex 2 (PRC2) are arguably some of the best characterised 'writer' complexes and function as potent repressors of gene expression [57,58]. Components of these complexes are de-

regulated across many cancer types where they can act as either tumor suppressors or oncogenes [59,60]. PRC2 is a multi-protein complex that contains either the HMT EZH1 or EZH2 and lays down histone H3 lysine 27 mono-, di- and tri-methylation. The trimethylated form (H3K27me3) is a hallmark of PRC2-EZH2 repressive activity. Several studies have demonstrated dysregulation of PRC2 in CML primary patient material, cell lines or murine models [61–64] and their expression levels may be altered in response to TKI [64,65] or progression to BP disease [66]. Two recent studies have demonstrated the important role of EZH2 in LSC survival. Loss of EZH2 HMT function in either a murine model of CML, or in CP patient samples examined *in vitro* or in murine xenografts, significantly impairs LSC survival [63,64]. In human LSC, this was shown to be due to an increased dependency of pro-apoptotic genes on PRC2-EZH2 repression which is not evident in HSC (Fig. 2c). Others have shown that EZH2 dysregulation (controlled by BCR-ABL1 via MYC and STAT5) may have other consequences in CML cells. EZH2 associates with β-arrestin to drive H4 lysine acetylation and BCR-ABL1 expression [61], or with PRAME to repress the function of the death receptor TNFSF10 [67]. The microRNA miR-219 is down-regulated through the action of EZH2 and DNA methylation at its promoter; this facilitates the up-regulation of XIAP, an anti-apoptotic factor and known miR-219 target. Whether all of these events occur in LSC is not known but provides the basis for further studies.

The PRC1 complex works co-operatively with PRC2 and presence of both PRC2 and PRC1 leads to chromatin compaction and transcriptional silencing of target genes [57]. PRC1 binds to H3K27me3 in chromatin, and lays down histone H2A lysine 119 ubiquitinylation, through the action of its catalytic components − the E3-ligases RING1 or RING2. The stem cell factor BMI1 (also known as PCGF4) is a core component of PRC1 activity and emerging evidence supports it having an important role in cancer. In CP-CML, levels of BMI1 are elevated in total mononuclear and $CD34^+$ cells compared to normal [68,69]. Several pathways known to be important in CML cell survival have been shown to be the targets of PRC1-BMI1 activity. In one study, BMI1 was shown to repress the expression of ZMYM3 in CML, a component of HDAC complexes [69] (Fig. 3a). ZMYM3 repression was linked to up-regulation of the oncogene FOS via histone H3 acetylation − thus activating a pathway recently shown to be critical for TKI-resistant LSC and progenitor survival [70]. BMI1 was also shown to directly down-regulate CCNG2 in CML cells − a regulator of the tumor suppressor PP2A, a known modulator of Wnt signalling [71,72]. Up-regulating CCNG2 was able to dissociate PP2A subunits and drive an autophagic response in CML cells via PKCζ and ERK/JNK signalling [73] (Fig. 3a). The role of autophagy in CML LSC is well documented [74–76] and BMI1 inhibition could sensitize CML cells to autophagy inhibitors.

2.5. Epigenetic 'writers' and non-histone targets

Repression of apoptosis is a central survival mechanism and unifying theme across cancer types. Therefore it follows that inactivation of TP53 itself is one of the few non-histone targets of epigenetic 'writer' activity in CML that has thus far been identified. Inactivation of TP53 can be achieved through acetylation by HATs (see also above) or through deacetylation by HDACs such as SIRT1, a NAD-dependent deacetylase [77]. SIRT1 expression is up-regulated in CP-CML $CD34^+$ cells and is further elevated during disease progression [78,79]. The dysregulation of SIRT1 expression in CML is likely to be epigenetically-driven by aberrant DNA methylation (Fig. 3b) and is discussed further below. Inhibition of SIRT1 has been shown to significantly increase TP53 acetylation, resulting in up-regulation of the apoptotic response and a reduction of LSC and progenitor cell survival *in vitro* and in murine models [79]. One unexpected and additional function of SIRT1 in CML is that it promotes the acquisition of genetic mutations by deacetylating components of the DNA repair machinery and increasing error-prone DNA repair [80]. Thus, the duality of SIRT1 function in CML allows DNA damage to be accumulated, whilst suppresses cell death − making SIRT1 an interesting player in the DNA damage response via its non-histone activities.

3. DNA methylation

DNA methylation represses gene transcription and occurs at cytosine residues in CpG dinucleotides where it is laid down by DNA methyl transferases (DNMTs) and removed passively through cell division or actively by methyl-cytosine dioxygenases (also known as ten-eleven translocation proteins; TETs) [81]. CpG methylation occurs throughout genomes [82,83], however, it is at promoter regions in CpG islands [84–86] that its effects on transcriptional repression are normally exerted. Cancer genomes have been shown to exhibit widespread global hypomethylation in addition to more targeted gains or loss of DNA methylation at tumor suppressors or oncogenes [87,88]. Spanning more than twenty years of CML research, candidate gene approaches have been instrumental in identifying changes in DNA methylation at specific genes (Table 3).

3.1. DNA methylation and CML survival pathways

Three examples of epigenetically-dysregulated genes in CML, in particular, highlight the impact that dysregulating DNA methylation may have on CML survival pathways. Firstly, the upregulation of SIRT1 in CML (see also above) can most easily be explained by hypermethylation of the HIC1 gene − a repressor that functions in concert with SIRT1 [89] to auto-regulate SIRT1 expression (Fig. 3b). The promoter of HIC1 is hypermethylated in CP, and this increases during disease progression [90] and coincides with upregulation of SIRT1 [78]. Thus, reduction of HIC1 expression would facilitate the up-regulation of SIRT1 via STAT5 [78]. However, whilst this mechanism has been proposed [79], it has not been empirically tested. Secondly, the tumor suppressor MTSS1 is down-regulated in LSC and progenitor cells of CML mouse models and CP patients at diagnosis, but is restored to normal levels during TKI therapy [91]. MTSS1 down-regulation is linked to higher DNA methylation levels at its promoter in CML compared to normal and is accompanied by the recruitment of the transcription factor ZBTB33 (KAISO) and the potent repressor REST1 [92,93] (Fig. 3c). MTSS1 is a known target of DNMT3B [94], and both methylation and DNMT3B levels have an inverse relationship with MTSS1 expression in naïve and TKI-treated cells. Repression of MTSS1 is likely to promote CML LSC and progenitor cell proliferation and motility, both of which can be reduced upon MTSS1 enforced expression [91]. Treatment with the de-methylating agent 5-azacytidine *in vitro* was able to strongly induce MTSS1 in CML cell lines. Finally, the CD70/CD27 axis has been shown to activate non-canonical Wnt signalling in the presence of TKI, thus contributing to LSC survival [95]. This is due to the opposing effects that TKI has on expression of DNMT1A and SP1 via the suppression microRNA miR-29 (Fig. 3d). Lowering miR-29 expression allows SP1 levels to increase, whilst reducing DNMT1A. This results in loss of DNA methylation at the CD70 promoter and CD70 activation by SP1 which can then drive Wnt signalling and β-catenin stabilization. CD70 knockdown synergized with TKI treatment to eliminate LSC in both xenograft and retroviral mouse models [95].

4. Non-coding RNAs

Non-coding RNAs are a more recently emerging epigenetic process that can regulate mRNA levels and protein translation through a variety of somewhat related processes (Fig. 1). Anti-sense transcripts are long non-coding RNAs (lncRNAs) that are transcribed from the strand opposite to that of the sense transcript; for this reason, they can result in transcriptional interference with the sense transcript by a variety of mechanisms [96,97]. miRNAs are small or short non-coding RNAs of ≈20–23 nucleotides, that are processed from longer precursor RNAs. They regulate gene expression through sequence-specific binding most

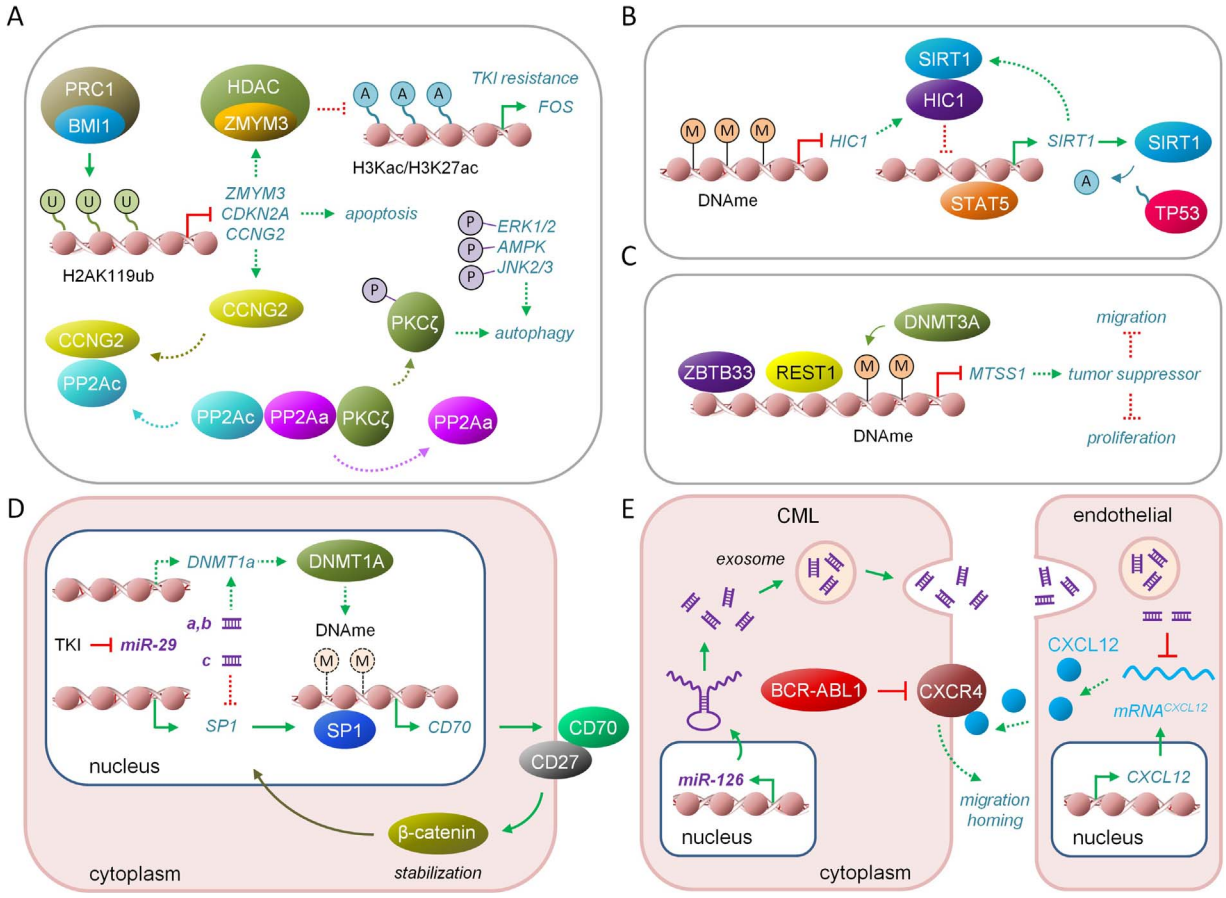

Fig. 3. The diversity of epigenetic mechanisms utilised in CML cells. **A.** BMI1 regulation inhibits the response to autophagy via repression of CCNG2 [73] and permits expression of FOS [69] – a critical survival factor [70]. **B.** Up-regulation of SIRT1 through its inability to auto-regulate lead to deacetylation and inactivation of TP53 [78,79,90]. **C.** The tumor suppressor MTSS1, which controls cell migration and proliferation, is down-regulated as a result of increased DNA methylation and recruitment of repressive transcription factors to its promoter [91]. **D.** TKI up-regulates the Wnt/β-catenin pathway by inhibiting miR-29 expression thus allowing increased CD70 expression and CD70/CD27 receptor/ligand interaction [95]. **E.** Cell non-autonomous regulation of the CXCL12/CXCR4 axis may involve the exosomal export of miR-126 to endothelial cells in the microenvironment where it reduces expression of CXCL12, thus inhibiting signalling via CXCR4 in CML cells [120]. Steps in pathways/processes that are active in CML cells are shown with solid lines; steps that are blocked in CML are shown with dotted lines. All other symbols are as described in Fig. 1.

often to the 3′ untranslated regions of target mRNAs and either prevent translation or induce cleavage of the mRNA [98]. miRNAs may also compete for target mRNAs, according to the competitive endogenous RNA (ceRNA) hypothesis [99–101]. Of these various processes, the roles of miRNAs, in particular, are well established in cancer biology [102,103]. While there are relatively few reports of lncRNAs or ceRNAs being dysregulated in CML cells compared to normal, the number of dysregulated miRNAs is considerable (Table 4).

4.1. MicroRNAs, the niche and the CXCL12/CXCR4 axis

The impact of dysregulated miRNAs on a number of cellular pathways in CML is shown in several of the examples above (Figs. 2b,c, 3d) and is also reviewed in detail elsewhere [104–111]. One other area of miRNA biology that is germane to the discussions here is how they regulate non-cell autonomous pathways via exosomal transfer between cell types [112–114]. In CML, the expression of the chemokine CXCL12 in the bone marrow microenvironment (BMM) and its receptor CXCR4 expressed on LSC have been demonstrated to play roles in LSC homing and survival [115–118]. In CML, interactions between leukemic cells and the bone marrow stroma are defective due to BCR-ABL1 suppression of CXCR4-mediated signalling (Fig. 3e). This, in turn, reduces homing capacity and allows primitive CML cells to escape from the bone marrow [119]. Extrapolation of recent evidence obtained from CML cell lines in co-culture with endothelial cells [120] suggests that exosomal transfer of miR-126 from leukemic cells to stromal cells may also inhibit CXCL12/CXCR4 signalling *in vivo* through down-regulation of CXCL12 in the stroma. Levels of miR-126 in exosomal vesicles of CML cell lines are higher than in the parent cells producing them. Tracking experiments demonstrated that miR-126 can be transferred from leukemic to endothelial cells, where it can target the down-regulation of both CXCL12 and VCAM1, the consequences of which are reduced cell motility and adhesion between the two cell types. This would support the view that exosomal 'shuttles' may have an important role in CML-stromal cell interactions in the BMM.

5. Epigenetics in progression and prognosis

In addition to epigenetic processes having roles in subverting critical cellular pathways in CML, they are also further dysregulated during disease progression.

5.1. Histone modifiers

Granulocytic H3K9me3 levels increase during AP and BP in concert with increased levels of the H3K9me3 binding protein, HP1, suggesting that both features may serve as biomarkers of disease progression [48]. BMI1 increases further during progression from CP to BP [65,66]. Furthermore, BMI1 was shown to be approximately two-fold elevated in AP- and BP-CML as compared to CP, both in PBMCs and PB $CD34^+$ cells [121]. In a retrospective cohort of 64 patients with CP CML, above-median levels of BMI1 mRNA expression in $CD34^+$ cells at diagnosis

Table 3
Genes and other features with altered DNA methylation in CML. Column one: gene/feature. Column two: encoded protein and function (if known). Column three: status with respect to hyper or hypomethylation in CML. Column four: CML cell type studied (primary patient material or cell lines). Column five: clinical significance as described in the cited reference(s). Column six: cited reference(s). Abbreviations: PB = peripheral blood; BM = bone marrow; MNC = mononuclear cells; LSC = leukemic stem cell; CP = chronic phase; AP = advanced phase; BP = blast phase; IFN = interferon; WBC = white blood count; CCR = complete cytogenetic remission; ND = not determined.

Gene/Region	Protein function	Status in CML	CML Cell type	Clinical significance	Reference
up to 897 genes	various	hyper/hypomethylation	PB MNC; BM MNC	disease progression	[147]
ABCB1	P-glycoprotein eflux pump	hypermethylation	BM MNC	imatinib resistance; imatinib response	[199]
ABL1 (Ph^+ chrom)	oncogene; tyrosine kinase		PB MNC; BM MNC	all CML stages; disease progression; independent of BCR-ABL1 mRNA levels; response to IFNα therapy; p210 form of BCR-ABL1	[130,133,139–146]
ATG16L2	autophagy-related protein 16-2		PB MNC; BM MNC	CP-CML; BP-CML; disease progression	[148]
ATP5B	mitochondrial ATPase		K562; BM MNC	disease progression; adriamycin resistance	[161]
BCL2L11	Bcl-2 interacting protein Bim		BM MNC	imatinib resistance	[159,200]
BCR	breakpoint cluster region		PB MNC	survival; imatinib response; imatinib dose; age	[201]
CADM1	cell adhesion molecule 1		PB MNC; BM MNC	BP-CML	[132]
CALCA	calcitonin; G-coupled receptor		PB MNC; BM MNC	disease progression	[134–136]
CBY1	beta-catenin antagonist		K562; BM MNC	CP-CML	[202]
CD70	tumor necrosis factor ligand		KBM5r	CP-CML; TKI persistent LSC	[95]
CDH13	caherin family member		PB MNC; BM MNC	all CML stages	[132,133]
CDKN2A	cell cycle inhibitor p16		PB MNC; BM MNC	AP-CML; BP-CML; disease progression	[125–127]
	cell cycle inhibitor p14		PB MNC	AP-CML; BP-CML; disease progression	[125,128,129]
CDKN2B	cell cycle inhibitor p15		PB MNC; BM MNC	CP-CML; BP-CML; disease progression	[126–133]
CEBPA	myeloid transcription factor		PB MNC	disease progression	[203]
CTSL	lysosomal cysteine proteinase		PB MNC	disease progression	[204]
DAPK1	death receptor 1		PB MNC; BM MNC	sex; disease progression; BP-CML; imatinib resistance	[126,127,137,138]
DDIT3	DNA damage response		BM MNC	reduced WBC	[205]
DLX4	homeobox protein		BM MNC	disease progression	[206]
DPYS	pyrimidine metabolism		K562; PB MNC	hypermethylator phenotype	[133]
EBF2	early B-cell factor 2; transcription factor		PB MNC; BM MNC	CP-CML; BP-CML; disease progression	[148]
ESR1	estrogen receptor 1		PB MNC; BM MNC	BP-CML	[132]
FHIT	cell cycle regulator		BM MNC	BP-CML	[126]
HOXA4	homeobox protein		PB MNC	imatinib resistance	[160]
HIC1	transcriptional repressor		PB MNC; BM MNC	disease progression	[90]
IGF2	insulin growth factor 2		PB MNC; BM MNC	loss of imprinting during disease progression	[207]
JUNB	transcription factor; oncogene		PB MNC	CP-CML; BP-CML	[208]
M-BCR	major breakpoint cluster region		PB MNC; BM MNC	Ph^- and Ph^+ CP-CML; IFN remission; distinguish lymphoid and myeloid BP	[209–211]
MGMT	DNA repair		PB MNC; BM MNC	CP-CML; BP-CML	[126,132]
MSH1	mismatch repair ATPase		PB MNC; BM MNC	CP-CML	[132]
MTSS1	actin dynamics		K562; PB MNC	CP-CML	[91]
NPM2	histone chaperone		K562; PB MNC	all CML stages; imatinib intolerance/resistance	[133]
OSCP1	tumor suppressor; pro apoptotic		K562; PB MNC	disease progression; survival (pre-imatinib); imatinib intolerance/resistance	[133]
PACRG	chaperonin-binding protein		BV173; TCC-S; KU812; KYO-1; K562; BM MNC	BP-CML (lymphoid)	[212]
PARK2	e3 ubiquitin ligase		BV173; TCC-S; KU812; KYO-1; K562; BM MNC	BP-CML (lymphoid)	[212]
PDLIM4	PDZ and LIM domain 4 protein		K562; PB MNC	survival (pre- and post-imatinib)	[133]
PER2	circadian clock gene		PB MNC	CP-CML; BP-CML	[213]
PER3	circadian clock gene		PB MNC	disease progression	[213]
PGRA	progesterone receptor		PB MNC	disease progression	[133]
PGRB	progesterone receptor		PB MNC	disease progression	[133]
PLCD1	phospholipase C		BM MNC	all CML stages	[214]
PRAME	repressor of retinoic acid receptor		BM MNC	disease progression (hypomethylation)	[215]
PTPN6	tyrosine phosphatase		PB MNC; BM MNC	disease progression	[216]
RARB	retinoic acid receptor β		BM MNC	BP-CML	[126]
RASSF1A	cell cycle; Ras signalling		K562	ND	[217]
sFRPs	secreted frizzled related proteins; Wnt signalling		BM MNC	imatinib resistance	[218]

(continued on next page)

Table 3 *(continued)*

Gene/Region	Protein function	Status in CML	CML Cell type	Clinical significance	Reference
SOCS1	repressor of cytokine signalling		PB MNC; BM MNC	disease progression; molecular remission	[219]
SOCS3	suppressor of cytokine signalling		K562	imatinib resistance	[220]
SPI1	transcription factor PU.1		K562; PB MNC; BM MNC	disease progression; CGR	[221]
TFAP2A	transcription factor AP-2-alpha		PB MNC; BM MNC	CP-CML; BP-CML; disease progression	[148]
TFAP2E	transcription factor AP-2 epsilon		K562; PB MNC	disease progression	[133]
TP53	p53 transcription factor; tumor suppressor		PB MNC	ND	[127]
TRCP4	transient receptor potential cation channel		PB MNC; BM MNC	CP-CML; BP-CML	[148]
CD7	T-cell leukemia antigen	hypomethylation	BM lin$^-$CD34$^+$	CP-CML	[222]
DDX43	ATP-dependent RNA helicase		BM MNC	all CML stages	[223]
LHX2	LIM-domain protein		BM MNC	ND	[224]
LINE1, Alu, Satellite-alpha and Satellite-2	repetitive DNA elements		BM MNC	disease progression	[225]
SOCS1	repressor of cytokine signalling		PB MNC; BM MNC	ND	[226]

were associated with significantly inferior survival as compared to below-median BMI1 levels [121]. Thus, high BMI1 expression was predictive of poor outcome in patients with CML.

Later work provided a possible explanation for the role of BMI1 in disease progression. Using the tetracycline-controlled SCLtTA/BCR/ABL mouse model reflecting CP CML [122], one study showed that BMI1 was able to reprogram B-lineage progenitor cells during CP CML-like disease and to turn them into B-cell acute lymphoblastic leukemia (B-ALL) initiating cells [123]. The B-ALL was serially transplantable. Overexpression of BMI1 in hematopoietic stem cells (HSCs) or multipotent progenitors (MPPs) did not result in B-ALL *in vivo*, as assessed by limiting dilution analysis [123]. The presence of continuous BCR-ABL1 was required for the ALL phenotype, since abrogation of BCR-ABL1 expression by doxycycline re-administration rescued the mice from ALL-mediated lethality [123]. Thus, these data suggest that in patients with CML, BMI1 may synergize with BCR-ABL1 to induce lymphoid blast phase by transforming B-lineage progenitors expressing BCR-ABL1. Immunophenotypic data on the type of blast phase were not provided in the retrospective expression cohort [121] but a second functional study showed that BMI1 overexpression in human CD34$^+$ cells from CML patients induced transplantable B-lineage ALL after transplantation of these cells into NOD/SCID mice [124]. This study also showed that BMI1 induced BCR-ABL1 positive acute leukemia was biased towards the lymphoid lineage, supporting the above-mentioned mouse model [123,124]. The mechanism may involve p16 and p19 (equivalent to human p14) repression and possibly EBF1, PAX5, and IKZF1 downregulation [123,124].

5.2. DNA methylation

Reports of hypermethylation during disease progression at genes such as CDKN2A [125–129], CDKN2B [126–133], CALCA [134–136], and DAPK1 [126,127,137,138] among others are all reviewed in detail elsewhere [106,109]. Aside from these, one of the most cited epigenetic hallmarks in CML is increased levels of DNA methylation at the Pa promoter of ABL1 in mononuclear cells from blood or bone marrow [130,133,139–145]. The Pa promoter is the second most 5′ promoter of the ABL1 gene and is normally retained within the chimeric BCR-ABL1 gene of the Ph chromosome in CML. Pa hypermethylation in CP is highly variable, though significantly different compared to normal where it is generally unmethylated. The percentage of CP patients showing increased Pa methylation ranged from as low as 26% [140] up to between 77 and 81% [130,133,142], although such variations may be attributable to the different technologies used in different studies. Both the percentage of patients with Pa methylation and the levels of methylation has been shown to increase during disease progression across several studies [133,139,141,142]. However, the degree of Pa methylation does not correspond to the level of full length BCR-ABL1 transcripts [144] in BP. Taken together, these data add further fuel to the discussion about the prognostic value of Pa promoter methylation in CML progression [146].

Recently, the true scope of changes in DNA methylation across CML methylomes during disease progression has been demonstrated. Reduced representation bisulfite sequencing (RRBS) was used to survey methylation at 2.6 million CpG dinucleotides and detected differences between controls and CML samples in all three phases of disease [147]. Only ≈ 600 CpG were found to be differentially methylated in CP disease compared to healthy controls. However, this number increased by ten-fold to ≈6500 in BP where 897 genes were dysregulated, with the majority showing increases in DNA methylation and reduced mRNA expression. Most of the 897 genes had not previously been identified as being differentially methylated in CML in two earlier microarray-based approaches which employed targeted bisulfite sequencing [133,148].

Table 4
Non-coding RNAs (ncRNAs) dysregulated in CML. Column one: ncRNA name. Column two: class of ncRNA. Column three: putative target gene or competitor RNA (predicted or experimentally validated). Column four: CML cell type studied (primary patient material or cell lines). Column five: clinical significance as described in the cited reference(s). Column six: cited reference(s). Abbreviations: PB = peripheral blood; BM = bone marrow; MNC = mononuclear cells; LSC = leukemic stem cell; CP = chronic phase; BP = blast phase; IFN = interferon; WBC = white blood count; CCR = complete cytogenetic remission; MMR = major molecular response; ND = not determined.

ncRNA	Class	Putative target/Competitor	CML Cell type	Clinical significance	Reference
lncRNA-BGL3	ceRNA	PTEN	K562, PB MNC	ND	[227]
ceRNA network		DLGAP1, DST, PHLDB2, SAMD9, STON1, TRIM6, MAGEA12	K562	disease progression	[228]
miR-126	exosomal	CXCL12, VCAM1	LAMA84	ND	[120]
miR-1908	miRNA	ND	K562	ND	[229]
miR-210		EFNA3	K562	ND	[230]
miR-298		ND	K562	ND	[229]
miR-92a		ND	K562	ND	[231]
ncCHES1	lncRNA	CHES1	PB MNC	dasatinib resistance	[232]
ncPRKCB1		PRKCB1	PB MNC	dasatinib resistance	[232]
ncRNPEP		RNPEP	PB MNC	dasatinib resistance	[232]
let-7a,b,d,f,g,i	miRNA	BCL2L1	K562	ND	[151]
miR-100		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-101		JAK2	PB MNC; K562	CP-CML; imatinib sensitivity	[150,233]
miR-103		CDK6; PIK3R1	PB MNC	ND	[152]
miR-106a		ND	PB MNC; PB CD34$^+$; K562	CP-CML; BP-CML	[149,152]
miR-106b		TGFBR2, CCND1	PB MNC	CP-CML	[150]
miR-107		CRKL	K562	ND	[151]
miR-10a		USF2 among many others	BM MNC; BM CD34$^+$	CP-CML	[162]
miR-10b		CDKN2A	K562	ND	[151]
miR-125a-5p		AKT3	K562	ND	[151]
miR-125b		AKT3, CDKN2A	K562	ND	[151]
miR-126		MAPK8, CRK, KRAS, TGFBR2, CCND1, RUNX1, TP53	PB MNC; BM MNC	CP-CML; BP-CML; imatinib resistance	[150,152,166]
miR-128		CRKL	K562	ND	[151]
miR130a		CCN3	K562; BM stroma; PB MNC	CML diagnosis	[165,234]
miR-130b		TGFBR2, CCN3	K562	ND	[151,234]
miR-134		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-141		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-142-3p		ACVR2A, ANK3, ARHGEF12, CCNJ, MAP3K11, MYH9, MYO5A, RBM47, RHEB, RNF38, ZNF618, C18orf25	PB MNC	CP-CML; prognostic	[163]
miR-144		TGFBR2; SMAD4; RUNX1	PB MNC; K562-R (R = imatinib resistant)	imatinib resistance	[152,235]
miR-145		TGFBR2	K562	ND	[151]
miR-146a		MAPK8, SMAD4, TP53, C12orf36, MMP16, NFASC; NFKB1	PB MNC; BM trephines; K562	CP-CML; imatinib response	[150,151,163,164]
miR-148b		ND	PB MNC	imatinib discontinuation	[236]
miR-150		E2F3, BCR, CBL, CCND1, TP53, MYB, C12orf36, MMP16, NFASC	PB MNC; BM MNC; BM CD34$^+$; BM trephines; BM stroma	CP-CML; BP-CML; relapse; imatinib response	[150,152,162–165]
miR-151		ND	BM MNC; BM CD34$^+$	CP-CML	[162]
miR-152		ND	PB MNC	CP-CML	[150]
miR-155		E2F2, E2F3, BCR, CBL, KRAS, SOS1, TGFBR2, SMAD4, CCND1, PIK3R1, RUNX1, TP53, JARID2, BACH1	PB MNC; K562; Meg-01; BM trephines	CP-CML; imatinib response	[150,152,164,237]
miR-15a		CRKL	PB MNC; K562	CP-CML	[150,151]
miR-16-1		E2F3, BCR, KRAS, CCND1, TP53	PB MNC	CP-CML	[150]
miR-17		E2F2, E2F3, CRK, MAPK1, ACVR1B, CCND1, RUNX1	PB MNC	BP-CML	[150,152]
miR-17-3p		ND	K562; PB CD34$^+$	CP-CML	[149,152]
miR-17-5p		ND	K562; PB CD34$^+$	CP-CML	[149]
miR181 family		MCL1	MYL-R; K562-R (R = imatinib resistant)	TKI resistance	[238]
miR181a		RALA, SOS1, PIK3R3	PB MNC; CD34$^+$; K562	imatinib sensitivity	[152,239,240]
miR-181c		PBX3, HSP90B1,NMT2, RAD21	BM MNC	CP-CML; imatinib resistance	[241]
miR-183		ABCA1	BM MNC	CP-CML; imatinib resistance	[166]
miR-188-5p		CRKL	K562	ND	[151]
miR-18a		ARHGAP26	K562, PB MNC, PB CD34$^+$	CP-CML	[149,192]
miR-18b		ARHGAP26	PB MNC	CP-CML	[192]
miR-19		CCND1	PB MNC	BP-CML	[152]
miR-191		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-193a-3p		CRKL	K562	ND	[151]
miR-195		AKT3; IKBKB	K562	ND	[151]
miR-196b		BCR-ABL1, HOXA9	K562; BM MNC	CP-CML; imatinib resistance	[166,242]
miR-199a		ABCC5	BM MNC	CP-CML; imatinib resistance	[166]
miR-199a-5p		IKBKB	K562	ND	[151]
miR-199b		ND	PB MNC; BM MNC; K562; CMLT1	CML with der(9) deletions; imatinib resistance	[243–245]

(continued on next page)

Table 4 *(continued)*

ncRNA	Class	Putative target/Competitor	CML Cell type	Clinical significance	Reference
miR-199b-5p		ACVR2A, ANK3, ARHGEF12, CCNJ, MAP3K11, MYH9, MYO5A, RBM47, RHEB, RNF38, ZNF618	PB MNC; BM trephines	CP-CML; imatinib response	[163,164]
miR-19a		RAF1; KRAS; MAPK1; TGFBR2; PIK3R3	PB MNC; K562; PB CD34$^+$	CP-CML; BP-CML	[149,151,152]
miR-19b		ND	PB MNC; PB CD34$^+$	CP-CML; BP-CML	[149,152]
miR-203		ABL1; BCR-ABL1	K562; PB MNC; BM MNC	imatinib response/sensitivity	[246–248]
miR-20a		E2F3, BCR, KRAS, TGFBR2, CCND1, RUNX1, TP53, AKT3	PB MNC; K562; PB CD34$^+$	CP-CML; BP-CML	[149–152]
miR-21		E2F1, E2F3, BCR, KRAS, TGFBR2, SMAD3, SMAD4, CCND1, RUNX1, TP53, PDCD4, BCL2	PB MNC; BM MNC; K562	CP-CML; BP-CML; sensitivity to arsenic trioxide	[150,151,249–251]
miR-212		ABCG2	PB CD34$^+$; K562	CP-CML; BP-CML; imatinib response	[149,252]
miR-214		IKBKB	K562	ND	[151]
miR-215		WNK1, ALCAM, RB1, ZEB2, PTPRT, others	plasma	imatinib discontinuation	[253]
miR-217		DNMT3A	K562	TKI resistance	[254]
miR-218		IKBKB	K562	ND	[151]
miR-219-2		ND	PB MNC; BM MNC; K562; CMLT1	CML with der(9) deletions	[243–245]
miR-219-5p		XIAP	K562	ND	[62]
miR-22		AKT3	K562	ND	[151]
miR-221		CRKL, PI3KR1	PB MNC	BP-CML	[152]
miR-222		E2F2, CBL, CDKN1B	PN MNC	BP-CML	[152]
miR-224		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-23a		ND	BM trephines; BM stroma; PB MNC; BM MNC	CP-CML; imatinib response/ resistance; CML diagnosis	[164–166,255]
miR-25		HDM2	K562	ND	[151]
miR-26a		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-29 family		RNAse-L	K562	ND	[256]
miR-29a		SMAD3, CCND1, TP53, TGFBR2, TGFB2	PB MNC; BM MNC; K562	CP-CML; imatinib resistance	[150,151,166]
miR-29b		ABL1, BCR-ABL1, TGFB2	BM MNC; K562	CP-CML	[151,167]
miR-29c		TGFB2; ABCB6	BM MNC; K562	ND; CP-CML; imatinib resistance	[151,166]
miR-301a,b		TGFBR2	K562	ND	[151]
miR-30a		ATG5, BECLIN1, BCR-ABL1, ABL1	K562; BM MNC	imatinib response/sensitivity	[257,258]
miR-30b		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-30c		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-30e		ABL1, BCR-ABL1	PB MNC; K562	CP-CML; imatinib sensitivity	[259]
miR-31		CBL; E2F2	PB MNC; K562; Meg-01	CP-CML	[237]
miR-32		HDM2	K562	ND	[151]
miR-320a		BCR, ABL1	PB MNC	CP-CML	[260]
miR-323-3p		NFKB1	K562	ND	[151]
miR-326		SMO	BM MNC; BM CD34$^+$	CP-CML; imatinib resistance; BP-CML	[166,261]
miR-328		PIM1, hnRNP E2	K562	BP-CML	[252,262]
miR-330-3p		IRF8	PB MNC	CP-CML	[192]
miR-339-5p		HMD2	K562	ND	[151]
miR-34a		SRC	K562; BM MNC	ND	[263]
miR-362-5p		GADD45A	PB MNC	CP-CML; imatinib response	[264]
miR-370		FOXM1; TGFBR2	BM MNC; K562	disease progression; response to omacetaxine	[151,265]
miR-377		IKBKB	K562	ND	[151]
miR-409-3p		IKBKB	K562	ND	[151]
miR-411		TGFBR2	K562	ND	[151]
miR-422b		ND	BM trephines; BM MNC	CP-CML; imatinib response/ resistance	[164,166]
miR-424		ABL1	PB MNC; K562; BM trephines	imatinib sensitivity; atypical CML (Ph$^-$)	[266,267]
miR-451		BCR-ABL1	PB MNC; K562-R (R = imatinib resistant)	CP-CML; relapse; TKI response/ failure/resistance; MMR	[150,152,168–170,235]
miR-454		TGFBR2	K562	ND	[151]
miR-485-3p		CTBP1	K562	ND	[151]
miR-486-5p		CTBP2, FOXO1, PTEN, ARID4b, AFF3, TWF1,	K562; BM CD34$^+$	ND	[151,268]
miR-493-5p		IL8	K562	imatinib response; CP-CML	[269]
miR-494		IKBKB	K562	ND	[151]
miR-520a		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-520a-5p		STAT3	K562	capsaicin sensitivity	[270]
miR-562		IRF8	PB MNC	CP-CML	[192]
miR-564		E2F3, AKT2	PB MNC; K562; Meg-01	CP-CML	[237]
miR-568		ND	PB MNC	CP-CML	[150]
miR-579		ARHGAP26	PB MNC	CP-CML	[192]
miR-607		ND	PB MNC	CP-CML	[150]
miR-625		NFKB1, CDKN2A	K562	ND	[151]
miR-7		ND	BM MNC	CP-CML; imatinib resistance	[166]
miR-9		ND	PB MNC	CP-CML; pterocarpanquinone-LQB-118 sensitivity	[150,271]
miR-92		ND	K562; PB CD34$^+$	CP-CML	[149]

(continued on next page)

Table 4 *(continued)*

ncRNA	Class	Putative target/Competitor	CML Cell type	Clinical significance	Reference
miR-92a-1		E2F3, BCR, KRAS, SMAD4, CCND1, RUNX1, TP53	PB MNC	CP-CML	[150]
miR-96		ND	BM MNC; BM CD34$^+$	CP-CML	[162]
miRNA network		numerous	in silico only	ND	[272]

5.3. MicroRNAs

The miR-17/92 cluster which encodes for six miRNAs processed from a single transcript is over-expressed in CML cell lines and CD34$^+$ cells from CP and BP [149–151]. However, there are conflicting views as to whether it is over-expressed in CP [152], with one study showing that expression of this cluster is only slightly elevated or at normal levels in PB MNC at diagnosis [152]. However, these conflicting data can be reconciled by hypothesizing that different miRNAs of the cluster may be dysregulated during different phases of disease and in different cell types (CD34+ versus total PB MNCs).

6. Epigenetics in therapeutic response and resistance

6.1. Drug resistance

Genetic aberrations such as point mutations in the BCR-ABL1 fusion gene [153–155] or additional chromosomal translocations [156,157] have been strongly implicated in primary and/or secondary resistance to TKI treatment in CML. However, epigenetic dysregulation is also increasingly found to play a causal role in TKI resistance and we have already pointed to several examples (EZH2, PRMT5, SIRT1, MTSS1, CD70) where combining TKI with novel drugs is able to overcome such resistance in LSC or progenitor cells in pre-clinical models [54,63,64,79,91,95]. However, there are other examples supported by analysis of CML cohorts during TKI therapy.

High expression of PRC1 members is associated with decreased imatinib sensitivity. In 30 patients with CML, pre- and post-imatinib bone marrow-derived samples were analyzed for the expression of PRC1 components [158]. During imatinib treatment, the mRNA expression of BMI1, PHC3, CBX6, and CBX7 was significantly increased, and post-treatment levels of CBX6, CBX7 were predictive of the 3-month response rate to imatinib. In addition, BMI1 expression post-treatment level measurements improved the predictive power of hOCT-1 genotyping as a predictor of imatinib response [158].

Increased DNA methylation was linked to down-regulation of BCL2-interacting mediator (BIM) in 36% of a cohort of 100 CML patients and was associated with a decrease of optimal imatinib responses [159]. BIM re-expression by 5-azacytidine treatment was shown to be required for imatinib-induced apoptosis of CML cell lines BV173 and KU812. In another study, HOXA4 promoter methylation was detected in cells from 95 CML patients and was positively correlated with imatinib resistance [160], but, here, no data on HOXA4 expression or function were provided. Two studies showed that DNA hypermethylation were also associated with resistance to adriamycin and interferon/cytarabine/hydroxyurea. In the first, down-regulation of mitochondrial ATPase β-subunit ATP5 B expression decreased the sensitivity of K562 cells to adriamycin [161]. Likewise, silencing of p16INK4A and p14ARF expression by DNA hypermethylation was associated with poor response to interferon and cytarabine +/− hydroxyurea therapy, which correlated with CML progression [125].

In a more comprehensive study, K562 cells or cells from 120 CML patients were subjected to analysis of DNA methylation of CpG islands in the promoters of ten genes (ABL1, CDH13, CDKN2B, DPYS, NPM2, OSCP1, PDLIM4, PGR-A, PGR-B, TFAP2E) which had previously been linked to myeloid malignancies [133]. Patients were imatinib-responsive (n = 30), imatinib-resistant (n = 50), imatinib-intolerant (n = 10), or imatinib-naïve (n = 30 from the pre-imatinib era). Sample were taken during CP (n = 65), AP (n = 40), or BP (n = 15). K562 cells showed extensive hypermethylation (15% of total CpG sites) and, although less extensive, also hypomethylation. There was an overall inverse correlation of gene expression with promoter methylation. Of the ten genes analyzed by bisulfite sequencing, five genes showed significantly increased fractions of CpG-methylated cases with increasing disease severity (with an average of 4.5, 6.2, and 6.8 methylated genes in CP, AP, and BP, respectively). More interestingly, there was a highly significant increase in the number of methylated genes in cells from imatinib-resistant or −intolerant vs. −responsive patients [133]. Finally, promoter methylation of the PDLIM4 gene was significantly inversely correlated with survival of the patients [133].

Dramatic down-regulation of miR-150 compared to normal is a hallmark of CP CML CD34$^+$, mononuclear cells and total leukocytes at diagnosis [150,152,162–165], and rapid reversal of this during imatinib therapy [163] is consistent with imatinib-responders [152]. Indeed, the degree of down-regulation of several miRNAs can distinguish imatinib responders from non-responders in drug-naïve CP diagnostic samples. These include miR-29 cluster [166,167], miR-23a [165,166] and miR-451 [150,152,168,169]. Furthermore, BCR-ABL1 is a validated target of miR-451 [170], and this may explain the inverse relationship between the expression of BCR-ABL1 and miR-451 that is observed in some patients during response to imatinib [169]. However, further mechanistic studies are required to understand why differing miRNA levels in diagnostic samples are able to define differing clinical outcomes.

Epigenomic variability may also play a major role in resistance to TKI treatment. In a functional assay using single-cell RNA-seq and GATA-mediated single-cell ATAC-seq in K562 cells, GATA accessibility was found to show large variations [171], and this was associated with high variability of CD24, CD44, and CD62 expression. Interestingly, functional analysis revealed that the CD24^{hi}-expressing but not the CD24^{lo}-expressing subpopulation showed increased resistance to imatinib-induced apoptosis and suppression of colony forming units [171]. These *in vitro* data suggest a model by which not only genetic but also epigenetic variation among subclones may provide the fertile grounds for therapy resistance, clonal evolution, and, ultimately, progression of CML during TKI therapy.

6.2. Epigenetic drugs in clinical trials

Given the impact of epigenetic dysregulation in CML, clinical trials have been conducted to assess the efficacy and tolerability of epigenetic drugs in CML. In a study of 50 patients with myeloid malignancies who were treated with decitabine, five patients with CML were included (1 CP, 1 AP, 3 BP). Of these five patients, two achieved a CR and two patients attained a PR. However, response duration was short (1–9 weeks), there was no correlation with CDKN2B promoter methylation, and no data on cytogenetic or molecular responses were reported [172]. In a subsequent study, 35 imatinib-resistant CML patients (12 CP, 17 AP, 6 BP) were treated with decitabine [173]. Toxicity was reported as mild. In CP, 50% of patients achieved a CHR, and the overall response rate was 83%, with 25% major cytogenetic responses. Again, these responses were generally short-lived, but occasional long-term responses occurred, leading to an overall significant superiority of survival in the decitabine responders vs. non-responders [173].

Hypomethylation of LINE elements was observed, but this was not durable [173]. Significantly better overall survival was also reported in a subsequent study of a combination of decitabine and imatinib in 28 CML patients (18 AP, 10 BP), most of whom were already imatinib-resistant [174]. In this cohort, 50% of AP and 30% of BP patients showed overall responses, with 39% and 20% of each group respectively achieving cytogenetic remission. Again, overall survival was significantly better in the responders, with a plateau during the first 50 weeks, but subsequently declined [174]. In a small case series of eight patients with imatinib-resistant CML (1 CP, 5 AP, 2 BP), addition of two HDAC inhibitors, hydralazine and magnesium valproate, to imatinib therapy resulted in clinical responses during a median of 18 months of follow-up. Adverse events included mild neurological symptoms but no grade 3 or 4 toxicities [175]. Thus, addition of HDAC inhibitors may be beneficial in TKI-refractory CML patients when no other options exist.

Together, the data from these clinical trials show that treatment with epigenetic drugs can induce objective responses in patients with CML, even in advanced stages and despite imatinib-refractoriness. However, these responses are usually not durable, and other treatment strategies have to be pursued. Currently, not only do several TKI options exist (i.e. imatinib, dasatinib, nilotinib, bosutinib, and ponatinib), but novel agents are being tested (i.e. ABL001 [176]), and allogeneic transplantation remains as a potentially curative option for patients with advanced or non-responsive disease. The reason for the short-lived responses may well be our limited understanding of the magnitude and complexity of epigenetic aberrations and the difficulty to revert these changes by a single drug.

7. Future prospects

The advent of the genomics era has greatly influenced the understanding, diagnosis, and treatment of cancer. Probably among the most affected are patients with chronic myeloid leukemia (CML). Soon after the realization of the dramatic success of targeted therapies against the BCR-ABL1 oncogene, molecular therapies have been spreading to other cancers, making CML one of the most important and best-understood paradigmatic malignancies in the field of oncology. Not only has high-sensitivity PCR monitoring of BCR-ABL1 transcripts long entered clinical practice, leading to important treatment decisions, but the concept of oncogene addiction of LSC, treatment-emergent oncogenic resistance due to BCR-ABL1 mutations, and, lately, the concept of TFR and operational cures have all been developed bench-to-bedside-and-back in the context of CML.

While genetic factors are clearly important, epigenetic modifications are now increasingly being recognized as crucial mechanisms of CML pathogenesis, progression, and treatment resistance. With the currently evolving technologies of whole-genome sequencing, single-cell RNA-seq, histone modification mapping, and genome-wide DNA methylation, etc, we are experiencing a time where a much more comprehensive description of CML biology comes within grasp. It can be expected that soon the diagnosis of patients with CML will be much more exact than currently, including sub-clonal analysis and ultra-deep monitoring. Yet, many questions still remain unanswered and unsolved, such as the question of optimal treatment of patients with accelerated and blast phase, the prerequisites for successful treatment discontinuation, and the factors for long-term remission. Recently, CML $CD34^+$ cells, highly enriched for LSC, were demonstrated to be killed by p53 stabilization combined with BET inhibitor-mediated chromatin disruption [177]. Furthermore, BET inhibitors can decrease PD-L1 expression on solid tumor cells [178,179], and it is tempting to speculate that this downregulation may facilitate activation of immune checkpoints and long-term clearance of LSC, similar to suppression of PD1 on T cells in CML patients with TKI-induced deep molecular remission [180]. The short-lived duration of responses to epigenetic drugs in the clinic is also an area that is poorly understood. However, recent studies suggests that BET inhibitor resistance is likely to be driven by pre-existing clones which display a high degree of transcriptional plasticity, making them highly adaptive with the possibility of reversion to BET sensitivity when treatment is discontinued [181,182]. Such resistant clones also have altered epigenetic landscapes − pointing to epigenetic-based resistance mechanisms that will require further investigation. These findings may also have broader implications for all types of epigenetic drugs as stand-alone therapies.

Thus, epigenetic factors clearly will continue to play a role in CML treatment and prognosis, and the elucidation of critical pathways in cancer initiation, maintenance, and successful elimination of LSC will continue to benefit from CML research.

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