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The BTB-ZF Family of Transcription Factors: Key Regulators of Lineage Commitment and Effector Function Development in the Immune System

Aimee M. Beaulieu* and Derek B. Sant’Angelo*,†‡

Successful immunity depends upon the activity of multiple cell types. Commitment of pluripotent precursor cells to specific lineages, such as T or B cells, is obviously fundamental to this process. However, it is also becoming clear that continued differentiation and specialization of lymphoid cells is equally important for immune system integrity. Several members of the BTB-ZF family have emerged as critical factors that control development of specific lineages and also of specific effector subsets within these lineages. For example, BTB-ZF genes have been shown to control T cell versus B cell commitment and CD4 versus CD8 lineage commitment. Others, such as PLZF for NKT cells and Bcl-6 for T follicular helper cells, are necessary for the acquisition of effector functions. In this review, we summarize current findings concerning the BTB-ZF family members with a reported role in the immune system. The Journal of Immunology, 2011, 187: 2841–2847.

Broad complex, tramtrack, bric-a-brac, and zinc finger (BTB-ZF) proteins are an evolutionarily conserved family of transcriptional regulators. Members of this group, of which there are >45 in human and mice, are characterized as having one or more C-terminal C2H2 Krüppel-type zinc finger DNA binding domains in combination with an N-terminal BTB domain that mediates protein–protein interactions. Transcriptional regulation, most often repression, is achieved by sequence-specific binding by the ZF domain to regulatory regions in target genes, coupled with the recruitment of cofactors involved in chromatin remodeling and transcriptional silencing/activation.

Cofactor complex formation is largely mediated by the BTB domain, which has been shown to interact directly with corepressors and histone modification enzymes, including SMRT, ETO, N-Cor, B-Cor, CtBP, Sin3A, DRAL/FHL2, and HDAC-1, -2, -4, -5, and -7 (1–11). Although most of these interactions were described in nonhematopoietic cells or transformed cell lines, BTB-ZF proteins likely regulate gene expression in primary lymphocytes via a similar mechanism. For example, the BTB-ZF protein PLZP has been shown to associate with HDAC-2 in Th2-skewed CD4+ and CD8+ T cells, and these two proteins colocalize at regulatory elements in the IL-13 gene where they likely act in concert to modulate transcription (12).

In addition to corepressor recruitment, the BTB domain, and in some cases the ZF domain, also facilitate heterodimerization and homodimerization among the different gene family members. For example, the BTB-ZF protein Bcl-6 can exist as a homodimer (13) but may also form heterodimers with other BTB-ZF proteins, including NAC-1, PLZF, LRF, BAZF, and Miz-1 (14–18). Similarly, overexpression and cotransfection systems have demonstrated an interaction between PLZF and PLZP, although PLZF can also exist as a homodimer (1, 19, 20). Like the cofactor studies, nearly all of this work has been done in nonhematopoietic cells or cell lines; nevertheless, the finding that Miz-1 and Bcl-6 physically interact in primary germinal center B cells (18) suggests that heterodimerization may be physiologically relevant to BTB-ZF protein function in primary cells of the immune system, and further studies are needed to shed light on this topic.

**BTB-ZF proteins control lineage commitment, development, and function in lymphocytes**

As powerful regulators of gene expression, BTB-ZF proteins are critical players in a wide variety of biological processes, including developmental events such as gastrulation and limb formation, control of DNA damage and cell cycle progression in normal and oncogenic tissues, maintenance of the stem cell pool, and gamete formation (21). Moreover, recent studies have highlighted a fundamental and nonredundant role for many BTB-ZF factors in the development and function of cells in the immune system. This review will summarize

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**Abbreviations used in this article:** BAZF, Bcl-6-associated zinc finger; BTB-ZF, broad complex, tramtrack, bric-a-brac, and zinc finger; CSR, class switch recombination; GC, germinal center; iNKT, invariant NKT; LRF, leukemia/lymphoma related factor; MAZR, Myc-associated zinc-finger protein-related factor; Miz-1, Myc-interacting zinc finger protein-1; PLZF, promyelocytic leukemia zinc finger; PLZP, PLZF-like zinc finger protein; SHM, somatic hypermutation; Th, T follicular helper; ThPOK, Th-inducing POZ/Krüppel-like factor.
The current findings on the eight family members with known roles in orchestrating lymphocyte development: Bcl-6, PLZF, Th inducing POZ/Krüppel-like factor (ThPOK), PLZP, MAZR, BAZF, LRF, and Miz-1 (Fig. 1).

Bcl-6. The BTB-ZF protein Bcl-6 was first identified as an oncogene in diffuse large B cell lymphoma, the most common form of non-Hodgkin’s lymphoma. The transformative properties of Bcl-6 stem largely from its ability to repress transcription of tumor suppressor and cell cycle arrest genes, including p53, ATR, CHEK1, and CDKN1A/p21 (18, 22–26). Bcl-6 is normally expressed at high levels in germinal center (GC) B cells. Early studies showed that mice lacking Bcl-6 were unable to form GCs after immunization with T cell-dependent Ags. Moreover, Ag-specific B cells in these mice were impaired for affinity maturation and class switch recombination (CSR) to IgG subtypes (27, 28). Reconstitution of RAG1-knockout mice with Bcl-6–deficient bone marrow showed that Bcl-6 was required in the hematopoietic compartment for GC formation and somatic hypermutation (SHM) but not for primary IgG responses (29, 30). Bcl-6 also represses expression of Blimp-1, a transcription factor that promotes plasma cell differentiation (31, 32). Given that Blimp-1 represses Bcl-6, the reciprocal antagonism of these two genes has been proposed to serve as a bimodal “switch,” by which B cell fate, as either a GC B cell or an Ab-secreting plasma cell, is established and maintained (33). Beyond promoting GC formation and suppressing plasma cell gene programs, Bcl-6 inhibits cell cycle arrest and apoptosis in GC B cells, allowing DNA damage, a natural byproduct of CSR and SHM, to occur in the absence of cell cycle checkpoint activation. To this end, it represses many of the same genes dysregulated during Bcl-6–mediated transformation, including p53, ATR, CHEK1, and CDKN1A/p21 (18, 24–26).

In addition to peripheral lineage commitment, Bcl-6 is important for B cell development in the bone marrow (34). High Bcl-6 expression is induced by pre-BCR signaling during the pro- to pre-B cell transition. Bcl-6 in turn suppresses DNA damage response genes, including CDKN1A/p21, CDKN1B/p27, and CDKN2A/Arf, during Ig L chain rearrangement, which would otherwise activate apoptosis and cellular senescence in response to RAG-induced DNA lesions. Consequently, Bcl-6–deficient mice have an immature B cell pool that is reduced in both size and clonal diversity (34).

Hints at a role for Bcl-6 in T cell function originated from early studies in which Bcl-6–deficient mice were found to develop spontaneous Th2 inflammation, characterized by enhanced IgE production and severe eosinophilia (27, 28). Upon stimulation in vitro, T cells from Bcl-6-deficient mice produce elevated levels of IL-4, IL-5, and IL-13, a phenotype that has been linked to direct binding by Bcl-6 in regulatory regions of genes for IL-5, IgE, and IL-4 (27, 35, 36).

More recently, Bcl-6 was shown to be necessary and sufficient for the development of CD4⁺ T follicular helper (Tfh) cells, which provide critical help to GC B cells undergoing SHM and CSR (37–39). Constitutive Bcl-6 expression in CD4⁺ T cells in vivo drives nearly complete commitment to the Tfh lineage, and these helper cells are highly effective inducers of GC formation and Ab production by B cells. Conversely, Bcl-6 deficiency abrogates Thf cell differentiation, and CD4⁺ T cells from these mice fail to mediate GC formation (38, 39). At a mechanistic level, Bcl-6 is induced in CD4⁺ T cells by IL-6 and IL-21, although neither cytokine is independently required for Tfh differentiation (40). Bcl-6 drives expression of molecules involved in Tfh cell homing and function, including CXCR5, CXCR4, IL-21R, IL-6R, PD-1, and IL-21, and is required to maintain Tfh identity by suppressing the expression of factors associated with other Th cell lineages, including IFN-γ, IL-17, T-bet, IL-4, GATA-3, and Blimp-1 (37–39). As in B cells, Blimp-1 and Bcl-6 counter-repress each other and play antagonistic roles in CD4⁺ T cell differentiation, with Blimp-1 suppressing and Bcl-6 promoting Tfh lineage commitment (39).

Bcl-6 is also expressed at high levels in memory CD8⁺ T cells. In mice lacking Bcl-6, CD8⁺ T cells proliferate poorly and fail to develop into central memory cells, highlighting a critical role for Bcl-6 in memory T cell formation. Overexpression of Bcl-6 leads to increased numbers of central memory CD8⁺ T cells after immunization and enhances CD8⁺ T cell proliferation after secondary stimulation (41). Similarly, Bcl-6–deficient CD4⁺ T cells exhibit increased apoptosis at the effector cell stage and fail to persist as long-lived memory cells (42). Beyond

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**FIGURE 1.** The key structural features of the eight BTB-ZF transcription factors discussed in this review are highlighted, and the reported functions of each transcription factor are listed.
its role in traditional T cell subsets, Bcl-6 is also important for the function of human CD8\(^+\) T suppressor cells, which may play a role in immunological tolerance in transplantation settings (43).

**PLZF.** Like Bcl-6, the BTB-ZF protein promyelocytic leukemia zinc finger (PLZF) was first identified in the context of hematopoietic cancer. In acute promyelocytic leukemia, chromosomal translocation fuses the genes for PLZF and the nuclear retinoic acid receptor \(\alpha\), ultimately leading to oncogenic transformation (44). In keeping with a putative function as a tumor suppressor gene in acute promyelocytic leukemia, PLZF has been associated with cellular quiescence and growth suppression in nontransformed cells of hematopoietic and nonhematopoietic origin (45–51).

Recent studies on PLZF have elucidated its function as a critical regulator of innate T cell lineages. PLZF is highly expressed in immature CD1d-restricted invariant NKT (iNKT) cells. In PLZF-deficient mice, iNKT cells fail to undergo thymic expansion and are substantially reduced in the thymus, liver, and spleen. The iNKT cells that do develop in these mice behave more like conventional naive T cells; these cells preferentially traffic to the lymph nodes and fail to express characteristic activation markers (e.g., CD44 and CD69). Moreover, PLZF-deficient iNKT cells show a marked reduction in cytokine secretion upon primary stimulation—most notable is their inability to produce simultaneously both IL-4 and IFN-\(\gamma\)—and instead require secondary activation to elaborate effector responses fully (52, 53). In contrast, ectopic PLZF expression in T cells results in the spontaneous acquisition of memory/effector phenotypes and functions. PLZF-transgenic T cells exhibit an activated phenotype (e.g., CD44\(^{hi}\) and CD62L\(^{lo}\)), migrate to nonlymphoid tissues, and transgenic T cells exhibit an activated phenotype (e.g., CD44\(^{hi}\) and CD62L\(^{lo}\)), migrate to nonlymphoid tissues, and express enhanced cytokine production upon primary activation even in the absence of costimulation (52, 54, 55).

In addition to iNKT cells, PLZF expression was recently shown in a subset of mature \(\gamma\delta\) T cells expressing the V\(y\)1.1V\(6\delta\)3 TCR (56, 57). V\(y\)1.1V\(6\delta\)3 T cells share many features with \(\alpha\beta\) TCR-expressing iNKT cells, including constitutive expression of activation markers, rapid and simultaneous production of IFN-\(\gamma\) and IL-4, requiring the SLAM-associated adapter protein for their development. Although PLZF-deficient mice harbored normal numbers of V\(y\)1.1V\(6\delta\)3 T cells, their function is dramatically impaired in the absence of PLZF. Indeed, in contrast to wild-type cells, PLZF-deficient V\(y\)1.1V\(6\delta\)3 T cells produce almost undetectable levels of IFN-\(\gamma\) and IL-4 in response to TCR stimulation (57, 58). Notably, transgenic mice expressing the V\(y\)1.1V\(6\delta\)4 TCR have large numbers of PLZF-positive T cells and develop spontaneous dermatitis, perhaps underscoring a proinflammatory and sometimes pathogenic role for these cells (56).

Several mouse strains have been described with increased numbers of innate CD8\(^+\) T cells, including mice lacking the Tec kinase Itk (59), the coactivator CBP (60), and the transcription factor KLF2 (61). Recently, this CD8\(^+\) T cell expansion was shown to be a cell-extrinsic consequence of elevated IL-4 produced by an expanded PLZF-positive T cell population in these mice (61).

In addition to \(\alpha\beta\) and \(\gamma\delta\) NKT cell subsets, PLZF is expressed in human MR1-specific mucosal-associated invariant T cells and in fetal MHC class II-restricted T cells that develop as a result of positive selection on other T cells (52, 62).

Plzf may also impact NK cell function either directly or indirectly; Plzf deficiency impairs protection against Semliki Forest virus infection, and this susceptibility was associated with reduced IFN-induced NK cell cytototoxicity (63). Given the innate lymphocyte features of all of these cells, future studies will be useful for understanding the role of PLZF in their development and/or function.

**ThPOK.** ThPOK, also known as Zbtb7b or cKrox, encodes a three-zinc-finger BTB domain protein originally identified as a regulator of development and function in cells from connective tissues. Within the hematopoietic compartment, ThPOK is upregulated in CD4\(^+\), but not CD8\(^+\), T cells upon differentiation from double- to single-positive thymocytes, and its expression is stably maintained in CD4\(^+\) T cells (64, 65). A spontaneous mutation in one of its zinc finger domains resulted in the loss of Th cells in helper deficient mice (65). MHC class II-restricted T cells from HD mice, as well as T cells with submaximal ThPOK expression, exhibit features of transdifferentiation to the CD8\(^+\) T cell lineage, highlighting a critical role for ThPOK in driving the CD4\(^+\) versus CD8\(^+\) lineage fate in naive T cells (65, 66). Indeed, constitutive ThPOK expression in developing thymocytes induces redirection to the CD4\(^+\) lineage, even among MHC class I-restricted cells, with many of the features of Th cells (65).

In a temporal and developmental sense, ThPOK functions downstream of GATA-3, an early CD4\(^+\) lineage transcription factor, and ThPOK upregulation and conventional thymocytes appears to depend on effective TCR signaling to the CD4\(^+\) stage (67–69). MHC class II-signaldependent CD4\(^+\)CD8\(^-\) thymocytes with impaired signaling through the TCR-associated kinases, Zap70 or Itk, fail to upregulate ThPOK and instead express cytotoxic T cell markers, including the transcription factor Runx3 and its targets, cemesodermin and perforin (70–72). Analogous to the antagonistic relationship of Blimp-1 and Bcl-6 in B-cell differentiation, ThPOK and the CD8\(^+\) T cell determinant, Runx3, counter-repress expression of each other. Thus, Runx-deficient MHC class I-restricted thymocytes, which lack functionality in both Runx3 and Runx1 or are genetically deficient for the obligatory Runx binding protein, Chb\(\beta\), retain ThPOK expression and exhibit features of the Th cell lineage, showing that Runx-mediated silencing of ThPOK is required to maintain CD8\(^+\) lineage commitment (73). Surprisingly, in animals lacking both Chb\(\beta\) and ThPOK, MHC class II-restricted thymocytes maintain Th cell characteristics, suggesting that in settings where commitment to the CD8\(^+\) T cell lineage is intrinsically limited (i.e., as a result of Runx deficiency), ThPOK is more important for the maintenance, rather than the induction, of the CD4\(^+\) T cell fate (74). Nevertheless, in mice capable of CD8\(^+\) versus CD4\(^+\) fate decisions, ThPOK plays a critical and active role in repressing CD8\(^+\) T cell lineage commitment.

Recent studies have uncovered critical roles for ThPOK in the development and function of other T cell subsets. In mature CD8\(^+\) T cells, ThPOK expression is upregulated as a result of TCR activation and is required for effective expansion during the primary and secondary responses to acute viral infection (75). In mice lacking functional ThPOK, memory CD8\(^+\) T cells are impaired for IL-2 secretion and granzyme B expression after Ag rechallenge (75). In innate T cell lineages, ThPOK controls the development and functional maturation of PLZF-positive NKT cells of both the \(\gamma\delta\) and \(\alpha\beta\) TCR
expression of markers associated with NKT function, including in iNKT cells depends on GATA-3 (76). Similarly, VgVg1.1+, ThPOK-deficient mice, suggestive of a broader role for ThPOK in the development of some, although not all, γδ T cell subsets (77). More striking, however, is the role of ThPOK in the effector function of iNKT and Vγ1.1+ Vδ6.3+ γδ T cells. ThPOK-deficient iNKT cells show impaired expression of markers associated with NKT function, including granzyme B, CD69, and, in one study, NK1.1, and produce less IL-4, IFN-γ, and TNF-α in response to αGal-Cer stimulation (76, 78). As in conventional T cells, ThPOK expression in iNKT cells depends on GATA-3 (76). Similarly, Vγ1.1+ Vδ6.3+ γδ T cells produce less IL-4, but more IFN-γ, in response to stimulation, and this impairment correlated with reduced PLZF expression (57).

PLZF. The BTB protein PLZF-like zinc finger protein (PLZF), also known as FAZF, TZFP, and ROG, shares many features with PLZF, including a high level of sequence similarity, recognition of the same target DNA sequences, and declining expression in hematopoietic progenitors cells as a function of lineage-specific differentiation (19, 79, 80). Among lymphocytes, PLZF is upregulated in primary CD4+ and CD8+ T cells after TCR activation in vitro (12, 80, 81). T cells from PLZF-deficient mice produce more IL-2 and are hyperproliferative in response to TCR stimulation compared with wild-type cells, suggesting an antiproliferative role for PLZF in activated T cells (80, 82).

In addition to controlling proliferation, several studies have highlighted a role for PLZF in controlling lymphocyte cytokine responses. When overexpressed in T cell lines, PLZF was shown to interact directly with the Th2-promoting transcription factor GATA-3 and could antagonize GATA-3 binding to target genes, such as IL-5 (81). Similarly, PLZF repressed GATA-3–induced IL-4 production when both transcription factors were cotransfected into primary CD4+ T cells (12). Moreover, overexpression in either Th1- or Th2-skewed T cells impaired cytokine production on a more global level, leading to reduced IL-4, IL-5, IL-10, IFN-γ, and IL-17 (12, 81). In Th2-skewed CD8+ T cells, endogenous PLZF was shown to bind directly a regulatory region in the IL-13 gene, hinting at a similar role for PLZF in cytokine production by CD8+ T cells (12).

Consistent with the overexpression studies, CD4+ T cells from PLZF-deficient mice express higher levels of IL-4, IL-5, and IL-13 when stimulated in vitro under Th2-promoting culture conditions, and PLZF-deficient CD8+ T cells produced more IFN-γ upon stimulation under neutral conditions (80). Nevertheless, PLZF-deficient CD4+ T cells are fully capable of differentiating into Th1 or Th2 cells in vitro, and PLZF-deficient mice mount normal Th1 and Th2 responses to myelin oligodendrocyte glycoprotein–induced experimental autoimmune encephalomyelitis and keyhole limpet hemocyanin immunization, respectively (82). In contrast, allergic responses in airway hypersensitivity models are impaired in PLZF-deficient mice, reflecting increased Th2 differentiation and Th2-driven inflammation in the affected airways (83). Similarly, these mice exhibit heightened Th2 inflammation in the context of a hapten-induced model of contact hypersensitivity, leading to exacerbated edema and mast cell degranulation at reaction sites and increased levels of IgE and hapten-specific IgG Abs in the circulation (84). These defects are directly linked to a cell-intrinsic requirement for PLZF in T cells, as transfer of PLZF-deficient or PLZF-overexpressing T cells exacerbated or ameliorated, respectively, disease progression in wild-type animals. Thus, additional studies will be needed to clarify the exact role of PLZF in lymphocyte function in vivo.

Beyond regulating cytokine production in T cells, PLZF may also play a role in lineage commitment during T cell development. In one study, overexpression of PLZF in developing double-positive thymocytes, in the context of a fetal thymic organ culture model, led to a preferential accumulation of single-positive CD8+ T cells. Similar to its function in mature T cells, this accumulation was linked to the ability of PLZF to inhibit GATA-3 function (85).

BAZF. The Bcl-6–associated zinc finger (BAZF) protein, also known as Bcl-6b, is a five-zinc-finger BTB protein with high similarity to Bcl-6. In addition to sharing significant sequence homology, both can recognize the same target DNA sequences (17). Within in the lymphocyte compartment, BAZF mRNA is detectable in CD4+ and CD8+ naive T cells (86). Notably, both Bcl-6– and BAZF-deficient animals exhibit aberrant hematopoietic progenitor cell proliferation, a defect that was linked to a cell-intrinsic requirement for BAZF in CD8+ T cells (87). In addition to naive T cells, BAZF is expressed at high levels in some Ag-specific, memory CD8+ T cells, and, although BAZF-deficient mice show normal CD8+ T cell activation in response to primary viral infection, recall responses by memory CD8+ T cells are greatly impaired in vitro and in vivo (88).

In contrast to the role of BAZF in memory CD8+ T cells, naive CD4+ T cells require BAZF expression for maximal TCR-induced proliferation in vitro, whereas memory CD4+ T cells do not (86). Moreover, naive CD4+ T cells from mice that ectopically express BAZF are hyperproliferative in response to TCR stimulation, but memory CD4+ T cells from these mice behave normally.

MAZR. Compared with the BTB-ZF proteins detailed earlier, relatively little is known about the role of the Myc-associated zinc-finger protein–related factor (MAZR) in lymphocyte and development. MAZR is expressed in thymocytes and B cells and, in the latter, activated c-Myc in overexpression studies (89). In double-negative thymocytes, MAZR has been postulated to function as a transcriptional repressor of the Cd8 locus, and its downregulation is required, in part, for CD8 expression at the transition to the double-positive stage (90). In double-positive thymocytes, ectopically expressed MAZR could bind enhancer elements in the Cd8 gene and suppress CD8 expression (90). Recent studies, however, show that MAZR deficiency is insufficient to allow CD8 expression in double-negative thymocytes. Instead, development of single-positive CD8+ T cells was impaired in these animals, and MHC class I–restricted thymocytes were redirected into the CD4+ lineage, leading to an increased CD4+ to CD8+ T cell ratio among mature thymocytes and peripheral T cells. This phenotype was linked
to MAZR-mediated repression of the ThPOK gene in double-positive thymocytes (91).

LRF. Leukemia/lymphoma related factor (LRF), also known as OCZF, Zbtb7a, FBI-1, and Pokemon, is a BTB-ZF transcriptional repressor and oncogene associated with malignancy in lymphomas and solid epithelial tumors, including breast cancer, and non-small cell lung carcinoma (92–94). LRF is expressed in a broad range of myeloid and lymphoid lineages, including most subsets of developing and peripheral B cells (95). Conditional deletion of the LRF gene in hematopoietic stem cells in vivo led to a profound reduction in peripheral B cells, consistent with a cell-intrinsic requirement for LRF for progression past the prepro-B cell stage during bone marrow development (93, 95). Unexpectedly, these mice exhibited extrathymic T cell development in the bone marrow. Additional experiments revealed that LRF was required in lymphoid progenitor cells in the bone marrow to suppress Notch-dependent T cell lineage commitment and allow B cell development to progress. In the absence of LRF, Notch genes were aberrantly upregulated in hematopoietic progenitors, abrogating B cell development and driving spontaneous T cell development outside of the thymus (95). It remains to be determined whether Notch is a direct target of LRF or whether aberrant Notch signaling in these mice is an indirect consequence of impaired LRF-dependent signals.

Miz-1. A critical role for Myc-interacting zinc finger protein-1 (Miz-1) in lymphocyte development has recently been appreciated. In the past year, two separate studies using Miz-1–defective mice revealed an essential function for Miz-1 in the development of both T and B lymphocytes (96, 97). Animals lacking the BTB domain of Miz-1 exhibit a profound reduction in the number of thymic early T cell progenitor cells. Moreover, T cell development in these animals is blocked at the double-negative to double-positive transition causing a severe reduction in thymic cellularity, which was mirrored by specific reductions in the number of αβ and γδ T cells. Transfer of Miz-1–deficient hematopoietic progenitors into wild-type recipients confirmed that the requirement for Miz-1 in T cell development was cell intrinsic. Consistently, pro-T cells from these mice failed to differentiate in vitro as a result of increased apoptosis (96). In addition to the T cell defect, Miz-1 deficiency leads to a complete loss of follicular B cells, underscoring a parallel role for Miz-1 in the development of certain B cell subsets (97). In both lymphocyte populations, Miz-1 was shown to be required downstream of IL-7R signaling in lymphocyte progenitor populations to promote STAT5 activation and expression of the antiapoptotic protein Bcl-2 (96, 97). In developing T cells, these effects were mediated in part by Miz-1–dependent repression of the STAT inhibitor SOCS-1; consistent with this, binding of Miz-1 to the SOCS-1 promoter could be detected in primary double-negative thymocytes. A similar relationship between SOCS-1 and Miz-1 was observed in developing B cells, although loss of Miz-1 also abrogated expression of two transcription factors, Tcl3 and Ebf1, critical for the survival and function of early B cell progenitors (97).

Conclusions

New studies are required to delineate further the exact molecular mechanisms by which BTB-ZF proteins regulate gene expression in lymphocytes. This will require a more thorough investigation of the cofactors recruited by these proteins for the purpose of regulating target gene transcription, as well as the identity of the gene targets themselves. In addition, relatively little is known about the upstream signals that regulate the spatial/temporal function of these transcription factors in distinct lymphocyte lineages. In this vein, several studies have highlighted posttranslational modification of BTB-ZF proteins as an important regulatory signal controlling their expression and function. For example, acetylation and sumoylation of PLZF may promote DNA binding and transcriptional repression (98–100), and acetylation of ThPOK blocks ubiquitin-mediated degradation, thereby stabilizing its expression in CD4+ T cells (101). In contrast, phosphorylation of PLZF and Bcl-6, by CDK2 and ATM, respectively, has been shown to trigger ubiquitylation and degradation via proteasome-dependent pathways (102, 103).

From development to effector function, recent studies have highlighted a central and indispensable role for BTB-ZF transcription factors in controlling nearly every aspect of lymphocyte biology. Moreover, the fact that fewer than 10 of the >45 factors in this protein family have been evaluated in this context suggests that future work is likely to uncover additional BTB-ZF proteins with roles in lymphocyte function, fate, and phenotype.

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