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REVIEW

Polycomb complexes in normal and malignant hematopoiesis

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Epigenetic mechanisms are crucial for sustaining cell type–specific transcription programs. Among the distinct factors, Polycomb group (PcG) proteins are major negative regulators of gene expression in mammals. These proteins play key roles in regulating the proliferation, self-renewal, and differentiation of stem cells. During hematopoietic differentiation, many PcG proteins are fundamental for proper lineage commitment, as highlighted by the fact that a lack of distinct PcG proteins results in embryonic lethality accompanied by differentiation biases. Correspondingly, proteins of these complexes are frequently dysregulated in hematological diseases. In this review, we present an overview of the role of PcG proteins in normal and malignant hematopoiesis, focusing on the compositional complexity of PcG complexes, and we briefly discuss the ongoing clinical trials for drugs targeting these factors.

Introduction

Adult blood cell production is a hierarchical process that takes place in the bone marrow, where low proliferating hematopoietic stem cells (HSCs) both self-renew and differentiate into every mature blood cell type. Based on reconstitution ability, HSCs can be subgrouped into a small fraction of quiescent, long-term (LT)-HSCs and a more active group of short-term (ST)-HSCs (Smith et al., 1991; Osawa et al., 1996; Yang et al., 2005). According to a classical hematopoietic lineage differentiation model, these populations give rise to multipotent progenitors (MPPs) that lack self-renewal ability, enter the cell cycle more frequently, and are primed for differentiation (Morrison et al., 1997). Either common lymphoid or common myeloid progenitors (CLPs and CMPs, respectively) arise from the commitment of MPPs. CLPs further differentiate to produce T and B cells as well as natural killer and dendritic cells. CMPs produce megakaryocytes and erythrocytes (with a common progenitor, megakaryocyte–erythroid progenitor [MEP]) along with granulocytes and macrophages (from the granulocyte–monocyte progenitor cell [GMP]; Kondo et al., 1997; Akashi et al., 2000; Na Nakorn et al., 2002). However, a large body of evidence is now challenging this classical view of differentiation (Woolthuis and Park, 2016).

The entire differentiation process is highly regulated by both extrinsic and intrinsic factors, the latter being mainly represented by epigenetic regulators of gene expression. Indeed, genome-wide sequencing approaches show that epigenetic regulators are frequently mutated in hematological malignancies (Plass et al., 2013), making it important that we obtain a better understanding of their roles in both physiological and malignant hematopoiesis. Numerous proteins of the Polycomb (Pc) and Trithorax (Trx) complexes have been identified among these epigenetic factors. These two complexes play crucial roles in gene expression regulation in mammals. The Pc repressive complexes 1 and 2 (PRC1 and PRC2) enforce gene silencing through chromatin compaction and repressive histone posttranslational modifications (Schuettengruber et al., 2017). Their activity is counteracted by the Trx complexes, which deposit activating histone marks and thus allow high levels of transcription (see text box).

In this review, we discuss the importance of the Pc complexes in normal hematopoiesis, with a particular focus on the specific subunits and complexes involved in the distinct differentiation steps. We also review the roles played by gain-of-function (GOF) and loss-of-function (LOF) mutations of Pc group (PcG) proteins responsible for altered epigenetic landscapes in hematological disorders. Finally, we focus on drugs designed to target PcG proteins, with the aim of counteracting aberrant epigenetic regulation in hematological disorders.

Composition and function of Pc complexes

Mutations in *Drosophila* that are associated with sex comb development were first isolated in the 1940s and termed *extra sex combs* (*esc*) and *Pc* (Slifer, 1942; Lewis and Mislove, 1947). More than 30 yr later, *esc* and *Pc* gene products were identified as negative regulators of the homeotic gene *Ultrabithorax* (*Ubx*; Lewis,

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Trx group (TrxG) proteins

In *Drosophila melanogaster*, Pc-mediated repression of the *Hox* gene cluster is counteracted by the activity of the *Trx* gene and TrxG proteins. The mixed-lineage leukemia (*MLL*) gene is a mammalian homologue of *Trx* and was first identified as frequently involved in chromatin rearrangements in infant leukemia patients (Ziemin-van der Poel et al., 1991; Rowley, 1993; Mbangkollo et al., 1995). MLL has seven paralogues in mammals (MLL1–5 and SETd1A/B). Analogous to PRC1/2, MLL assembles distinct complexes around the set of evolutionarily conserved core subunits WDR5, RbBP5, ASH2L, and DPY30 (WRAD; Nakamura et al., 2002). These proteins are necessary to enhance MLL histone methyltransferase activity and to regulate MLL complex recruitment to chromatin (Bochyńska et al., 2018). Association of additional subunits such as the histone demethylase UTX (specific for H3K27) extends the catalytic repertoire of the complex by simultaneously providing erasing of H3K27me3 repressive marks deposited by EZH2 and deposition of the H3K4me3 activating mark by MLL (Agger et al., 2007; Lan et al., 2007).

In hematopoiesis, MLL is necessary for self-renewal in adult (but not fetal) hematopoietic stem/progenitor cells (HSPCs; Jude et al., 2007; McMahon et al., 2007; Gan et al., 2010) as well as for proliferation and lymphopoiesis by maintaining proper expression of *HOX* genes (Yu et al., 1995; Yagi et al., 1998; Ayton et al., 2001; Ernst et al., 2004). However, the catalytic activity of MLL seems to be dispensable (Terranova et al., 2006; Mishra et al., 2014). Heterozygous translocations involving the *MLL* gene are found in a very high percentage of infant leukemia patients affected by either acute myeloid leukemia (AML; >35%) or acute lymphoblastic leukemia (ALL; >70%). In >90% of the cases, the breakpoint region is localized between exon 9 and intron 11 (Meyer et al., 2018), resulting in the production of chimeric gain-of-function (GOF) proteins containing an N-terminal truncated form of MLL. To date, 135 distinct translocation partner genes (TPGs) have been described. The five most common TPGs (*AF4*, *AF9*, *ENL*, *AF10*, and *ELL*) account for ∼80% of the translocations (Meyer et al., 2018). All of these gene products belong to multiprotein complexes involved in transcription elongation either in the super elongation complex (SEC), the DOT1L complex (DotCom), or both (Okada et al., 2005; Lin et al., 2010; Mohan et al., 2010). Molecular mechanisms behind MLL chimera–mediated leukemogenesis are not yet fully understood; however, this process seems to involve the aberrant expression of the *HOXA9* and *MEIS1* genes, two master regulators of myeloid lineage. Both of these genes are targeted by SEC and DotCom (Okada et al., 2005; Lin et al., 2010) as well as by WT MLL and MLL chimeras in leukemic cells (Milne et al., 2005; Faber et al., 2009). *HOXA9* and *MEIS1* expression is necessary for survival of leukemic cells, and their overexpression in normal HSPCs is sufficient to induce leukemic transformation (Kroon et al., 1998; Zeisig et al., 2004; Faber et al., 2009). In line with a GOF scenario, most of the proteins involved in physiological regulation of these loci are necessary for MLL chimera–mediated leukemogenesis, including WT MLL, its interactor menin (Yokoyama et al., 2005), and the SEC subunits pTEFb and DOT1L (Okada et al., 2005; Krivtsov et al., 2008). Indeed, drugs targeting the WRAD–MLL interaction (Karatas et al., 2013; Senisterra et al., 2013; Cao et al., 2014) or the menin–MLL interaction (Grembecka et al., 2012; Shi et al., 2012; Borkin et al., 2015) or that inhibit the DOT1L H3K79 methyltransferase activity (Cai et al., 2015) have been shown to be effective in arresting proliferation of leukemic cells.

MLL2 and -3 appear to play an oncogenic role in AML (Chen et al., 2014, 2017; Santos et al., 2014). Conversely, these proteins seem to act as tumor suppressors in B cells and derived lymphomas (Ortega-Molina et al., 2015; Zhang et al., 2015). In line with this, loss-of-function (LOF) mutations of MLL2 and -3 are found at relatively high frequencies in diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and ALL (Morin et al., 2011; Lohr et al., 2012; Zhang et al., 2013; Green et al., 2015; Lindqvist et al., 2015; Neumann et al., 2015). UTX, another important accessory factor, is also found mutated in various types of leukemia (van Haaften et al., 2009; Jankowska et al., 2011; Mar et al., 2012).

1978; Struhl, 1981). Genes whose mutations give rise to developmental defects resembling those of *esc* and *Pc* were thereafter termed PcG genes (Jürgens, 1985). The proteins encoded by PcG genes were described as part of two distinct multiprotein complexes, PRC1 and PRC2 (Shao et al., 1999; Kuzmichev et al., 2002), which are highly conserved in mammals (Kuzmichev et al., 2002; Levine et al., 2002). Gene silencing by these complexes is associated with their ability to catalyze posttranslational modifications of histone tails, namely histone H2A monoubiquitylation for PRC1 and histone H3 lysine 27 methylation for PRC2 (Cao et al., 2002; Wang et al., 2004a). In both cases, the enzymatic activity is endowed in the core subunits, around which different sets of accessory factors assemble to modulate catalysis and to regulate PRC1 and -2 recruitment to chromatin. The six subtypes of PRC1 (PRC1.1–6) are specified by the incorporation of one of the six PcG ring finger (PCGF) proteins: NSPC1/PCGF1, MEL-18/PCGF2, PCGF3, BMI-1/PCGF4, PCGF5, or MBLR/PCGF6 (Fig. 1 A; Gao et al., 2012). PRC2 has two main configurations, PRC2.1 and PRC2.2 (Fig. 1 B; Beringer et al., 2016). A list of PcG proteins along with their reported function is shown in Table 1 (see also Aranda et al., 2015; Holoch and Margueron, 2017; Schuettengruber et al., 2017).

In the classical model of recruitment for these two complexes, the H3K27me3 mark is deposited by PRC2, which is in turn recognized by chromobox homolog (CBX) proteins contained in PRC1.2/4 (also termed canonical PRC1 [cPRC1]; Wang et al., 2004b). However, noncanonical PRC1s (PRC1.1, 3, 5, and 6), which contain RING1- and YY1-binding protein (RYBP), rely on an alternative, H3K27me3-independent mode of recruitment (Tavares et al., 2012). Moreover, PRC2.2 is able to recognize ubiquitylated H2A (H2Aub; Cooper et al., 2016), suggesting that there is more than a single way of crosstalk between PcG proteins.

PRC1 and -2 are responsible for repressing pluripotency genes during embryonic stem cell (ESC) differentiation in both mouse and human (Boyer et al., 2006). For both complexes, changes in the expression and arrangement of the different subunits occur along the differentiation pathways, suggesting that their dynamic expression is relevant for committing cells to a specific fate (Morey et al., 2012, 2015; Kloet et al., 2016). Notably, however, the influence of PcG is not limited to early developmental stages but extends to various subtypes of adult stem cells (Aloia et al., 2013; Schuettengruber et al., 2017).

PcG proteins in hematopoiesis

Canonical PRC1

The B cell–specific Moloney murine leukemia virus integration site 1 (BMI-1/PCGF4) was first identified as an oncogene in MYC-mediated lymphomagenesis (Haupt et al., 1991; van Lohuizen et al., 1991) and has since been thoroughly studied in both normal and malignant hematopoiesis. PRC1 containing BMI-1 (PRC1.4) appears to be responsible for both the commitment of mesoderm layer to primitive HSC formation and the maintenance of LT-HSC self-renewal and proliferation capacities. Specifically, BMI-1 overexpression in ESCs leads to enhanced proliferation of embryoid body–derived primitive HSCs (Ding et al., 2012). Moreover, HSCs that overexpress BMI-1 display increased proliferation and self-renewal rates both in mouse models and human cell models (Iwama et al., 2004; Rizo et al., 2008). In accordance with this, BMI-1–depleted mice show defects in self-renewal and increased apoptosis of HSCs (Park et al., 2003; Iwama et al., 2004; Oguro et al., 2006; Liu et al., 2009; Rizo et al., 2009). In particular, PRC1.4 enables HSCs to overcome

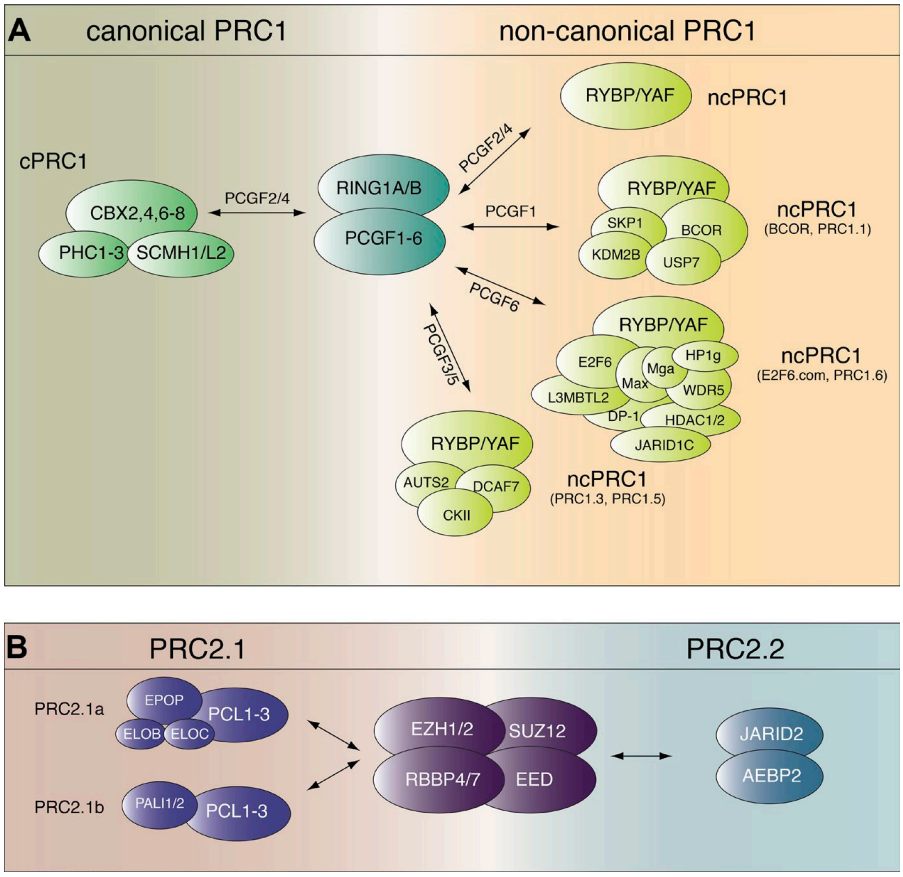

Figure 1. **Mammalian PRC1/2 compositional complexity. (A)** PcG proteins RING1A/B and PCGF1–6 compose a core around which accessory subunits associate. cPRC1 incorporates one PHC and one CBX protein. Noncanonical PRC1 (ncPRC1) complexes incorporate RYBP/YAF2 along with specific sets of additional proteins. **(B)** PRC2 shares a similar organization, with a tetrameric core composed of EZH1/2, SUZ12, EED, and RBBP4/7. Association with PCL proteins defines a PRC2.1 subtype that can associate with either EPOP or PALI1/2 (PRC2.1a/b). Conversely, association with AEBP2 and JARID2 defines a PRC2.2 subtype.

senescence and apoptosis by repressing the *Ink4a/Arf* (*Cdkn2a*) locus as well as by preventing DNA damage (Fig. 2).

In addition to its role in HSCs, PRC1.4 seems to have a fundamental function in regulating lymphoid specification by preventing B cell lineage commitment. Specifically, RING1B and BMI-1 are localized at the bivalent promoters of B-lineage master regulators *Ebf1* and *Pax5*, and their depletion in T cells leads to accelerated activation of these transcription factors, resulting in T-to-B cell conversion (Oguro et al., 2010; Ikawa et al., 2016). Notably, MEL-18/PCGF2 seems to play an opposite role, which is however limited to adult hematopoiesis: mice lacking MEL-18 show no defects in fetal liver cell proliferation (Iwama et al., 2004) but display spleen and thymus hypoplasia at birth as well as perinatal lethality, which are associated with defects in B cell production (Akasaka et al., 1997; Tetsu et al., 1998). Moreover, HSCs from *Mel-18*$^{-/-}$ mice are more quiescent and less proliferative than those from WT mice. These studies point to complementary functions for PRC1.2 and PRC1.4 in regulating HSC self-renewal and proliferation as well as in maintaining the balance between B and T cells in lymphoid lineage (Fig. 2).

Along with the BMI-1/MEL-18 duality, cPRC1 activity in hematopoiesis is modulated by incorporation of alternative CBX proteins. In particular, LT-HSCs seem to preferentially express and incorporate CBX7; in mice models, CBX7 overexpression results in an enhanced self-renewal ability and overproliferation of HSCs, eventually leading to T cell leukemia/lymphoma in transplanted mice, while its depletion has the opposite effect (Scott et al., 2007; Klauke et al., 2013). In HSCs, PRC1 that contains CBX7 is located on genes that are progressively up-regulated during the HSC-to-progenitor transition, consistent with the rapid down-regulation of CBX7 during this phase (Klauke et al., 2013). Indeed, concomitant posttranscriptional up-regulation of CBX8 at the progenitor stage results in retargeting PRC1 to myeloid-specific genes (Klauke et al., 2013), suggesting that CBX8 plays a specific role at the level of MPPs and during lymphoid differentiation. This dynamics resembles that observed in ESCs: CBX7, which is responsible for maintaining the pluripotent state, is progressively down-regulated and then replaced with CBX2/4 during differentiation (Morey et al., 2012). In contrast, CBX8 appears dispensable for HSC activity. Recent evidence points to a fundamental function for the CBX8-containing PRC1, which works together with PRC2 to determine B cell germ cell formation (Béguelin et al., 2013, 2016, 2017; Caganova et al., 2013), suggesting that it is functional more for lineage commitment than for HSC maintenance (Tan et al., 2011). CBX2 impairs HSC and progenitor proliferation by regulating p21 expression in human cells (van den Boom et al., 2013). CBX2 also has a specific role in committing cells toward B-lymphoid lineage as irradiated mice transplanted with HSCs overexpressing CBX2 are only able to reconstitute B cells (Coré et al., 1997; Klauke et al., 2013). Analogously, CBX4 seems to play a role in differentiation rather than in maintaining pluripotency: depletion of this protein results in arrest of T cell development shortly after birth as a result of impaired thymic epithelial cell proliferation (Liu et al., 2013). Altogether, these studies reveal nonredundant roles for CBX proteins, with CBX7 sustaining LT- and ST-HSC proliferation

Table 1. **PcG proteins and their molecular functions**

Complex	Protein	Function
Core PRC1	RING1A/B	H2A monoubiquitylation and nucleosome binding
	PCGF1–6	Stimulation of enzymatic activity
PRC1.2, 4	CBX2,4,6–8	H3K9/K27me3 binding
	PHC1–3	Oligomerization and chromatin compaction
	SCMH1/L2	Histone methyl–lysine binding and RNA binding
PRC1.1, 3, 5, 6	RYBP/YAF2	DNA binding (unspecific) and interaction with YY1
PRC1.1	BCOR/BCORL1	Scaffold
	KDM2B	H3K36 demethylation and DNA binding (unmethylated CpG islands)
	SKP1	Ubiquitin ligase and interaction with CUL1
	USP7	Stimulation of enzymatic activity
PRC1.3, 5	DCAF7	Scaffold
	CK2	Inhibition of enzymatic activity
	AUTS2/FBRS/FBSL	Transcription activation
PRC1.6	WDR5	Scaffold
	L3MBTL2	Histone methyl–lysine binding and chromatin compaction
	HP1γ/CBX3	H3K9me3 binding
	JARID1C	H3K4me2/3 demethylase
	G9a	H3K9 methyltransferase
	HDAC1/2	Histone deacetylase
	DP-1	DNA binding (E2F recognition site)
	E2F6	DNA binding (E2F recognition site)
	MAX	DNA binding (E-boxes)
	MGA	DNA binding (E-boxes)
Core PRC2	EZH1/2	H3K27 methyltransferase
	SUZ12	DNA/RNA binding
	EED	H3K27me3 binding
	RBBP4/7	Histones binding
PRC2.1	PCL1/PHF1	H3K36me2/3 binding, DNA binding (unspecific), and stimulation of enzymatic activity
	PCL2/MTF2	H3K36me2/3 binding and DNA binding (unmethylated CpG islands)
	PCL3/PHF19	H3K36me2/3 binding
	EPOP	Inhibition of enzymatic activity and interaction with Elongin B and C
	PALI1/2	Stimulation of enzymatic activity
PRC2.2	JARID2	DNA/RNA binding, H2Aub binding, and stimulation of enzymatic activity
	AEBP2	DNA binding, H2Aub binding, and stimulation of enzymatic activity

and self-renewal, and CBX2, -4, and -8 mainly playing specific roles during hematopoietic lineage commitment but unable to functionally compensate for each other. These differences could be explained by differential recruitment mechanisms; however, mechanistic insights that could support this hypothesis are still missing (Fig. 2).

PHC1 is essential for PRC1 functioning in hematopoiesis, and in particular in B cell development. Knockout (KO) of *Phc1* in mice results in impaired B cell development and perinatal lethality (Takihara et al., 1997; Tokimasa et al., 2001). Defects in B cell maturation are also visible in Phc1 heterozygous mice. Moreover, Phc1-deficient HSCs are not able to reconstitute blood in transplanted irradiated mice (Ohta et al., 2002; Kim et al., 2004). Although mechanistic insight is still lacking about the role of this protein (as well as its paralogues PHC2/3) in hematopoiesis, evidence suggests a role for PRC1.2/4 in regulating lymphopoiesis.

Noncanonical PRC1

PCGF1-containing noncanonical PRC1 (PRC1.1) seems to be involved in allowing hematopoietic progenitor cells to escape from pluripotency. Thus, PCGF1 is necessary for shutting down the HSC pluripotency program by repressing *HoxA* genes, thereby

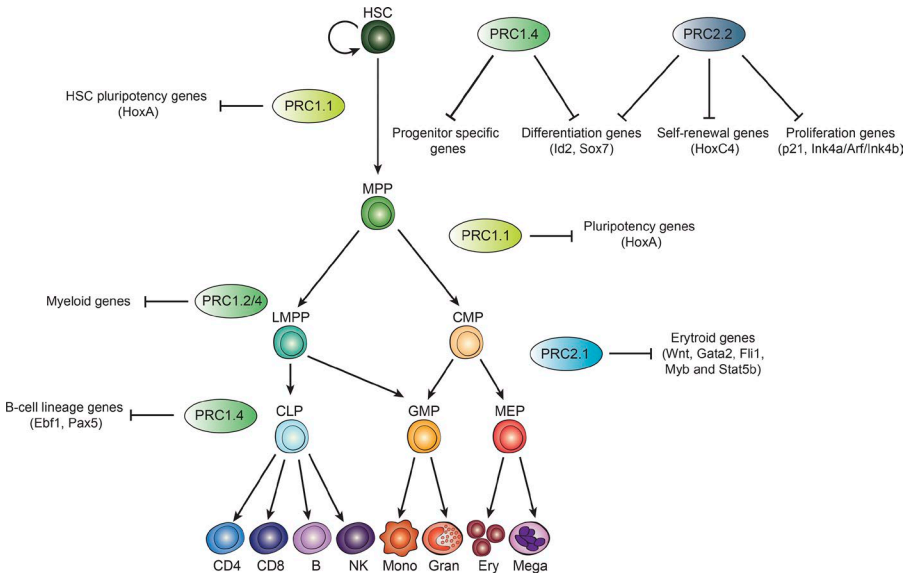

Figure 2. **PRC1/2 in normal adult hematopoiesis.** Schematic representation of the hematopoietic differentiation according to the classical model. PRC complexes that were described to have a role in regulating gene expression at specific stages are shown along with their reported genomic targets. Adapted from Corces et al. (2016).

priming them for further commitment by the master regulator RUNX1 (Ross et al., 2012). Upon PCGF1 depletion, HSCs are biased toward the myeloid lineage (van den Boom et al., 2013). Ectopic overexpression of the H3K36me2 demethylase KDM2B (also in PRC1.1) increases T-lymphoid commitment in a way that is dependent on its demethylase activity, while KDM2B depletion results in myeloid skewing; this is comparable with that observed for PCGF1 (Andricovich et al., 2016). Similarly, overexpression of BCL6 corepressor (BCOR; another PRC1.1 member) in myeloid-committed cells impairs proliferation by repressing *HoxA* genes, while mutations in BCOR give a proliferative advantage for this lineage (Cao et al., 2016). In patients with X-linked oculofacio-cardio-dental (OFCD) syndrome, 90–100% of white blood cells undergo inactivation of the X chromosome containing the BCOR-mutated allele, indicating that BCOR-expressing cells have a proliferative disadvantage and cannot fully contribute to hematopoiesis; this was confirmed in a chimeric mouse model (Ng et al., 2004; Wamstad et al., 2008). These observations reinforce the notion that PRC1.1 activity is specifically needed to commit progenitors toward lymphopoiesis (Fig. 2).

The roles played by remaining PRC1 complexes (PRC1.3/5/6) in hematopoiesis still have not been fully addressed. However, results for PCGF5 and PCGF6 suggest that PRC1.5 and -1.6, respectively, do not play a major role in hematopoiesis (van den Boom et al., 2013; Si et al., 2016).

PRC2

The PRC2 components EZH2 and SUZ12 are highly expressed in both fetal and adult bone marrow, while EZH1 is preferentially expressed in adult HSCs (Lessard et al., 1998, 1999; Mochizuki-Kashio et al., 2011; Xie et al., 2014). Consistent with these patterns of expression, EZH1 KO mice do not display defects in primitive HSCs, while adults show impaired B cell development (Hidalgo et al., 2012). Conversely, EZH2 KO mice display embryonic lethality, while EZH2 inactivation at the adult stage produces defects in B cell maturation. This suggests that EZH1 can compensate for EZH2 loss, thereby maintaining self-renewal capacity, only at the HSC stage (Su et al., 2003; Mochizuki-Kashio et al., 2011); similar results have been observed for other types of stem cells (Fig. 2; Shen et al., 2008; Ezhkova et al., 2009, 2011).

As depletion of EZH2 (or of any PRC2 core component) leads to early embryonic lethality (Faust et al., 1995; O'Carroll et al., 2001; Su et al., 2003; Pasini et al., 2004; Mochizuki-Kashio et al., 2011), the roles of these proteins in hematopoiesis were addressed using lineage-specific KOs and heterozygous models. Heterozygous depletion of EZH2, SUZ12, or embryonic ectoderm development (EED) increases hematopoietic stem/progenitor cell (HSPC) activity, suggesting that PRC2 has an antiproliferative effect on HSPCs and thus an opposite role with respect to BMI-1–PRC1 (Lessard et al., 1999; Majewski et al., 2008, 2010). Nonetheless, more recent studies have shown that hematopoiesis-specific KO of either SUZ12 or EED results in HSC exhaustion at the fetal or adult stage (likely depending on the developmental stage at which the KO is induced) rather than hyperproliferation, arguing for a dosage-dependent effect of PRC2 on HSC activity (Xie et al., 2014; Lee et al., 2015; Yu et al., 2017). PRC2 also plays a key role in the lymphoid branch: lineage-specific dissection revealed that SUZ12 is essential for T and B cell maturation but dispensable for proper myelopoiesis (Lee et al., 2015). Moreover, EZH2 is needed to prevent aberrant activation of naive T cells toward Th1/2 by repressing crucial regulators (e.g., *Il10*, *Ifng*, and *Gata3*; Zhang et al., 2014). In B cells, EZH2 is necessary for *Igh* rearrangement (Su et al., 2003) and germinal center (GC) formation by silencing *p21/p27* and *Blimp1* loci (Béguelin et al., 2013, 2016, 2017; Caganova et al., 2013). Indeed, the GC reaction is accompanied by a marked up-regulation of all PRC2 core components as well as of PHF19, suggesting a possible role for this accessory subunit in modulating PRC2 activity in this process (Béguelin et al., 2016; Ning et al., 2018). For PRC2 accessory factors, JARID2 knockdown in HSPCs phenocopies that of SUZ12, resulting in higher repopulating capacity in competitive transplants. Accordingly, JARID2 chromatin localization in HSPCs largely overlaps that of SUZ12 and H3K27me3 on genes associated with self-renewal in fetal HSCs. Conversely, depletion of PHF1, MTF2, or PHF19 does not affect HSPC proliferation (Kinkel et al., 2015), suggesting that HSPCs mainly rely on PRC2.2 activity. In

the myeloid lineage, MTF2 is necessary for proper PRC2.1 targeting at master regulators of erythrocyte maturation such as the Wnt signaling pathway and its downstream targets *Gata2*, *Fli1*, *Myb*, and *Stat5b* (Fig. 2; Rothberg et al., 2018). Altogether, these studies prove that PRC2 is necessary for long-term maintenance of hematopoiesis and maturation of lymphoid lineage as well as for erythropoiesis, and they point toward functional roles of specific accessory subunits in recruiting PRC2 to specific genomic targets at each differentiation step.

Oncogenic functions of PcG proteins

PRC1

Numerous PcG proteins have been linked to hematological diseases (Table S1). Early on, BMI-1 was identified as a protooncogene that cooperates with MYC in repressing the *Ink4a/Arf* gene locus (Haupt et al., 1991; van Lohuizen et al., 1991; Jacobs et al., 1999). Ectopic expression of BMI-1 in the lymphoid compartment is also sufficient to perturb normal lymphogenesis, giving rise to B and T cell lymphomas in mice (Alkema et al., 1997). A role for BMI-1 has also been proposed in leukemia in which LOF of the gene in mice delays the onset of primary leukemia and blocks the development of secondary leukemia, probably due to cancer stem cell exhaustion (Jacobs et al., 1999; Park et al., 2003; Rizo et al., 2009). In pediatric acute lymphoblastic leukemia (ALL), Bmi-1 mRNA is expressed at high levels and correlates with poor prognosis, while it is significantly decreased in patients in complete remission (Peng et al., 2017). Indeed, BMI-1 expression has been proposed as a molecular marker to follow disease progression in B cell lymphomas (Raaphorst et al., 2000; Beà et al., 2001; van Kemenade et al., 2001; van Galen et al., 2007), myelodysplastic syndromes (MDSs), and leukemia; in all cases, its expression correlates with reduced survival and poor prognosis (Sawa et al., 2005; Mihara et al., 2006; Chowdhury et al., 2007; Mohty et al., 2007; Saudy et al., 2014; Peng et al., 2017).

Another PRC1 component associated with cell transformation and lymphomas is CBX7 (Klauke et al., 2013). Under normal conditions, CBX7 is highly expressed in HSCs and GCs, where B cells proliferate and maturate. However, in vivo experiments have demonstrated a role for CBX7 in initiating T cell lymphomas and, in cooperation with MYC, in accelerating aggressive B cell lymphomagenesis through the regulation of the *Ink4a/Arf* locus (similar to BMI-1; Scott et al., 2007; Klauke et al., 2013).

PRC2

Together with BMI-1, EZH2 is the most studied PcG protein that has been determined to have a strong link with cancer. EZH2 is overexpressed or amplified in several distinct hematological disorders as well as in solid tumors (Piunti and Pasini, 2011). EZH2 plays a pivotal role in controlling the correct formation of GCs. While its deletion suppresses GC formation, expression of mutant EZH2 with hypermethylation activity causes GC hyperplasia, due at least in part to a greater repression of PRC2 target genes such as *p21* (*Cdkn1a*) and *Ink4a/Arf/Ink4b* (Béguelin et al., 2013; Caganova et al., 2013). Additionally, EZH2 cooperates with BCL6, a transcriptional repressor involved in the GC reaction, to recruit a PRC1–BCOR–CBX8 complex to repress gene expression, thus regulating GC formation and lymphomagenesis (Hatzi and Melnick, 2014; Béguelin et al., 2016). These roles are in line with evidence linking high levels of EZH2 expression with poor prognosis and survival outcome, both of which are dependent on its enzymatic activity in B cell lymphomas (Raaphorst et al., 2000; van Kemenade et al., 2001; Visser et al., 2001; Sneeringer et al., 2010; Okosun et al., 2014).

EZH2 GOF mutations have also been identified in non–Hodgkin lymphomas (NHLs) and solid tumors. Mutations of the tyrosine 641 (Y641F/N/S/H/C) are found in 22% of GC B cells and DLB CLs as well as in 7% of FLs, where they are considered an early clonal event leading to the disease (Morin et al., 2010; Caganova et al., 2013; Okosun et al., 2014). These mutations occur in the EZH2 SET domain and alter the substrate-binding pocket. They were initially believed to be LOF mutations as mutated EZH2 prefers substrates with a higher state of methylation (H3K27me0: me1:me2 kcat/Km ratio = 1:2:13) as compared with the WT one (H3K27me0:me1:me2 kcat/Km ratio = 9:6:1), suggesting a decreased capacity to deposit the correct mark (Sneeringer et al., 2010; McCabe et al., 2012). However, these mutations are always heterozygous; thus, while the WT form is responsible for mono- and dimethylation, the mutated isoform enhances the di- to trimethylation conversion. The result of this cooperation is an aberrant, strong overall increase in H3K27me3 (Morin et al., 2010; Sneeringer et al., 2010; Yap et al., 2011; Béguelin et al., 2013; Bödör et al., 2013). Two additional EZH2 point mutations, A677G and A687V, occur less frequently (in 1–2% of lymphoma patients), and only A687V shows a slight preference for methylating H3K27me2; both mutations result in decreased H3K27me2 levels and a hypertrimethylation phenotype (Majer et al., 2012; McCabe et al., 2012; Ott et al., 2014).

Posttranscriptional mechanisms can also alter EZH2 protein levels. For instance, a molecular circuit with a potential role in Burkitt's lymphoma has been proposed in which EZH2 is negatively regulated by miR-26a; when MYC is present at high levels, it represses miR-26a, leading to increased EZH2 expression (Sander et al., 2008).

The scenario is even more complex in leukemias in which fusion proteins with oncogenic activities act together with PRC1 and PRC2 complexes. PML-RARα and PLZF-RARα fusion proteins interact with SUZ12 and BMI-1, respectively, to tether Pc complexes to retinoic acid response elements. In both cases, depletion of PcG proteins decreases the oncogenic potential by promoting cellular differentiation (Villa et al., 2007; Boukarabila et al., 2009). Likewise, in MLL-AF9 acute myeloid leukemia (AML), EED is necessary for leukemia initiation and progression, likely due to derepression of the *Ink4a/Arf* tumor suppressor locus. However, other studies examining the role of EZH2 suggest that EZH1 can partially compensate for its function (Neff et al., 2012; Tanaka et al., 2012; Shi et al., 2013). CBX8 has an important role in MLL-AF9 leukemia as well through its direct interactions with AF9 and TIP60 proteins, which regulate proliferation and survival of leukemic cells in a PRC1-independent way (Tan et al., 2011).

Tumor-suppressive functions of PcG proteins

PRC1

Various PcG proteins also have been shown to act as tumor suppressors (Table S2). For instance, BMI-1 is not only crucially

involved in HSC maintenance and differentiation (Jacobs et al., 1999; Park et al., 2003; Rizo et al., 2009) but also has a role as a tumor suppressor. Its genetic ablation promotes myeloid malignancies (primary myelofibrosis [PMF]) through direct derepression of a cohort of genes including that of *Hmga2*, a well-known oncogene usually expressed at high levels in PMF (Oguro et al., 2012). Likewise, PHC1 has a role as a tumor suppressor in the proper B cell maturation and differentiation, and its expression is lost in leukemic cells from pediatric patients with ALL (Tokimasa et al., 2001).

BCOR and BCORL1 (proteins that cooperate in recruiting the complex to CpG islands) are frequently mutated in myeloid malignancies. Several deletions and mutations affecting the mRNA levels of these factors have been identified in patients with MDS; these account for 4.2% and 0.8% of the cases for BCOR and BCORL1, respectively (Damm et al., 2013). Notably, both proteins are also often down-regulated in cytogenetically normal AML patients (in 4–6% of cases); this down-regulation is associated with poor prognosis. In AML, BCOR disruptive alterations frequently occur together with DNMT3A mutations, suggesting a crosstalk between these two epigenetic factors (Grossmann et al., 2011; Li et al., 2011).

PRC2

EZH2 acts as a tumor suppressor in myeloid malignancies such as MDS and myeloproliferative neoplasms (MPNs). It is a frequent target of chromosomal deletions and missense and frameshift mutations, which have an adverse effect on survival (Ernst et al., 2010; Nikoloski et al., 2010; Bejar et al., 2011; Mochizuki-Kashio et al., 2015; Shirahata-Adachi et al., 2017; Gangat et al., 2018). Missense mutations usually affect EZH2 regions involved in protein–protein interactions or the catalytic pocket, suggesting that the functional integrity of the complex is crucial for PRC2 tumor suppressor functions in these malignancies. EZH2 levels can also be altered by indirect effects. For instance, mutations in the splicing factors SF3B1 and SRSF2 occur in 24% and 14% of MSD cases, respectively, and are considered an early event in disease progression (Yoshida et al., 2011; Papaemmanuil et al., 2013). In mice, a premature termination codon (in a cassette exon) is introduced into EZH2 by a mutant SRSF2 (with P95H), which leads to nonsense mediated decay of EZH2 (Kim et al., 2015).

Other PRC2 components are also mutated in myeloid disorders, although to a lesser extent. Mutations in SUZ12 or EED lead to reduced EZH2 methyltransferase activity in vitro (Score et al., 2012), and JARID2 mutations can potentially alter PRC2 targeting, suggesting that distinct genetic alterations can affect the same pathway (Score et al., 2012). Accordingly, SUZ12 mutations found in patients with MDS or MPN usually affect its VEFS domain, which is necessary for SUZ12's interaction with EZH2 (Brecqueville et al., 2012; Score et al., 2012). Likewise, point mutations in EED can alter its protein stability or its interaction with EZH2 (Lessard et al., 1999; Score et al., 2012; Ueda et al., 2012).

Alterations in these epigenetic modifiers can have wide-ranging effects through modulation and aberrant interactions with other transcription factors and epigenetic regulators. For instance, RUNX1, a master regulator of hematopoietic cell differentiation, is mutated in ∼25% of MDS cases that present EZH2 deletions (Bejar et al., 2011). RUNX1 collaborates with EZH2, and loss of these two factors causes ineffective hematopoiesis and initiation and propagation of an MDS phenotype (Sashida et al., 2014). However, RUNX1 mutants recruit PRC1 to PRC2 target genes such as *HOXA9*, a gene that is usually activated in high-risk MDS and MDS/AML, thus preventing progression to AML (Sashida et al., 2014).

LOF mutations of PRC2 members also have roles in leukemia outcome and progression: inactivating mutations affecting EZH2, EED, and SUZ12 correlate with poor prognosis in both T cell ALL (T-ALL) and early T cell precursor (ETP) ALL (Ntziachristos et al., 2012; Simon et al., 2012; Zhang et al., 2012). Likewise, deletions affecting JARID2 have been associated to various types of leukemia (Su et al., 2015). EZH2 and SUZ12 are misregulated in 25% of all T-ALL cases, and 65% of these mutations associate with an oncogenic increase of NOTCH1. In T-ALL, NOTCH1 binding sites and the PRC2-deposited H3K27me3 mark overlap, suggesting that the absence of PRC2 can reinforce altered NOTCH1 signaling (Ntziachristos et al., 2012). For both EZH2 and EED, a role in ETP-ALL development has also been proposed: they cooperate with the mutated form of GTPase NRAS (Q61K) to enhance cell growth and survival signaling (Danis et al., 2016).

PRC2 components act as tumor suppressors also in AML, in which deletions of PRC2 genes (*EZH2*, *JARID2*, *SUZ12*, and *AEBP2*) have been identified in 35% of AML patients with a previous history of MPN/MDS (Puda et al., 2012). These mutations alter the correct enzymatic activity of the complex, thus facilitating leukemia progression (Puda et al., 2012). Accordingly, in vivo experiments confirmed that an EED missense mutation (I363M) found in AML affects the region close to the aromatic cage, altering the correct deposition of the H3K27me3 mark. This mutation also increases the susceptibility to leukemia in cooperation with other genetic alterations such as EVI1 (myeloid leukemia) and RUNX1 (T cell leukemia; Ueda et al., 2016).

Targeting PcG proteins in hematologic cancers

Considering the strong link between PcG protein alterations and hematological diseases, major efforts have been directed to developing compounds that aim to restore the correct levels of these chromatin modifiers for disease treatment (Bhaumik et al., 2007; Copeland et al., 2009). Importantly, directly targeting epigenetic regulation has the advantage of being more plastic than therapies that aim to correct the patient's genomic DNA.

For PRC1, inhibitors targeting BMI-1 have been developed that provide good responses in distinct tumor types. The first BMI-1 inhibitor identified was PTC-209, which is able to lower BMI-1 transcript levels without affecting those of RING1B or CBX7. In models of human colorectal cancer, it reduces the number of functional cancer-initiating cells, resulting in a strong reduction of tumorigenic potential in xenograft models (Kreso et al., 2014). PTC-209 has shown promising results both in primary AML and chronic myeloid lymphoma (CML) cell lines: it induces the expression of CDKN2A and CCNG2, two direct targets, leading to significant arrest in G1 and apoptosis in both (Mourgues et al., 2015; Nishida et al., 2015).

The first BMI-1 inhibitor to enter clinical trials was PTC596 (Nishida et al., 2017). PTC596 increases BMI-1 protein degra-

dation by enhancing CDK1 association with BMI-1, followed by phosphorylation at two N-terminal sites. In the AML cell line, PTC596 induces p53-independent apoptosis through MCL-1 down-regulation. Even more promisingly, it has shown antileukemia activity in vivo (in xenograft models; Nishida et al., 2017), and it has been recently tested for patients with advanced solid tumors (NCT02404480).

Several EZH2 inhibitors as well as compounds that disrupt the PRC2 complex have been developed over the years that have distinct selectivity/specificity. Some of these are in preclinical or clinical trials (Lund et al., 2014; Kim and Roberts, 2016). The first compound, DZNep (developed in 1986), is an *S*-adenosyl-l-homocysteine (SAH) hydrolase inhibitor that causes an increase of the cellular levels of SAH, which in turn blocks methyltransferase activity. This compound is not specific for EZH2, has a short half-life, and is toxic in animal models (Glazer et al., 1986; Miranda et al., 2009; Sandow et al., 2017). Several inhibitors have been further developed that have greatly increasing selectivity toward EZH2. For instance, GSK126 and EPZ005687 have been tested in lymphomas carrying EZH2-activating mutations and have been found to reduce tumor growth and increase survival in xenograft mouse models in a dose-dependent way (Knutson et al., 2012; McCabe et al., 2012; Verma et al., 2012). A further compound, EI1, does not alter EZH2 protein levels but rather reduces H3K27me2 and H3K27me3 levels by competing with the cofactor SAM. In DCBCL-carrying EZH2 mutations, EI1 reduces cell growth, apoptosis, and induction of genes involved in memory B cell differentiation (Qi et al., 2012).

An important breakthrough in EZH2 inhibitors came with the development of orally bioavailable inhibitors. The first one developed was UNC1999, which can block both EZH2 and EZH1, making it advantageous for treating cancers that rely on both enzymes. Accordingly, UNC1999 reduces global levels of H3K27 trimethylation/dimethylation (H3K27me3/2), thus inducing apoptosis and differentiation of *MLL*-rearranged acute leukemia cells. Moreover, in a MLL-AF9 mouse model, UNC1999 gives rise to a phenotype similar to that of EED KO, altering the correct deposition of the H3K27me3 mark and affecting CDKN2A levels, with strong effects on the mouse survival (Konze et al., 2013; Xu et al., 2015). Another potent EZH2 inhibitor, EPZ6438 (Tazemetostat), is being tested in several clinical trials for treating B cell lymphomas and solid tumors (NCT02220842, NCT03456726, NCT01897571, NCT03028103, NCT03009344, and NCT03010982; Knutson et al., 2013, 2014a; Italiano et al., 2018); one is already in phase 2 for patients with DLBCL and FL, in order to test the efficacy and safety of this compound either alone or in combination with prednisolone (NCT01897571). OR-S1 and OR-S2 are methyltransferase inhibitors that are highly specific for EZH1 and EZH2, and their efficacies have been tested in preclinical studies in AML murine models (MOZ-TIF2 and MLL-AF10) in which they lead to a complete remission of AML (Honma et al., 2017; Fujita et al., 2018).

Another possible therapeutic approach is to target the stability of the PRC2 complex, which disassembles in the absence of a core subunit, to reduce or eliminate its methyltransferase activity. The drug SAH-EZH2$_A$ was modeled on the α-helical domain of EZH2 that interacts with EED, a stabilized α-helix of EZH2 peptide capable of disassembling the PRC2 complex and impairing its function by impeding their association. This reduces H3K27me3 levels and increase cell differentiation in MLL-AF9 leukemia cell lines (Kim et al., 2013). Two more compounds (EED226 and A-395) have been developed that impair PRC2 function by targeting EED; specifically, EED226 disrupts the integrity of the complex, while A-395 prevents H3K27me3 recognition, and both cause tumor regression in xenograft mouse models of DLBCL (He et al., 2017; Huang et al., 2017). Finally, GNA002, a gambogenic acid derivative, covalently binds to the Cys668 residue of EZH2, causing its proteasome-mediated degradation and consequent PRC2 disassembly. In xenograft models, GNA002 reduces tumor growth (Wang et al., 2017).

Drug resistance is a major issue in addressing cancer treatments, considering that cell populations vary greatly and are continuously evolving. Two EZH2 amino acid substitutions (Y111L and Y661D) were identified after EI1 inhibitor treatment; these mutations cooperate in conferring acquired resistance in EZH2-mutated lymphoma models (Gore et al., 2006; Gibaja et al., 2016). In particular, Y111L was able to restore PRC2 activity and methylation levels in the presence of distinct PRC2 inhibitors (Gibaja et al., 2016). Acquired resistance has also been observed to be associated with EZH2 protein levels in AML patients: many patients have low EZH2 protein levels after chemotherapy, which correlates with poor prognosis. AML cell lines treated with PKC412, a kinase inhibitor, can develop drug resistance due at least in part to EZH2 protein degradation. This EZH2 reduction in turn alters gene expression of various factors associated to the *HOX* genes. Interestingly, knocking down HOXB7 and HOXA9 proteins in AML cell lines partially rescues sensitivity to drugs. Furthermore, a combination of Ara-C and bortezomib, used both ex vivo on primary AML samples and in vivo in AML patients, rescues EZH2 protein levels and reduces levels of immature blasts from peripheral blood (Göllner et al., 2017).

Many other combination of treatments have been proposed for lymphomas (Zhao et al., 2013; Knutson et al., 2014b; Béguelin et al., 2016), leukemias (Kowolik et al., 2016; Wen et al., 2018), and myelomas (Bolomsky et al., 2016; Alzrigat et al., 2017). In general, these show synergistic effects, leading to increased apoptosis and reduced tumor burdens. Overall, these reports provide an encouraging avenue that warrants continued work on identifying additional compounds and on studying more thoroughly different combinations of therapies as a way to achieve better and more durable antitumor effects.

Conclusions

Hematological diseases are characterized by lower levels of genetic mutations but higher levels of alterations of epigenetic factors as compared with other diseases (Haladyna et al., 2015). These alterations (GOF, LOF, and aberrant recruitment of complexes) greatly affect gene expression and play a major role in hematopoietic malignancies. Of note, both overexpression and LOF of the PcG proteins are strongly correlated with cancers. These apparently contradictory observations could be due to the distinct roles played by the complexes during the differentiation process. Additionally, they could also be due to misregulation of these proteins causing a general alteration of gene expression

that, together with the distinct tumor niches, can lead to very distinct outcomes. This topic is of particular interest for therapeutics: development of new molecules with increased selectivity and decreased toxicity should be encouraged, but we should keep in mind that we still lack knowledge about many biological processes. In any case, an accurate patient selection will be mandatory to avoid secondary health problems. Another possible caveat is the risk of development of drug resistances (Gibaja et al., 2016); nevertheless, with the use of combinational therapies, this phenomenon can be greatly reduced and controlled.

Results from GOF studies of PRC1 and PRC2 have highlighted that mutations in distinct proteins (especially for PRC2 subunits) down-regulate common genes that have tumor suppressor functions such as the *CDKN2A* locus. Distinct complexes can, of course, affect the same pathway; however, it is crucial to point out that most of our knowledge focuses on BMI-1 and EZH2 and that PcG proteins can potentially form numerous distinct complexes with many different targets. We now need to focus on studying the other subunits in order to clarify their contribution to normal and malignant hematopoiesis.

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