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REVIEW ARTICLE

Regulation of hematopoietic development by ZBTB transcription factors

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Abstract Hematopoietic development is governed by the coordinated expression of lineage- and differentiation stage-specific genes. Transcription factors play major roles in this process and their perturbation may underlie hematologic and immunologic disorders. Nearly 1900 transcription factors are encoded in the human genome: of these, 49 BTB (for broad-complex, tram-track and bric à brac)-zinc finger transcription factors referred to as ZBTB or POK proteins have been identified. ZBTB proteins, including BCL6, PLZF, ThPOK and LRF, exhibit a broad spectrum of functions in normal and malignant hematopoiesis. This review summarizes developmental and molecular functions of ZBTB proteins relevant to hematology.

Keywords Transcription factor · Hematopoiesis · Co-repressor

Introduction

Hematological malignancies may emerge from perturbed function of transcription factors (TFs) resulting from chromosomal translocation, loss- or gain-of-function mutations, or deregulated expression. Furthermore, mutations causing aberrant DNA methylation (such as the *DNMT3A* mutation), which may alter the kinetics of TF binding to DNA, are critical epigenetic events that precede malignant transformation [1, 2]. Aberrant transcriptional regulation is also prevalent in non-malignant hematologic disorders. For example, germ-line *GATA1* mutations are implicated in familial X-linked anemia and/or thrombocytopenia [3]. Hereditary persistence of fetal hemoglobin (HPFH), a condition characterized by persistent high levels of fetal globin in adults, is observed in individuals harboring mutations in genes encoding TFs [4]. Recent sequencing efforts have revealed mutations in epigenetic factors functioning in the pathogenesis of aplastic anemia [5].

There are 1700–1900 genes encoding TFs in the human genome [6], and at least 49 are classified as ZBTB proteins [7]. This family plays critical roles in hematopoietic differentiation, lineage fate determination and malignant transformation [8–11]. In this review, I discuss emerging themes in ZBTB protein function relevant to hematology.

ZBTB protein molecular mechanisms

ZBTB proteins are prototypical TFs consisting of an N-terminal BTB domain functioning in protein–protein interactions and C-terminal C2H2/Krüppel-type zinc fingers, which bind DNA (Fig. 1a). Between those domains lies a linker domain, whose amino acid sequence is less conserved among family proteins (Fig. 1a). The BTB domain was named after three *Drosophila* genes, *broad-complex*, *tram-track* and *bric à brac*, all encoding proteins essential for *Drosophila* development [12]. The BTB domain is also known as the POZ (for poxvirus and zinc finger) domain, as it is present in many poxvirus-related proteins [13]; thus ZBTB proteins are sometimes referred as POK (POZ and krüppel-type zinc fingers) proteins.

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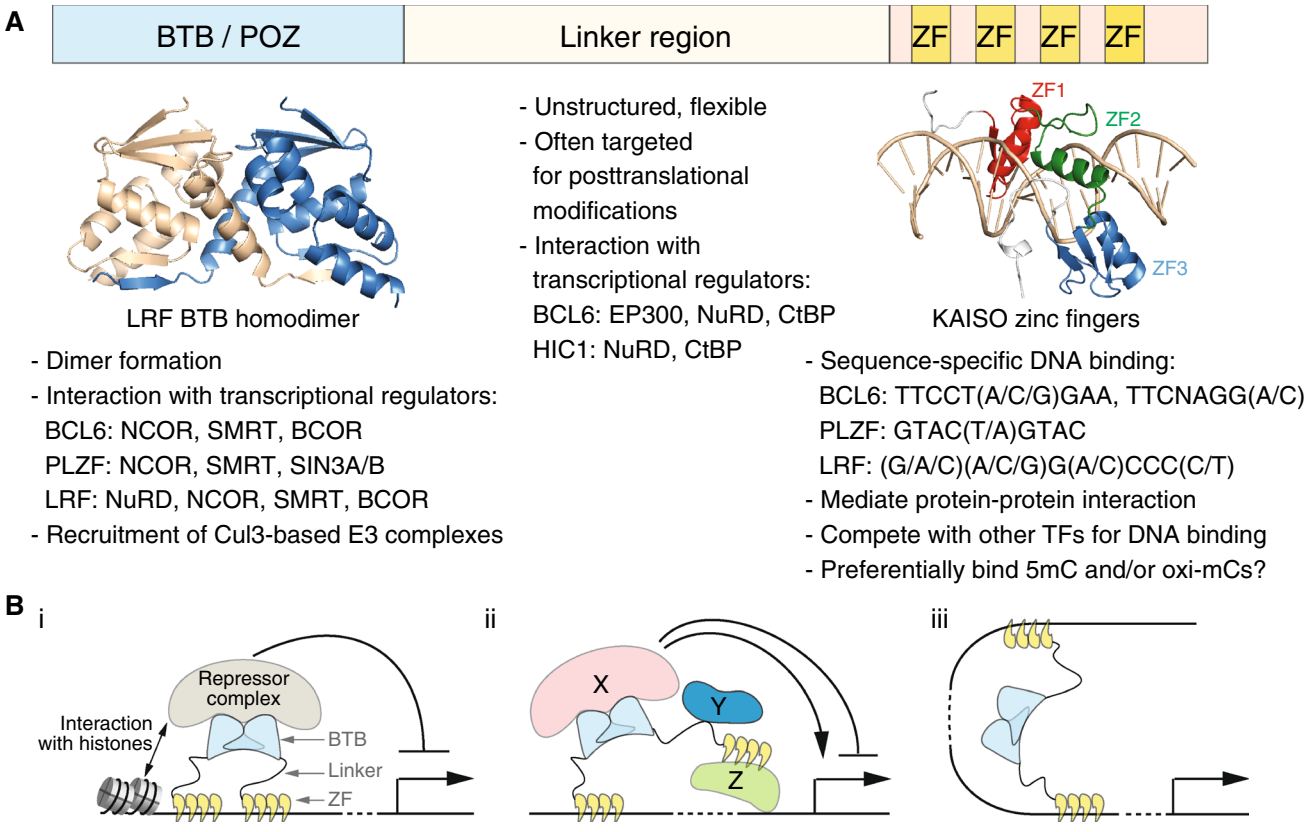

Fig. 1 Structure and function of ZBTB protein domains. **a** The BTB domain serves as a protein/protein interaction module, while zinc fingers primarily function as a DNA binding module. The linker domain is unstructured and often targeted for posttranslational modification. The number of zinc finger motifs (ZF) varies among ZBTB proteins. Structures of the LRF-BTB domain and KAISO zinc fingers were obtained from PDB files 2NN and 4F6 N, respectively. **b** (*i*) Classical model of ZBTB/DNA interaction. Histone-binding modules of SMRT/NCOR (such as the SANT domain) or PHD domains of CHD3/4, subunits of the NuRD complex, could stabilize ZBTB/DNA binding in a chromatin context-dependent manner. (*ii*) A ZBTB dimer can bind DNA through one chain and interact with other proteins via the linker domain and/or zinc finger motifs. (*iii*) ZBTB protein may facilitate long-range interactions with regulatory regions (at promoters or enhancers)

The BTB domain

The BTB domain exerts two major functions: dimer formation and recruitment of transcriptional regulators (Fig. 1a). Biochemical and structural analyses revealed that the domain forms an obligate homodimer [7], which is essential for ZBTB protein function in some contexts. For example, wild-type LRF [for Leukemia/lymphoma-Related Factor [14] (also known as FBI-1 [15], POKEMON [16], OCZF [17]); encoded by *ZBTB7A*] can rescue germinal center B cell defects observed in *Lrf* conditional knockout (KO) mice, while a dimerization-deficient LRF mutant cannot [18]. The BTB domain can also mediate heterodimer formation. Among heterodimers identified are LRF and BCL6 (B cell Lymphoma 6; encoded by *ZBTB27*) [14], BCL6 and MIZ-1 (Myc-interacting zinc finger protein-1; encoded by *ZBTB17*) [19], BCL6 and BCL6B (a.k.a. BAZF; encoded by *ZBTB28*) [20] and PLZF (Promyelocytic Leukemia Zinc Finger; encoded by *ZBTB16*) and FAZF (also known as ROG [21], PLZP [22], or TZFP [23]; encoded by *ZBTB32*). It remains unclear whether only BTB domains mediate heteromeric interactions. Higher order oligomerization through the BTB domain has also been reported: PLZF-BTB domain can form oligomers through its N-terminal β-sheet [24], whereas the MIZ-1 BTB domain forms a tetramer [25].

BTB domains can also recruit transcriptional regulators (Fig. 1a). The transcriptional co-repressors NCOR (nuclear receptor co-repressor) and SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) are homologous proteins originally identified as co-repressors for retinoic acid receptors (RARs) and thyroid hormone receptors [26, 27]. These co-repressors function via recruiting histone deacetylases (HDACs), namely HDAC3 [28]. The functional connection between BTB domains and co-repressors became apparent when NCOR and SMRT were identified in a complex with the leukemia-associated RAR fusion proteins, PML-RARα and PLZF-RARα [29–31].

The latter interacts with SMRT/NCOR not only through the C-terminal RAR moiety but also through the N-terminal PLZF-BTB domain [29, 32, 33]. The BCL6 BTB domain was subsequently found to associate with both SMRT and NCOR [34, 35]. Importantly, BTB homodimer formation is a prerequisite to co-repressor recruitment [36]. Structural analysis revealed that a 17 amino acid residue of SMRT, called SMRT-BBD (SMRT-BCL6 binding domain), binds to a surface created by a BTB homodimer [36]. Thus, any potential BCL6 monomer cannot recruit the co-repressor complex. A recent study suggested that BCL6 serves as a critical downstream effector of SMRT/NCOR [37]. ChIP-seq (chromatin immunoprecipitation with massively parallel DNA sequencing) analysis revealed that nearly half of SMRT/NCOR binding sites were reduced or lost in *Bcl6* KO macrophages [37]. Furthermore, almost 70 % of DNA occupancy sites are shared between SMRT-BCL6 and NCOR-BCL6 complexes, indicating a high degree of overlap between both co-repressors in the context of BCL6-mediated gene silencing [37].

BTB-mediated co-repressor recruitment was initially thought to be a general mechanism shared with other ZBTB proteins; however, later biochemical and structural studies suggested it was not. BTB domains of HIC1 (hypermethylated in cancer 1; encoded by *ZBTB29*), MIZ1 and FAZF do not interact with SMRT/NCOR or SMRT-BBD [38, 39]. The BTB domain of KAISO (encoded by *ZBTB33*) associates with NCOR but not with SMRT [40]. Importantly, BCL6-BTB residues responsible for SMRT-BBD binding are not conserved among other ZBTB proteins, and SMRT-BBD does not directly interact with either LRF- or PLZF-BTB [36, 41]. Thus, reported interactions between SMRT/NCOR and LRF-BTB or PLZF-BTB [42–44] likely occur via a different binding interface (such as a charged pocket [43]), either directly or indirectly [36, 41].

The BTB domain can also associate with other transcriptional regulators, among them the co-repressors BCOR (BCL-6 interacting co-repressor) [45], SIN3A/B (SIN3 transcription regulator family member) [46] and the NuRD (nucleosome remodeling deacetylase) complex [47]. BCOR was originally identified as a BCL6-interacting protein by a yeast two-hybrid screen using BCL6-BTB as bait [45]. Remarkably, BCOR and NCOR/SMRT interact with the same surface of the BCL6-BTB homodimer [36, 45, 48]. Since one BCL6-BTB homodimer forms two co-repressor binding surfaces, two different co-repressors could associate with a dimer simultaneously [36, 48, 49].

The NuRD complex is a 1MDa multi-subunit protein complex that consists of histone deacetylases (HDAC1/2), ATP-dependent chromatin remodelers (CHD3/4, a.k.a. Mi2-α/β), methyl-CpG-binding domain protein (MBD2/3), histone chaperone protein (RBBP4/7, a.k.a. RbAp46/48), MTA1/2/3, and GATAD2A/B (a.k.a. p66α/β) [50, 51]. The complex is implicated in multiple cellular functions, including transcriptional repression or activation, DNA repair and DNA replication [50, 51]. In fact, some subunits of the complex contain motifs binding to histone tails (CHD3/4, GATAD2A/ and RBBP4/7) and/or DNA (CHD3/4 and MBD2/3) [51]. The LRF-BTB domain reportedly associates with GATAD2B and CHD3, an interaction necessary for γ-globin silencing in adult erythroid cells [47].

BTB domains of ZBTB proteins can also serve as an adaptor for protein degradation. A link between the BTB domain and the ubiquitin pathway was first reported in the BTB-BACK-Kelch protein family [52]. In this context, two protein domains, BTB and BACK, join to form a platform to recruit cullin 3 (CUL3)-based E3 ubiquitin protein ligase complexes [7, 52]. Direct interaction between CUL3 and the PLZF- or BCL6-BTB domain was subsequently reported [53]. PLZF (or BCL6) reportedly recruits the CUL3 complex via the BTB domain, and the E3-ligase complex in turn ubiquitinates PLZF-interacting proteins to promote their degradation by the proteasome. Strikingly, conditional *Cul3* KO mice partially phenocopy *Plzf* or *Bcl6* KO mice, suggesting that Cul3-mediated protein degradation is necessary for Plzf and/or Bcl6 function in vivo [53]. The structural basis for these interactions remains to be determined.

C2H2-type zinc fingers

The ZBTB proteins contain multiple C-terminal C2H2-type zinc fingers (Fig. 1a). The number of fingers varies [8–10]: for example, LRF harbors 4 zinc finger motifs, while BCL6 contains 6. Variations in position and number of fingers allow them to bind to DNA in a sequence-specific manner, and many of their DNA binding motifs have been identified in vitro [for example, by CAST (cyclic amplification and selection of targets) assays] [16] and/or in vivo by ChIP-seq [37, 47, 49, 54, 55] (Fig. 1a). Interestingly, DNA binding motifs may vary in a cell type-specific manner: BCL6 reportedly binds distinct sequences depending on cell type [55]. Furthermore, ZBTB proteins may compete with other TFs for DNA occupancy. For example, the consensus sequence of STAT family transcriptional activators resembles that of BCL6 [56]. BCL6 and STATs compete for the same DNA binding sites in the context of inflammatory gene regulation in macrophages [57]. Similarly, BCL6 and NFkB reportedly compete for the same DNA loci downstream of TLR (Toll-like receptor) signaling in macrophages [54].

An emerging aspect of ZBTB protein function is the capacity to bind methylcytosine (5mC) and/or oxidized methylcytosine (oxi-mCs). During DNA replication, the CpG methylation pattern is faithfully inherited by daughter cells due to activity of the DNA methyltransferase 1

(DNMT1) [58]. The de novo DNA methyltransferases, DNMT3A and DNMT3B, can establish new DNA methylation patterns catalyzing formation of 5mC at a palindromic CpG dinucleotide [58]. Members of ten–eleven-translocation (TET) family proteins are dioxygenases that catalyze active demethylation, which can occur independently of DNA replication [58]. TET proteins convert 5mC to 5-hydroxymethylcytosine (5hmC) and successively catalyze conversion of 5hmC to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC). Both 5fC and 5caC are excised by thymine DNA glycosylase (TDG) and restored to unmodified cytosines via the base excision repair pathway [58]. An outstanding question in the field is whether modified cytosine residues are recognized by specific "reader" proteins, enabling distinct functional outputs. This question is particularly relevant to hematology and oncology, as mutations in *DNMT3A* and *TET1/2* are among the most common mutations observed in hematologic malignancies [2] and are often seen in age-related clonal hematopoiesis [59].

KAISO (encoded by *ZBTB33*) is one of the few factors that can preferentially bind to methylated CpG [60]. *Kaiso* KO mice exhibit no overt developmental phenotypes, but show resistance to tumor development when crossed with an intestinal tumor model [60]. Two other ZBTB proteins, ZBTB4 and ZBTB38, may also preferentially bind to methylated CpG [61]. Their functions in hematopoietic development remain unknown. Recently, unbiased proteomic screens focusing on reader proteins of 5hmC, 5fC and 5caC identified some ZBTB proteins as oxi-mC readers [62]. For example, ThPOK [T helper-inducing POZ/Krüppel-like factor (a.k.a. cKrox); encoded by *ZBTB7B*] [63, 64] was found to preferentially bind 5caC. It remains unclear whether some ZBTB proteins are indeed readers of specific DNA methylation status and execute unique functions in normal or malignant hematopoiesis.

In addition to DNA binding, zinc fingers mediate protein–protein interactions. The histone acetyltransferase EP300 reportedly interacts with the zinc fingers of PLZF and acetylates lysines in those motifs necessary for DNA binding [65]. PLZF also associates with the transcription factor GATA2 through its zinc fingers and inhibits GATA2-dependent transcriptional activation [66]. The zinc fingers of MIZ-1 interact with MYC, an activity necessary for MIZ-1-mediated gene repression [67].

The linker region

The linker (or hinge) region between the BTB domain and zinc fingers is poorly conserved among ZBTB proteins and predicted to be unstructured [7]. This region enables ZBTB proteins to flexibly bind DNA in terms of spacing and orientation (Fig. 1b) [7, 68]. In the classic model, a dimeric ZBTB protein recruits co-repressors through the BTB domain, and two zinc finger chains bind to two nearby DNA sequences in promoter or enhancer regions (Fig. 1b, i). The BCL6 linker region, called the second repression domain (RD2), is the most well characterized linker region. It contains a lysine KKYK (aa376-379) motif, in which K379 is a target for acetylation by EP300 [69]. Acetylation of this residue abrogates BCL6-mediated transcriptional repression: a mutant from mimicking a constitutively acetylated state ($BCL6^{QQYQ}$) fails to recruit HDAC2 or repress target genes [69]. The KKYK motif also mediates direct interaction with metastasis-associated protein 3 (MTA3) [70], a subunit of the NuRD complex. Strikingly, mice harboring either the $Bcl6^{QQYQ}$ or $Bcl6^{KKYQ}$ mutation largely phenocopy *Bcl6* KO mice [71, 72], suggesting that BCL6 acetylation serves as a molecular switch governing BCL6-mediated repression in vivo. The BCL6 RD2 also contains a PEST motif, which is phosphorylated by mitogen-activated protein kinase (MAPK) following B cell receptor (BCR) signaling [73]. PEST phosphorylation induces BCL6 degradation [73].

Linker regions of other ZBTB proteins are also modified post-translationally (Fig. 1a). Residues within the PLZF linker region undergo phosphorylation [74, 75] and sumoylation [76]. These modifications reportedly modulate PLZF DNA binding capacity [74, 76] or protein stability [75]. Lysine (K314) in the HIC1 linker is modified by acetylation or sumoylation, regulating HIC1 affinity to MTA1, a NuRD subunit. Similarly, ZBTB1 sumoylation in the linker alters its subcellular localization and abrogates binding to SMRT [77]. The co-repressor CtBP (C-terminal binding protein) also associates with linkers of HIC1 [78] and BCL6 [79].

In summary, the linker region could serve as a platform to recruit enzymes or complexes that induce posttranslational modification of ZBTB protein to regulate its stability or transcriptional activity. Furthermore, the linker region is predicted to be unstructured, which may allow multiple modes of DNA binding. For instance, a ZBTB dimer could bind DNA through a zinc finger chain, while another chain functions as a platform for protein/protein interactions (Fig. 1b, ii). ZBTB protein may also mediate long-range DNA interactions as reported for the *Drosophila* BTB domain-containing protein CP190 (Fig. 1b, iii) [80].

ZBTB function in hematopoietic development

The link between ZBTB proteins and the hematopoietic system emerged from discovery of chromosomal translocations in leukemia and lymphoma. In the early 90s, *PLZF* was cloned from the chromosomal translocation t(11;17)(q23; q21), which is observed in rare acute promyelocytic leukemia (APL) cases [81]. That translocation gives rise

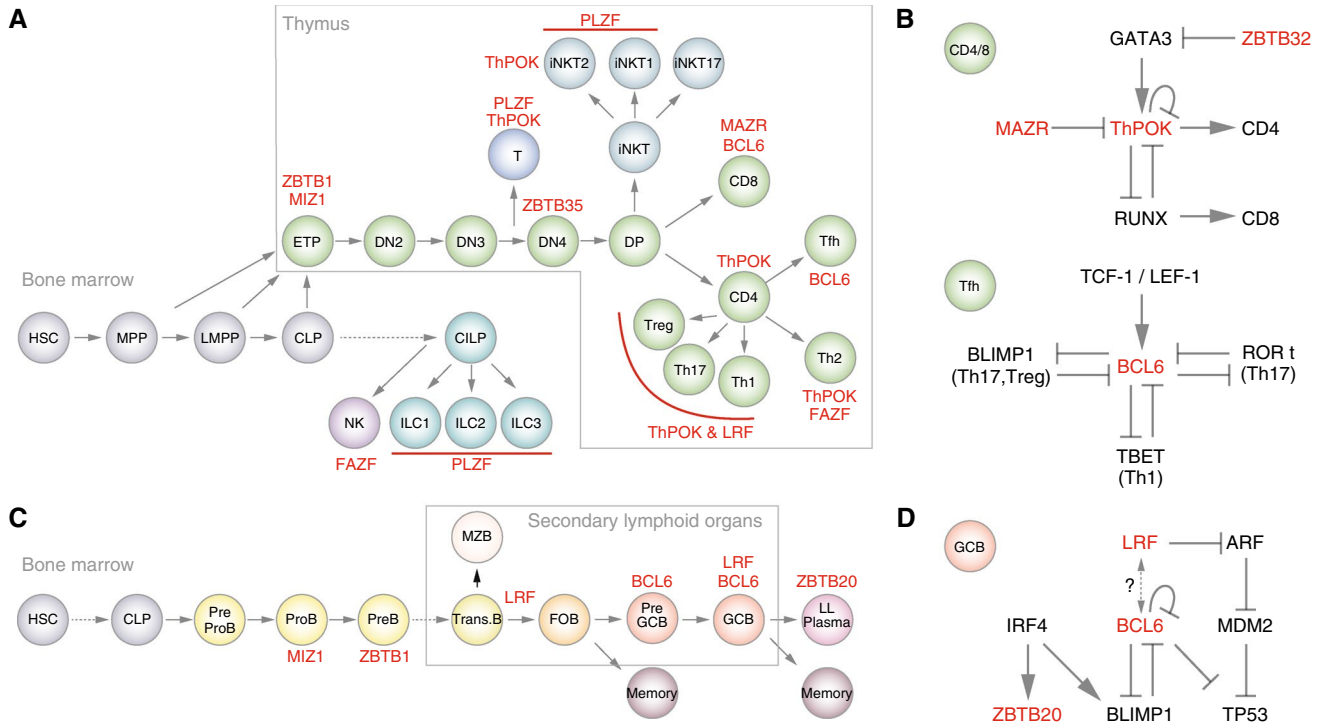

Fig. 2 ZBTB proteins and lymphoid development. **a** Schematic view of T cell and innate lymphoid cell development in mice. ZBTB proteins necessary for development and/or maintenance are indicated. *HSC* hematopoietic stem cell, *MPP* multi-potential progenitor, *LMPP* lymphoid-biased MPP, *CLP* common lymphoid progenitor, *ETP* early T cell precursor, *DN* CD4/8 double-negative T, *DP* CD4/8 double-positive T, *iNKT* invariant natural killer T, *Th1* T helper 1, *Th2* T helper 2, *Tfh* follicular helper T, *Treg* regulatory T, *Th17* T helper 17, *CILP* common innate lymphoid progenitor, *ILC* innate lymphoid cell. **b** Transcriptional regulation of genes necessary for CD4/8 T (*top*) or Tfh cell development (*bottom*). ZBTB proteins are depicted in *red*. **c** B cell development in mice. MIZ1 and ZBTB1 are necessary for early B cell development in BM, while LRF, BCL6 and ZBTB20 function in mature B cell compartments. *Trans. B* transitional B, *MZB* marginal zone B, *FOB* follicular B, *Pre-GCB* pre-germinal center B, *GCB* germinal center B, *LL Plasma* long-lived plasma cell. **d** Transcriptional regulation of genes necessary for GCB and plasma cell development

to the PLZF/RARα fusion oncoprotein [81]. Around the same time, BCL6 was cloned and characterized as a gene participating in chromosomal translocations t(3;14) (q27; q32) and t(3; 22) (q27; q11), both commonly observed in non-Hodgkin lymphoma (NHL) [82–84]. The *BCL6* gene, which located on human chromosome 3, is fused downstream of the immunoglobulin heavy chain locus (*IGH*) or lambda locus (*IGL*), de-regulating BCL6 expression in mature B cells and promoting lymphoma development [85]. Since these seminal discoveries, critical roles of ZBTB proteins in hematopoietic development have been defined primarily through mouse models. At least 12 *Zbtb* genes are implicated in hematopoietic development in mice. Notably, each of the ZBTB proteins they encode plays a unique role in specific hematopoietic lineages or differentiation stages, as detailed below.

T and innate lymphoid development

In hematopoiesis, T cells are the most studied cell types in terms of ZBTB function [11] (Fig. 2a). ThPOK is among the first ZBTB proteins identified as a factor critical for T cell development [63, 64], and mutation of the gene that encodes it reportedly underlies phenotypes observed in a spontaneous mutant mouse strain called “helper-deficient” (HD). HD mice exhibit a selective absence of $CD4^+$ T cells with a concomitant increase in $CD8^+$ T cells [63]. The causal mutation was mapped to a single amino acid change in the second zinc finger of Thpok [63]. *Thpok* KO mice phenocopy HD mice [86–88], while forced Thpok expression in CD4/8 double-positive T cells directs MHC-class I-restricted cells to become $CD4^+$ cells [64]. Collectively, these data indicate that Thpok is a master regulator of CD4/CD8 lineage determination in thymus (Fig. 2a). A recent study further demonstrated that Thpok and LRF cooperate to regulate T helper (Th) cell gene expression and function [89]. Thpok is also necessary for the development and function of post-thymic effector Th cells [90] and innate-like T cells such as γδT [91] and invariant natural killer T (iNKT) cells [92]. In mice, Thpok expression is positively or negatively regulated through its proximal enhancer [86], located ~3.6 kb downstream of exon 1, or

through a silencer region located ~ 3 kb upstream exon 1 [93], respectively. The transcription factor Gata3 activates Thpok expression via the proximal enhancer [87], while Runx transcription factors suppress Thpok expression through the silencer [93, 94]. Mazr (also known as PATZ1; encoded by *ZBTB19*) reportedly represses Thpok expression [95, 96]. The T cell transcriptional network regulated by ThPOK (Fig. 2b) is reviewed in detail elsewhere [11, 97].

PLZF plays a major role in development and function of innate-like T cells and innate lymphoid cells (ILCs). Unlike conventional T cells, which recognize peptide antigens bound to MHC molecules, innate-like T cells are poised to rapidly respond by producing cytokines without clonal expansion [98]. Plzf was among the first TFs identified as a factor critical for iNKT cell development [99, 100]. Plzf also regulates development or function of other innate effector cells, including γδT cells [101], mucosal-associated invariant T cells (MAIT) [100] and innate lymphoid cells (ILCs) [102, 103]. Of note, human PLZF protein is present in a greater variety of lymphocytes than is seen in mice [104]. PLZF may be a useful marker to define the subset of peripheral T cell lymphomas (PTCL), a heterogeneous disease category of mature T cell lymphoma [105]. Fazf is induced in NK cells upon viral infection and stimulates their proliferation by antagonizing Blimp1 function [106].

T follicular helper (Tfh) cells are specialized $CD4^+$ T cells that help B cells to effectively respond to protein antigens via the germinal center (GC) reaction [107]. Bcl6 is preferentially expressed in Tfh cells among $CD4^+$ effector T cell subsets, and its depletion in those cells leads to reduction in the number of Tfh and GCB cells [108–110]. Bcl6 maintains Tfh identity by counteracting other $CD4^+$ effector T cell programs [111]. To do so, Bcl6 represses Blimp1 [110], Tbet/Tbx21 [108, 111] and Rorγt/Rorc [108, 111] (Fig. 2b). Interestingly, T cell-specific *Bcor* KO mice exhibit significantly reduced Tfh cell numbers, suggesting a functional link between Bcl6 and Bcor in Tfh development [112, 113]. The transcription factor Tcf-1, a downstream effector of Wnt signaling, reportedly induces Bcl6 expression in T cells upon viral infection [114]. Bcl6 is also implicated in maintenance of memory $CD8^+$ T cells [115].

Three ZBTB proteins reportedly function during early T cell development. *Zbtb1* mutant mice exhibit a near complete lack of T cells in thymus, suggesting a role in development of early T cell precursors [116]. Miz1 is necessary for early T cell development by functioning downstream of IL7 receptor signaling [67, 117]. Finally, *Zbtb35* KO mice show severe impairment in the transition from CD4/8 double-negative to double-positive stages [118].

B lymphoid development

Following exposure to stimulation by T cell-dependent antigens, a fraction of naïve B cells is first activated within the follicle in secondary lymphoid organs and then migrates to the inter-follicular region (IFR), where they establish stable interactions with antigen-specific T cells (Tfh). This interaction further activates antigen-specific B cells, which subsequently migrate back to the follicle center and proliferate extensively [119], pushing follicular B (FOB) cells aside to form the GC, a unique histological structure observed in secondary lymphoid organs. During this process, GCB cells undergo two major modifications: somatic hypermutation (SHM) and class switch recombination (CSR) to enable efficient affinity maturation and effector function, respectively. At the final stage of the GC reaction, memory B cells and long-lived plasma cells develop. Plasma cells are effector cells producing a high level of antibodies, while memory B cells maintain a rapid immunological response upon later exposure to the same antigen. GC-independent memory B cells, which preserve germline antibody specificities, have also been reported [120] (Fig. 2c).

Conventional *Bcl6* KO mice exhibit impaired GC responses and severe inflammatory disease [56, 121], the latter due to de-repression of genes encoding inflammatory cytokines and chemokines in macrophages [122]. B cell-specific *Bcl6* KO mice (mb-1 Cre+) exhibit significantly reduced GCB cell numbers upon T cell-dependent immunization, while other B cell lineages are largely unaffected [123]. GC-specific *Bcl6* deletion (through Cγ1-Cre) also promotes impaired GC formation, indicating that Bcl6 is necessary for GCB cell development in a cell intrinsic fashion. In secondary lymphoid organs, BCL6 expression increases when activated B cells associate with Tfh cells [120, 124]. Imaging studies reveal that migration of Bcl6-deficient B cells to nascent GCs is greatly impaired [120]. Since T cell-specific Bcl6 inactivation also abrogates GC formation [108–110], Bcl6 likely regulates GC formation through at least three distinct mechanisms: (1) induction of Tfh cell development; (2) initiation of pre-GCB cell migration to the follicle; and (3) support of GCB cell proliferation and survival. Notably, two groups independently showed that co-repressor recruitment via BCL6-BTB domain is necessary for GC development in vivo, although there remain discrepancies regarding the contribution of Tfhs to observed phenotypes [57, 71, 72, 113].

BCL6 regulates expression of a variety of genes during GCB cell development [49, 57, 85]. For example, at the pre-GCB cell stage, Bcl6 represses expression of the key trafficking receptors S1pr1 and Gpr183 and facilitates pre-GCB cell migration to the follicle center [71]. In GCB

cells, BCL6 suppresses apoptosis and protect cells from DNA damage responses during CSR and SHM. In this context, BCL6 directly represses genes necessary for DNA damage sensing as well as checkpoint genes (such as ATR [125]) and inducers of apoptosis or cell cycle arrest (such as TP53 [126] and CDKN1A [19]). BCL6 also inhibits the plasma cell differentiation program by repressing genes necessary for development of those cells, such as BLIMP1 [70, 127, 128] (Fig. 2d).

LRF is another ZBTB protein required for GCB cell development. LRF protein is highly expressed in normal GCB cells and in a majority of diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL) cases [16]. Of note, LRF levels are primarily regulated post-translationally in GCB cells: Lrf protein levels are greatly induced in those cells, while corresponding transcript levels decrease [18]. Both pan B cell (mb1-Cre) and GCB-specific (Cγ1-Cre) *Lrf* conditional KO mice exhibit a significant reduction in GCB number upon immunization [18]. Lrf is necessary for GCB cell proliferation and survival, at least in part, by directly repressing p19Arf expression [18] (Fig. 2D). As described, LRF forms an obligate homodimer essential for GCB development in vivo [18]. A yeast two-hybrid screen using the LRF-BTB domain as bait identified a series of transcriptional regulators, including NuRD subunits and chromatin remodelers, as interacting proteins [47]. Thus, NuRD recruitment via the BTB domain may modulate LRF function in GCB cells. LRF also regulates lineage fate decisions between FOB and marginal zone B (MZB) cells in secondary lymphoid organs. A slight increase in MZB cell number and a concomitant decrease in the number of FOB cells is seen in pan B cell *Lrf* KO mice [18].

GCB cells terminally differentiate into long-lived plasma cells that can sustain high levels of antibody production. They also produce memory B cells that respond quickly upon later exposure to the same antigen (Fig. 2c). Zbtb20 deficiency causes a defect in plasma cell development, while its exogenous expression induces plasma cell differentiation [129, 130]. Irf4, a factor necessary for GC formation and plasma cell differentiation, reportedly binds to and activates the *Zbtb20* promoter [129] (Fig. 2d). Heterozygous germ-line missense mutations in human *ZBTB20* were recently identified in Primrose syndrome, which is characterized by multisystem failures [131]. Interestingly, mutations observed in a *ZBTB20* zinc finger have a dominant-negative effect [131]. It is unclear whether humoral immunity is altered in patients harboring these mutations.

ZBTB proteins are also implicated in early B cell development in bone marrow (BM). Miz1 reportedly plays a dual role downstream of IL7 receptor signaling in early B cells by inducing the anti-apoptotic factor Bcl2 on one hand and repressing Socs1, a negative regulator of JAK/STAT signaling, on the other [67]. ProB cell numbers are greatly reduced in *Miz1* KO mice, as is also observed in *Il7* or *Il7r* KO mice [67]. *Zbtb1* KO mice exhibit a block in B cell development at around the Hardy fraction D (small PreB) [116]. Conditional depletion of *Lrf* in HSCs (Mx1-Cre) leads to development of CD4/8 double-positive T cells in BM at the expense of B cell development due to constitutive activation of Notch signaling [132]. This robust phenotype was initially attributed to HSC-intrinsic mechanisms; however, later it was shown that Lrf-deficient erythroblasts, rather than myeloid or lymphoid cells, aberrantly express the Notch ligand Dll4, which activates otherwise silenced Notch signaling in HSCs [133]. Lrf-mediated Dll4 silencing in erythroblasts is necessary for HSC maintenance and normal lymphoid fate determination, although its physiological significance remains unclear.

Erythroid/myeloid development

LRF is necessary for terminal erythroid differentiation. Conventional *Lrf* KO mice exhibit embryonic lethality at around 16.5 d.p.c. due to anemia [134]. Lrf inactivation in adult mice (through Mx1-Cre) also promotes macrocytic anemia [134]. In these cases, anemia phenotypes are attributable to increased apoptosis of mature erythroblasts (poly- and orthochromatophilic erythroblasts) and impaired terminal differentiation (Fig. 3a) [134]. LRF knockdown in human $CD34^{+}$-derived hematopoietic stem progenitor cells (HPSCs) delays erythroid differentiation [47]. GATA1, a master erythroid TF, directly binds to and activates the *LRF* promoter [134]. EKLF (a.k.a. KLF1), a GATA1 target, also induces LRF expression [135] (Fig. 3b). LRF target genes relevant to erythroid differentiation are yet unknown.

A recent study uncovered a novel LRF function in the globin switch. Mutations in adult globin genes cause hemoglobinopathies such as sickle cell disease (SCD) and thalassemia, which are among the most common monogenic inherited human disorders [136, 137]. Induction of fetal-type globin (γ-globin) is a promising means to treat these disorders; however, precisely how γ-globin expression is silenced in adult erythroid cells is not fully understood [136]. LRF inactivation re-activates γ-globin expression in human adult erythroid cells independently of BCL11A [47], a master regulator of γ-globin expression [138]. LRF presumably represses γ-globin expression through LRF-BTB/NuRD-mediated mechanisms [47] (Fig. 3b).

ZBTB46 (a.k.a. BTBD4 or zDC) was recently identified as a TF predominantly expressed in classical dendritic cells (cDCs) and their committed progenitors, but not in plasmacytoid DCs (pDCs) [139, 140], although both of these functionally distinct DCs share a common progenitor [141] (Fig. 3a). Zbtb46-deficient $CD4^{+}$ cDCs aberrantly express myeloid genes, such as G-CSF (granulocyte colony-stimulating factor) [139]. In contrast, BM myeloid progenitors

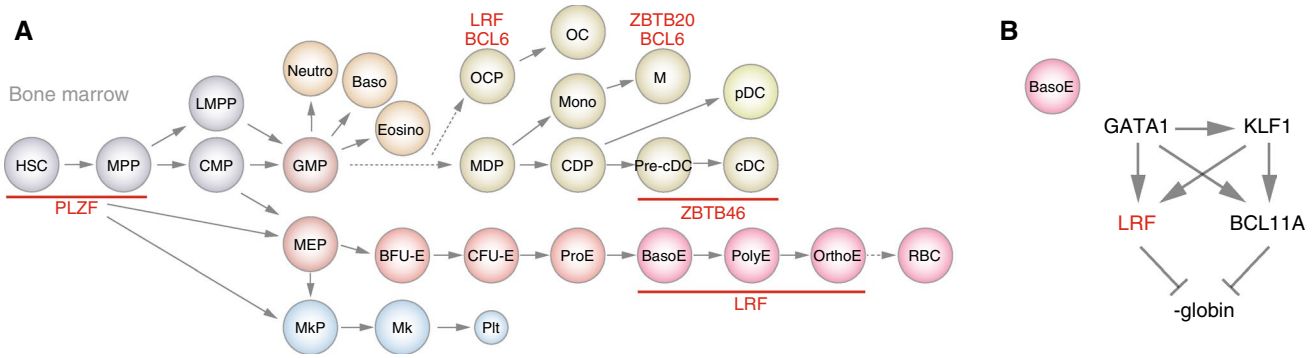

Fig. 3 ZBTB proteins and myeloid development. **a** Schematic view of myeloid development in BM. ZBTB proteins necessary for the development and/or function are indicated. *GMP* granulocyte-macrophage progenitor, *Neutro* neutrophil, *Baso* basophil, *Eosino* eosinophil, *MDP* macrophage dendritic cell (DC) progenitor, *CDPs* common DC progenitors, *cDC* classical DC, *pDC* plasmacytoid DC, *Mono* monocyte, *Mφ* macrophage, *OCP* osteoclast progenitor, *OC* osteoclast, *MEP* megakaryocyte erythroid progenitor, *BFU-E* burst forming unit erythroid, *CFU-E* colony forming unit erythroid, *ProE* proerythroblast, *BasoE* basophilic erythroblast, *PolyE* polychromatophilic erythroblast, *OrthoE* orthochromatophilic erythroblast, *RBC* red blood cell, *MkP* megakaryocyte progenitor, *Mk* megakaryocyte, *Plt* platelet. **b** Transcriptional cascade regulating γ-globin expression in erythroblasts

preferentially differentiate into cDC cells upon Zbtb46 overexpression [139]. Although Zbtb46 depletion does not affect cDC development per se, Zbtb46 may help myeloid progenitors to acquire cDC identity [139, 142].

Other ZBTB proteins relevant to myeloid development or function include BCL6, LRF and ZBTB20. LRF protein is acutely induced upon induction of osteoclast differentiation from BM myeloid progenitors [143]. In contrast, BCL6 protein is gradually down-regulated during osteoclast differentiation [144]. LRF reportedly represses NFATc1, a positive regulator of osteoclastogenesis, and conditional inactivation of *Lrf* in BM progenitors (using Mx1-Cre) reduces bone mass (an osteoporotic phenotype) [143]. *Bcl6* KO mice are also osteoporotic, suggesting that BCL6 negatively regulates osteoclastogenesis [144]. Remarkably, BLIMP1 represses BCL6 expression in osteoclast precursors, as it does in T and B cells [110, 144, 145].

Bcl6 conventional KO mice exhibit severe inflammation due to de-repression of cytokine and chemokine genes in macrophages [121, 122, 146–148]. Bcl6 and Nfkb reportedly antagonize downstream TLR signaling in macrophages: Bcl6-deficient macrophages are hypersensitive to TLR-mediated signals due to high Nfkb activity [37, 54]. *Bcl6* knock-in mutant mice ($Bcl6^{BTBMUT}$), in which the interaction between the BCL6-BTB domain and NCOR/SMRT is abrogated, do not exhibit the prominent inflammatory phenotypes seen in *Bcl6* KO mice [57]. Thus, loss of Bcl6 from DNA occupancy sites might be necessary for NF-κB recruitment to overlapping DNA binding sites [57]. By contrast, Zbtb20 may function as a positive regulator of TLR signaling in macrophages [149].

PLZF is implicated in development of spermatogonial progenitor cells [150–153] and the musculoskeletal and limb system [154]. In the hematopoietic system, PLZF is expressed at high levels in HSCs/progenitors, and its expression declines as HSCs differentiate [155]. In human hematopoietic cells, PLZF prevents myeloid progenitors from differentiating by repressing myeloid-specific factors, such as GFI-1 and CEBPα, while inducing ID2, an anti-differentiation factor [156]. *Plzf*-deficient LT-HSCs (long-term HSCs), which are the most primitive HSCs, are prone to enter cell cycle, lose repopulating capacity, and exhibit skewed differentiation toward the myeloid over the lymphoid lineage [157]. Taken together, PLZF is necessary not only for HSC maintenance but to restrict proliferation and differentiation of myeloid progenitors [156, 157].

ZBTB proteins and hematologic malignancies

Among ZBTB proteins, BCL6 and PLZF have been studied extensively in the context of B cell malignancies and APL, respectively [85, 158–160]. During GC development, BCL6 drives GCB cell proliferation and prevents apoptosis induced by DNA damage. Although these functions are essential for GCB cells to undergo efficient SHM and CSR, BCL6 expression must be turned off when cells differentiate into long-lived memory B cells or plasma cells (Fig. 2c). Chromosomal translocations involving *BCL6* are observed in 28–45 % of DLBCL and 11–14 % of FL cases [161–163]. Approximately 50 % of gene rearrangements involving *BCL6* occur at immunoglobulin loci, including *IgH* [t(3;14)(q27;q32)], *IgL* [t(3;22)(q27;q11)] and *IgK* [t(2;3)(p12; q27)]. At least 20 genes are targeted in *BCL6*-involved gene rearrangements [164]. As the consequence, the *BCL6* 5′ regulatory region is replaced with the gene partner of the rearrangement, allowing uncontrolled BCL6 expression in mature B cells. Somatic hypermutations within the 5′ *BCL6* regulatory region, through which

IRF4 silences BCL6 expression, are observed in ~40 % of DLBCL cases [165]. BCL6 acetylation status may also contribute to lymphomagenesis: inactivating mutations in *CREBBP* or *EP300*, both of which encode histone acetyltransferases that also acetylate BCL6, are observed in approximately 40 % of DLBCL or FL cases [166]. These mutations lead to defective BCL6 acetylation and deregulate BCL6 transcriptional activity [166]. In Hodgkin lymphoma (HL), BCL6 protein is predominantly expressed in nodular lymphocyte-predominant HL (NLPHL), but not in classical HL, and *BCL6* rearrangements are seen in ~50 % of NLPHL cases [167]. Of note, LRF protein, like BCL6, is also uniquely expressed in NLPHL cases [168].

BCL6 is an attractive target for NHL therapy, given how frequently its expression is deregulated. As described, the BCL6-BTB domain interacts with short sequence motifs in co-repressors, including SMRT, NCOR and BCOR [36, 48, 169, 170]. A cell-penetrating BCL6 peptide inhibitor containing the SMRT BCL6-BTB binding domain (BPI) inhibits BCL6 transcriptional repressor activity in vitro and in vivo [169, 170]. Furthermore, small molecules targeting the BCL6-BTB lateral groove pocket, where BPI binds, inhibit BCL6 repressor function [170]. These reports are encouraging and warrant attention as therapeutic approaches.

The translocation t(11;17) (q23; q21), which produces *PLZF/RARα* and *RARα/PLZF* fusion genes, is observed in rare APL cases [81, 158]. Resulting PLZF/RARα and RARα/ PLZF fusion proteins exert leukemogenic activity, at least in part, by disrupting normal PLZF and RARα function [158]. The PLZF/RARα fusion functions as a dominant-negative form of RARα [171, 172]. The fusion can disrupt normal RAR/RXR-mediated signaling by forming a PLZF/RARα/RXR heteromeric complex and/or PLZF/RARα homodimer through the PLZF-BTB domain [158]. The PLZF/RARα fusion could inhibit normal PLZF function by sequestering PLZF binding proteins such as co-repressors. The RARα/PLZF reciprocal fusion could also act as a dominant-negative form of PLZF by interfering with its DNA binding activity, as the fusion retains a large portion of the PLZF zinc finger motif [158].

While APLs harboring the *PML/RARα* fusion respond to treatment with all-trans retinoic acid (ATRA), those with the *PLZF/RARα* fusion exhibit poor ATRA responsiveness [173]. The latter outcome was originally attributed to the ability of the fusion's PLZF moiety to recruit co-repressors [29, 33]; however, later studies showed that mouse APL cells harboring only *PLZF/RARα* could fully differentiate upon ATRA treatment [174, 175]. In agreement, transgenic mice expressing only *PLZF/RARα* develop a chronic myeloid leukemia (CML)-like disease, while mice expressing both *PLZF/RARα* and *RARα/PLZF* develop acute leukemia with a myeloid differentiation block, reminiscent of human APL [172]. Furthermore, a human APL case expressing only *PLZF/RARα* transcripts reportedly achieved complete hematologic remission upon ATRA treatment [176]. Thus, the *RARα/PLZF* fusion may drive ATRA resistance observed in t(11;17) (q23; q21) APL.

LRF protein is overexpressed in 60–80 % of DLBCL and FL cases, and transgenic mice, in which LRF is ectopically expressed in immature T and B cells, develop fatal acute T lymphoblastic leukemia/lymphoma [16]. Since LRF knockdown is toxic to human NHL cell lines, LRF is necessary not only for normal GCB cell development but for maintenance of B cell lymphoma cells [18]. In agreement with LRF's proposed proto-oncogenic activity, a recent genome-wide CRISPR/Cas9-mediated screen identified LRF as an essential gene for survival in human leukemia cell lines [177].

LRF function in myeloid development is not well understood. *Lrf* conditional knockout mice do not exhibit gross defects in myeloid development (except for erythroid cells and osteoclasts) [132–134]. Of note, recent sequencing studies reveal *LRF* mutations in human AML cases. Ivey et al. reported 3 cases with *LRF* mutations out of 223 *NPM1*-mutated AML cases (1.3 %) [178]. Furthermore, *LRF* frameshift mutations, which generate a truncated LRF protein, were recently reported in 3 of 20 cases of AML exhibiting t(8;21) (q22;q22); *RUNX1-RUNX1T1* [179]. It remains unclear whether and how these mutations contribute to leukemogenesis.

Future perspective

Recent progress in sequencing technology has greatly advanced our understanding of basic biology and human genetics. It is now possible to systemically analyze genome-wide profiles of DNA, RNA or the epigenome; protein-bound DNA (or RNA); long-range genome interactions; chromatin structure. These new technologies will greatly further our understanding of molecular function of ZBTB proteins in normal and malignant hematopoiesis. Furthermore, current efforts in human genome sequencing will certainly reveal novel mutations and/or variants relevant to hematology or oncology within ZBTB genes. From a clinical standpoint, the biggest challenge lies in pharmacological targeting of ZBTB protein. As described, BCL6 inhibition is a promising strategy for NHL therapy, while LRF or the LRF–NuRD complex may warrant attention as a drug target for NHL or hemoglobinopathies. Team efforts by scientists in the fields of hematology and oncology and medicinal chemistry should pave the way for future drug development.

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Compliance with ethical standards

Conflict of interest The author has no conflict of interest to declare.

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