

# The Role of BTB-Zinc Finger Transcription Factors During T Cell Development and in the Regulation of T Cell-mediated Immunity

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**Abstract** The proper regulation of the development and function of peripheral helper and cytotoxic T cell lineages is essential for T cell-mediated adaptive immunity. Progress made during the last 10–15 years led to the identification of several transcription factors and transcription factor networks that control the development and function of T cell subsets. Among the transcription factors identified are also several members of the so-called BTB/POZ domain containing zinc finger (ZF) transcription factor family (BTB-ZF), and important roles of BTB-ZF factors have been described. In this review, we will provide an up-to-date overview about the role of BTB-ZF factors during T cell development and in peripheral T cells.

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**1 Introduction**

***1.1 A Brief Summary of  $\alpha\beta$ T Cell Development***

T-lineage lymphocytes, which are defined as a cell population expressing either the  $\alpha\beta$ TCR or the  $\gamma\delta$ TCR chains, develop in the thymus. After immigration into the thymus, early T cell progenitors that still retain the developmental potency to develop into other hematopoietic lineages undergo several regulatory processes to be fully committed to the T lymphocyte lineage. These early immature T cells neither express CD4 nor CD8 and therefore are called double-negative (DN) thymocytes. The early development of thymocytes is accompanied with the initiation of the recombination of either the *Tcrb* or *Tcrd* gene loci that encode for the TCR $\beta$  or TCR $\delta$  chains, respectively. The successful generation of a functional TCR $\beta$  chain results in the formation of the pre-TCR complex, which is a heterodimeric complex on the surface of DN thymocytes formed by the newly generated TCR $\beta$  chain with the invariant pre-T $\alpha$  protein. The expression of a functional pre-TCR, a checkpoint known as  $\beta$ -selection, results in the inhibition of a further rearrangement of the *Tcrb* locus as well as in a rapid proliferation and leads to the induction of *Cd4*, and *Cd8a* and *Cd8b1* (*Cd8*) gene expression. Hence, DN thymocytes progress to the CD4 and CD8 expressing double-positive (DP) stage of T cell development. The transition to the DP stage is accompanied with the functional rearrangement of the *Tcra* locus and DP thymocytes express a mature  $\alpha\beta$ TCR formed by the TCR $\alpha$  and TCR $\beta$  chains. CD4<sup>+</sup>CD8<sup>+</sup> DP phenotype cells are subjected to another selection process, known as a positive/negative selection, during which reactivity of  $\alpha\beta$ TCR to self-peptide/MHC is evaluated and CD4 and CD8 proteins serve as coreceptors for peptide/MHC recognition during this process. As a consequence of positive and negative selection, only limited numbers of DP thymocytes are allowed to further differentiate and to face the cell fate decision to become either helper or cytotoxic T cells. It has been known that both TCR specificity to MHC types and CD4/CD8 coreceptor expression perfectly correlates with outcome of helper/cytotoxic lineage choice. Thymocytes selected via MHC class I molecules differentiate into cytotoxic T cells and shut-off *Cd4* gene expression, thereby acquiring a CD4<sup>-</sup>CD8<sup>+</sup> single-positive (CD8SP) surface phenotype. On the contrary, those DP cells selected by MHC class II develop toward the helper T lineage and become CD4<sup>+</sup>CD8<sup>-</sup> single-positive (CD4SP)

thymocytes by loosing *Cd8* gene expression. Thus, the CD4/CD8 coreceptors expression profile is a good marker to define distinct developmental stages of thymocytes (Carpenter and Bosselut 2010; Singer et al. 2008). Progress made during the last 10–15 years led to the identification of several transcription factors and the characterization of a transcription factor network that is essential for *Cd4* and *Cd8* gene regulation and for helper/cytotoxic lineage choice during T cell development (Taniuchi and Ellmeier 2011; Ellmeier et al. 2013). Among the transcription factors identified are ThPOK and MAZR, two members of the so-called BTB/POZ domain containing zinc finger (ZF) transcription factor family (BTB-ZF) (Stogios et al. 2005). Moreover, members of the BTB-ZF family play also important roles at other stages of T cell development and BTB-ZF factors have been identified as crucial regulators of peripheral T cell function (Bilic and Ellmeier 2007; Siggs and Beutler 2012; Beaulieu and Sant'Angelo 2011). In this review, we will provide an up-to-date overview about the role of BTB-ZF factors during T cell development and in peripheral T cells.

## ***1.2 The BTB/POZ Domain Containing Family of Zinc Finger Transcription Factors***

The BTB (broad-complex, tramtrack, and bric-a-brac) domain, also known as POZ (Pox virus and ZF) domain, is an eukaryotic protein–protein interaction motif. The BTB domain, which is approximately 90–120 amino acids long, can mediate homo-oligomerization, hetero-oligomerization, and facilitates also interactions with other proteins that lack BTB domains (Bardwell and Treisman 1994; Stogios et al. 2005; Collins et al. 2001). It has been reported that there are approximately 200 genes in the human genome that contain a BTB domain (Stogios et al. 2005). These BTB domain containing factors can be divided into several subgroups dependent on the presence of additional domains, such as C<sub>2</sub>H<sub>2</sub> ZF motifs (BTB-ZF), factors containing a so-called Kelch motif (Stogios and Prive 2004) and proteins with a potassium channel tetramerization T1 domain (KCTD proteins; Liu et al. 2013) among others (Stogios et al. 2005). Although there is little amino acid sequence homology in the BTB domain between members of different subgroups, a structural analysis reveals conservation in the tertiary protein structure (Stogios et al. 2005). The various BTB proteins have a broad range of biological functions and regulate a variety of different cellular and molecular processes. These include the transcriptional control of development, differentiation, cancer (Kelly and Daniel 2006; Bilic and Ellmeier 2007; Beaulieu and Sant'Angelo 2011; Lee and Maeda 2012; Siggs and Beutler 2012; Lunardi et al. 2013), the regulation of actin and cytoskeleton dynamics (Perez-Torrado et al. 2006; Albagli et al. 1995), protein targeting for ubiquitination (Pintard et al. 2004; Genschik et al. 2013) and others (Stogios et al. 2005).

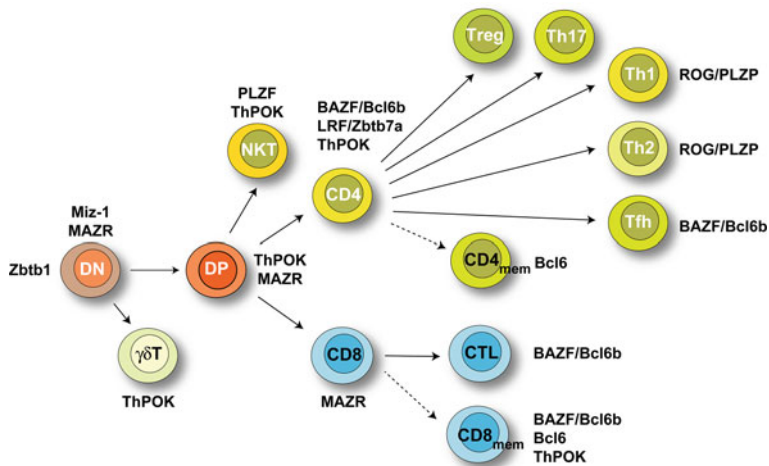
BTB-ZF factors form one large subgroup of BTB domain containing proteins. There are 49 BTB-ZF genes in mammalian genomes (Gray et al. 2013) and all members have their BTB domain, like many other BTB factors, located at the N-terminus, while the ZF DNA binding domain is located at the C-terminal end (Stogios et al. 2005). Several studies have shown that the BTB domains of some BTB-ZF proteins mediate homo- as well as hetero-oligomerization of BTB-ZF proteins (Hoatlin et al. 1999; Takenaga et al. 2003; Kobayashi et al. 2000). In addition, BTB-ZF factors interact with via their BTB domain nuclear corepressors such as NCoR1, SMRT, and BCoR (Huynh and Bardwell 1998; Ahmad et al. 2003; Melnick et al. 2000, 2002; Polo et al. 2004; Huynh et al. 2000; Bilic et al. 2006), which are part of large, multi-subunit complexes that can contain various chromatin-modifying enzymes like members of the BAF complex, methyl-DNA binding proteins, and histone deacetylases (HDACs) (Jepsen and Rosenfeld 2002; Mottis et al. 2013). Thus, it is likely that BTB-ZF factors might serve as site-specific recruitment factors for chromatin-modifying complexes to their target genes. Moreover, BTB-ZF factors such as PLZF and Bcl6 interact with the E3 ubiquitin ligase Cullin 3 (Mathew et al. 2012), which influences the ubiquitination status of several components of chromatin-remodeling complexes (Lydeard et al. 2013). BTB-ZF proteins have been linked with transcriptional repression, although they can also activate target genes. It is likely that the protein composition as well as posttranslational modifications of such multi-subunit complexes recruited via BTB-ZF proteins will determine whether a BTB-ZF factor will act as a repressor or activator of its target gene.

## 2 BTB-ZF Proteins and the Regulation of T Cell Development and Function

So far, nine BTB-ZF proteins have been implicated in the regulation of various aspects of T cell development and function (Fig. 1 and Table 1). All these factors show a similar domain-like structure with an N-terminal BTB domain and the C-terminal Zn finger motifs; however, the number of ZFs and the spacing between consecutive ZFs within the C-terminal ZF domain differs greatly (Fig. 2).

### 2.1 *Zbtb1*: A Determinant of Lymphocyte Development

*Zbtb1* (ZF and BTB domain containing 1), encoded by the *Zbtb1* gene, has been identified by Butcher and colleagues in an ENU screen as an important regulator of lymphocyte development, in particular the T cell lineage (Siggs et al. 2012). Mice homozygous for a missense mutation (C47R) in *Zbtb1* (designated as *scanT* mutant strain) were developmentally normal and fertile; however, mutant mice were devoid



**Fig. 1** BTB-ZF factors regulating T cell development and the differentiation/function of peripheral T cell subsets. The drawing shows an overview about the various developmental stages of thymocyte development and different subsets of peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T cells. The name of the BTB-ZF factors implicated in the regulation of a particular thymocyte and T cell subset are indicated. See text for more details. *DN* double-negative, *DP* double-positive, *NKT* natural killer T cells, *Th1* T-helper 1, *Th2* T-helper 2, *Th17* IL-17-producing Th cells, *Treg* regulatory T cells, *Tfh* follicular helper T cells, *CTL* cytotoxic T lymphocytes. The dotted lines with arrowheads indicate less well-defined differentiation pathways leading to the generation of memory CD4 (CD4<sub>mem</sub>) and CD8 (CD8<sub>mem</sub>) T cells

of T cells, while NK cell numbers and to a lesser extent also B cell numbers were reduced in comparison to wild-type mice. The generation of BM chimeras revealed that the phenotype was intrinsic to the hematopoietic system, although hematopoietic cell development was not affected before lymphoid specification. In a competitive environment in mixed BM chimeras, all lymphoid lineages were absent, while the myeloid compartment was not affected (Siggs et al. 2012). Puck and colleagues independently identified *Zbtb1* as an important regulator of the generation of T cells in a homozygous transgenic strain that lacked T cells due to an insertion of the transgene in the *Zbtb1* locus (Punwani et al. 2012). The generation of *Zbtb1*-null mice confirmed that *Zbtb1* is essential for the generation of T cells due to hematopoietic cell-intrinsic defects, while NK cells were less affected in comparison to T cells. B cell numbers were almost normal in *Zbtb1*<sup>-/-</sup> mice. The analysis of fetal thymi showed that already decreased numbers of early DN1 thymocytes and a failure to progress beyond this stage. *Zbtb1* is also expressed in the spleen and in lymph nodes. In developing thymocytes, *Zbtb1* is upregulated during the DN to DP transition. Two splicing isoforms of *Zbtb1* have been identified, one encoding for a full-length *Zbtb1* protein with eight ZF motifs, while a shorter *Zbtb1* isoform expressed at lower levels encodes for a protein with only five ZF motifs (Punwani et al. 2012). Although not demonstrated in T cells, *Zbtb1* can function as a transcriptional repressor (Liu et al. 2011; Matic et al. 2010) and the repressor activity of

**Table 1** This table shows the murine and human gene names encoding for BTB-ZF factors implicated in T cell development and the regulation of peripheral T cell function. The function of BTB-ZF factors and the reference reporting the activity is shown at the right

Murine gene	Human gene	Synonym (alternative names)	Functions during T cell development and in peripheral T cell
<i>Bcl6</i>	<i>BCL6</i>	(BCL5, BCL6A, LAZ3, ZBTB27, ZNF51)	Key factor for Tfh differentiation and Tfh survival (Johnston et al. 2009; Nurieva et al. 2009; Yu et al. 2009; Hollister et al. 2013) Bcl6 <sup>-/-</sup> Tregs failed to suppress Th2-type immune responses in vivo leading to strong lung inflammation in an allergic airway inflammation model (Dent et al. 1997; Ye et al. 1997; Sawant et al. 2012) Bcl6 is an important regulator of both CD4 <sup>+</sup> and CD8 <sup>+</sup> memory T cell generation and homeostasis (Ichii et al. 2002, 2004, 2007)
<i>Bcl6b</i>	<i>BCL6b</i>	<b>BAZF</b> (ZBTB28, ZNF62)	Regulates activation of naïve CD4 <sup>+</sup> T cells (Takamori et al. 2004) Modulates secondary response of CD8 <sup>+</sup> memory T cells (Manders et al. 2005) BAZF/Bcl6b-null CD8 <sup>+</sup> T cells influence the number of cycling hematopoietic progenitor cells in the spleen (Broxmeyer et al. 2007)
<i>Patz1</i>	<i>PATZ1</i>	<b>MAZR</b> (RIAZ, ZBTB19, ZNF278, ZSG)	Represses CD8 expression in DN thymocytes (Bilic et al. 2006) Part of the transcription factor network controlling CD4/CD8 cell fate choice (Sakaguchi et al. 2010)
<i>Zbtb1</i>	<i>ZBTB1</i>		Regulates the generation of the lymphoid lineage, in particular T cells and NK cells (Siggs et al. 2012; Punwani et al. 2012)
<i>Zbtb7a</i>	<i>ZBTB7A</i>	<b>LRF</b> (FBI1, FBI-1, pokemon, ZBTB7, ZNF857A)	Indirectly affects B versus T cell choice via upregulation of Notch ligand Delta-4 on erythroblasts (Lee et al. 2013a) Controls Th cell-specific gene expression (Carpenter et al. 2012)
<i>Zbtb7b</i>	<i>ZBTB7B</i>	<b>ThPOK</b> (cKrox)	Key commitment factor for CD4 lineage specification (He et al. 2005; Sun et al. 2005) Represses CD8 lineage genes in CD4 <sup>+</sup> T cells (Wang et al. 2008a; Egawa 2009; Rui et al. 2012) Regulates expansion of CD8 <sup>+</sup> memory T cells (Setoguchi et al. 2009) Important for $\gamma\delta$ T cell maturation (Park et al. 2010) Regulates functional differentiation of invariant NKT cell subsets (Engel et al. 2010, 2012; Enders et al. 2012)

(continued)

**Table 1** (continued)

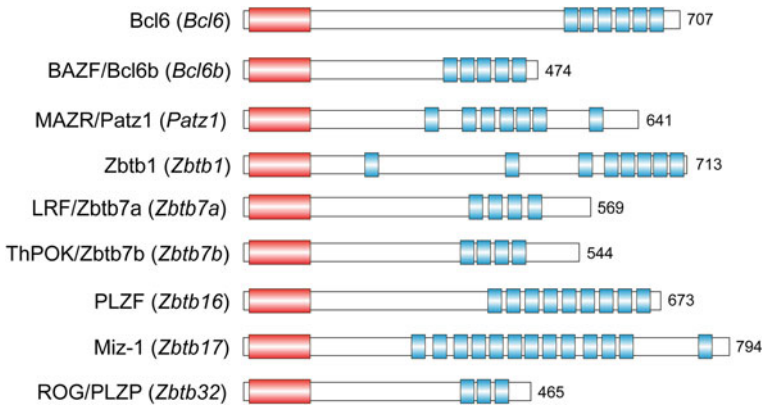
Murine gene	Human gene	Synonym (alternative names)	Functions during T cell development and in peripheral T cell
<i>Zbtb16</i>	<i>ZBTB16</i>	<b>PLZF</b> (green's luxoid, ZNF145)	Essential for the development and function of invariant NKT (Kovalovsky et al. 2008; Savage et al. 2008) Important for the regulation of an effector program and effector function in innate-like T cells (Savage et al. 2008; Raberger et al. 2008; Kovalovsky et al. 2010) Important for the development of innate-like CD8 <sup>+</sup> T cells (Weinreich et al. 2010; Verykokakis et al. 2010)
<i>Zbtb17</i>	<i>ZBTB17</i>	<b>Miz-1</b> (pHZ-67, ZNF151, ZNF60)	Essential for early T cell lineage development at ETP/DN1 stage (Saba et al. 2011b) Ensures proper pre-TCR expression and the regulation of P53 target genes in DN3 thymocytes (Saba et al. 2011a)
<i>Zbtb32</i>	<i>ZBTB32</i>	<b>Rog, PLZP</b> (FAXF, FAZF, TZFP, ZNF538)	Important regulator of Th2-type immune responses in vitro (Miaw et al. 2000, 2004) and in vivo (Hirahara et al. 2008; Hirasaki et al. 2011)

*Zbtb1* is regulated by SUMOylation (Matic et al. 2010). Together, these data indicate an essential role for *Zbtb1* in the generation of the T cell lineage and also for the generation of NK and B cells.

Of note, *Zbtb1*<sup>-/-</sup> mice show increased numbers of short-term HSC, multipotent progenitors, and common lymphoid progenitor cells (Punwani et al. 2012), while *scanT* mice do not (Siggs et al. 2012). This might indicate that the mutant *Zbtb1* generated from the C47R *Zbtb1* allele might still have some residual function. Further studies are required to reveal the molecular mechanisms of how *Zbtb1* regulate lymphocyte development and the differentiation of the hematopoietic system.

## 2.2 *Miz-1: A Regulator of Early T Cell Differentiation*

Miz-1 (Myc-interacting ZF protein 1), encoded by the *Zbtb17* gene, is a transcription factor that has been initially identified as a c-myc interacting factor (Peukert et al. 1997). Like many other BTB-ZF factors, Miz-1 can both positively and negatively regulate its target genes, dependent on interaction with other factors (Moroy et al. 2011). Germline deletion of Miz-1 results in embryonic lethality due to defects during gastrulation (Adhikary et al. 2003). Therefore, Möröy and colleagues generated a conditional *Miz-1* allele that lacks the BTB domain upon Cre/loxP-mediated recombination (Kosan et al. 2010). Initially, studies using *Vav-Cre*-mediated deletion of Miz-1 focused on B cells and revealed a crucial role for Miz-1 in IL-7



**Fig. 2** Domain structure of BTB-ZF proteins. The drawing shows the location of the BTB domain (in red) and the C<sub>2</sub>H<sub>2</sub> zinc finger motifs (in blue) in BTB-ZF factors implicated in the regulation of T cells. The name of the protein and the gene name (in parenthesis) are indicated at the left. The numbers at the right indicate the length in amino acids. For MAZR/Patz1, an alternative splice variant encoding for a 537 amino acids long BTB-ZF protein that contains six zinc finger motifs has been described (Kobayashi et al. 2000)

receptor signaling during early B cell development (Kosan et al. 2010). Subsequent studies showed that Miz-1 is also essential for the T cell lineage. Loss of Miz-1 (using the *Vav-Cre*-deleter strain) led to a severe reduction (>100 fold) of thymocyte numbers accompanied also by a severe reduction of DN subsets, in particular ETP/DN1 and DN2 stages (Saba et al. 2011b). By performing a comprehensive in vitro analysis using the OP9-DL1 system, the drop in ETP/DN1 cells could be linked to extensive cell death in the absence of Miz-1. A further analysis showed that Miz-1 regulates the expression of SOCS1, most likely by a direct regulation since Miz-1 binds to the *Socs1* promoter region and loss of Miz-1 leads to an upregulation of *Socs1* expression. As a consequence, STAT5 activation and Bcl-2 expression in response to IL-7 signaling is impaired. The functional importance of Bcl-2 upregulation was confirmed genetically, since transgenic overexpression of Bcl-2 rescues the survival defect of Miz-1-null ETP/DN1 cells, indicating a crucial role for Miz-1 for the survival of ETP/DN1 cells (Saba et al. 2011b).

Although the transgenic expression of Bcl-2 restored in part thymocyte numbers in the absence of Miz-1, there was still a reduction of DP thymocytes due to a developmental block at the DN3 stage, indicating another role for Miz-1 during early T cell development (Saba et al. 2011a). Despite normal expression of many genes required for the generation of a pre-TCR including *Rag1*, *Rag2*, *Cd3e*, *pTa*, and intact VDJ recombination, only a few Miz-1-null cells expressed a surface pre-TCR. Miz-1-null DN3 cells do not proliferate and display increased cell death and this correlated with the enhanced expression of p53 target genes such as *Cdkn1a*, *Puma*, and *Noxa*. However, transgenic TCR expression together with transgenic Bcl-2 rescued partially the developmental block at the DN3 stage, suggesting that the role of Miz-1 in DN3 cells is in part to ensure proper pre-TCR expression and



the regulation of P53 target genes (Saba et al. 2011a). Of note, thymocyte development and the appearance of mature CD4SP and CD8SP cells was normal when Miz-1 was deleted at DN2/3 stage by *Lck-Cre* (Saba et al. 2011b), indicating that Miz-1 mainly controls early T cell development but has rather a minor role at later stages of thymocyte maturation beyond the DN stage. Alternatively, other factors can compensate for loss of Miz-1 thymocyte differentiation after  $\beta$ -selection.

### ***2.3 ThPOK/Zbtb7b: A Master Commitment Factor for CD4 Lineage Differentiation***

ThPOK (T-helper-inducing POZ/Krueppel-like factor, initially known as cKrox), encoded by the *Zbtb7b* gene, was first identified as a binding protein to the promoter regions of collagen genes (Widom et al. 1997), indicating that the expression in this protein is not restricted to hematopoietic cells. Indeed human *Zbtb7b* gene expression was detected in foreskin and fibroblast (Widom et al. 2001). During T cell differentiation, *Zbtb7b* gene exhibits a quite unique expression pattern, since it is induced in MHC class II-signaled DP thymocytes and expressed in CD4<sup>+</sup> helper T cells, while developing CD8 lineage T cells remain ThPOK negative (He et al. 2005; Sun et al. 2005).

Two groups independently identified that ThPOK is a key regulator of CD4 lineage development. Kappes and colleagues unraveled the role of ThPOK during T cell development by using a combination of classical positional cloning approaches to identify the responsible gene locus causing the helper-deficient (HD) phenotype (Dave et al. 1998) and transgenesis to rescue the gene defect identified in HD mice (He et al. 2005). A spontaneous missense mutation in the *Thpok* gene, which alters an arginine residue in the second zinc finger domain to a glycine, resulted in a severe reduction of CD4<sup>+</sup> T cell in the periphery through redirected differentiation of MHC class II-restricted thymocytes toward CD4<sup>-</sup>CD8<sup>+</sup> T cells (He et al. 2005). Bosselut and colleagues identified ThPOK in a screen for genes induced in DP cells during CD4 lineage differentiation (Sun et al. 2005). Both groups showed that enforced expression of ThPOK from CD4<sup>+</sup>CD8<sup>+</sup> DP preselection thymocytes and onward prevents generation of CD8<sup>+</sup> cells through directing MHC class I-restricted cells to become CD4<sup>+</sup>CD8<sup>-</sup> T cells (He et al. 2005; Sun et al. 2005). Subsequent loss of function studies of ThPOK during thymocyte differentiation by gene targeting confirmed the important role for ThPOK in the regulation of CD4/CD8 cell fate choice (Egawa and Littman 2008; Muroi et al. 2008; Wang et al. 2008b). Together, these results indicate that ThPOK expression is not only essential but also sufficient to endow CD4<sup>+</sup>CD8<sup>-</sup> phenotype during thymocyte maturation beyond a MHC restriction of cells (Kappes et al. 2006).

A key mechanism by which ThPOK endows CD4 expression to the helper T cells is the antagonistic function of ThPOK against the *Cd4* silencer (Wildt et al. 2007; Muroi et al. 2008). Moreover, ThPOK represses CD8 lineage genes such as *Runx3* and cytotoxic effector genes such as *Granzyme B* and *Perforin* (Egawa and Littman 2008; Wang et al. 2008a) and might also directly repress the *Cd8* gene complex via binding to *Cd8* enhancers (Rui et al. 2012). However, it remains uncharacterized how ThPOK contributes to confer total helper function to MHC class II-restricted T cells. A recent study indicated that MHC class II-restricted cells retained some helper-related functions in the absence of ThPOK (Carpenter et al. 2012). As we discussed later in detail, LRF/Zbtb7a, which is the most-related BTB-ZF family member to ThPOK, is shown to compensate for loss of ThPOK function in some helper T cell subsets (Carpenter et al. 2012).

The findings that revealed an essential role of ThPOK for CD4 lineage development stimulated studies addressing the mechanism that restricts ThPOK expression only to MHC class II-restricted cells. These studies led to the identification of a transcriptional silencer element, hereafter referred to as a *Thpok* silencer, in the *Thpok* gene locus (He et al. 2008; Setoguchi et al. 2008). Kappes and colleagues utilized transgenic reporter expression assays and identified two *cis*-regulatory regions, designated as distal and proximal regulatory elements (DRE and PRE, respectively). Interestingly, DRE was shown to function both as a transcriptional enhancer and as a silencer, while only an enhancer function was associated with PRE (He et al. 2008). The *Thpok* silencer was independently identified by Taniuchi and colleagues (Setoguchi et al. 2008). The silencer is essential to repress *Thpok* expression during differentiation of MHC class I-restricted cells (He et al. 2008; Setoguchi et al. 2008), thereby preventing an aberrant differentiation pathway toward CD4<sup>+</sup> cells in those cells. Along with a *Thpok* derepression by lack of Runx complex function (Setoguchi et al. 2008), “knock-in” mutagenesis approaches within the *Thpok* silencer showed that *Thpok* silencer activity requires binding of Runx complexes (Tanaka et al. 2013). However, Runx binding to the silencer was also detected in cells expressing *Thpok* gene (Setoguchi et al. 2008), indicating that Runx binding alone is not sufficient to activate the *Thpok* silencer. Thus, it is possible that an uncharacterized mechanism in addition to Runx binding is involved in a control of the *Thpok* silencer activity. As we will discuss below, MAZR, another member of the BTB-ZF gene family, was shown to be necessary for full *Thpok* repression in MHC class I-signaled cells through regulation of the *Thpok* silencer function (Sakaguchi et al. 2010). A further characterization of protein complexes bound to the *Thpok* silencer will be important to unravel the mechanism(s) that facilitates the switch in *Thpok* silencer activity between CD4 and CD8 lineage cells.

In addition to the inactivation of the *Thpok* silencer, several positive *cis*-regulatory elements (i.e., enhancers) are also necessary for appropriate ThPOK expression in CD4 lineage T cells. It was recently shown that distinct sequences within DRE are responsible for enhancer and silencer activity of DRE (He et al. 2008; Muroi et al. 2013). While the enhancer activity in DRE is responsible for the initiation of *Thpok* gene, the enhancer within PRE functions later to upregulate and

maintain ThPOK expression (Muroi et al. 2008). It is likely that these two enhancers, which display a distinct stage-specificity, cooperatively regulate *Thpok* expression.

Interestingly, ThPOK also regulates CD8<sup>+</sup> T cells function. In vitro stimulation of CD8<sup>+</sup> T cells leads to the derepression of ThPOK in a fraction of CD8<sup>+</sup> T cells (Setoguchi et al. 2009). Although the loss of ThPOK does not affect CD8 T cell differentiation into effector T cells and the long-term persistence of Ag-specific memory T cells, the clonal expansion is significantly less in both primary and secondary CD8<sup>+</sup> T cell responses in the absence of ThPOK (Setoguchi et al. 2009), indicating an unexpected role for ThPOK in CD8 lineage T cells in vivo.

In addition to its function in conventional  $\alpha\beta$ T cells, ThPOK also plays a role in the regulation of innate-like T cells such as  $\gamma\delta$ T cells and invariant NKT (iNKT) cells. ThPOK expression is upregulated during the developmental transition from CD24<sup>+</sup> immature to CD24<sup>-</sup> mature  $\gamma\delta$  thymocytes and the maturation of  $\gamma\delta$ T cells in the thymus, in particular NK1.1<sup>+</sup>  $\gamma\delta$  thymocytes subsets, is impaired in ThPOK-deficient mice (Park et al. 2010). iNKT cells are another innate-type T cells expressing invariant V $\alpha$ 14 chain (Constantinides and Bendelac 2013; Rossjohn et al. 2012) and are recently characterized to be composed of several functionally different subsets (Lee et al. 2013b). The emergence of CD8<sup>+</sup> iNKT cells in ThPOK-deficient mice indicates that ThPOK also represses *Cd8* gene expression in this innate cell subset as observed in conventional  $\alpha\beta$ T cell differentiation pathways (Engel et al. 2010). ThPOK also contributes to confer IL4 producing property to iNKT cells during maturation of iNKT cells (Engel et al. 2010). In addition, ThPOK-deficient mice contain a higher proportion of IL-17-producing cells (NKT17) (Enders et al. 2012; Engel et al. 2012), indicating that ThPOK negatively regulate differentiation of this NKT17 subset. Thus, ThPOK is involved in the specification of distinct NKT cell subsets.

It has been proposed that separation of CD4 helper and CD8 cytotoxic lineage in the thymus is stably inherited after activation of cells. Indeed, the findings of an involvement of epigenetic mechanism in the repression of the *Cd4* and *Thpok* genes provided supportive mechanistic insight into how *Cd4* and *Thpok* genes are kept silenced in CD8<sup>+</sup> cytotoxic T cells (Zou et al. 2001; Tanaka et al. 2013). However, little is known about how *Cd8* gene expression is repressed and conversely how *Cd4* and *Thpok* expression is stably maintained in helper T cells. Current studies have unraveled an unappreciated developmental plasticity retained in CD4<sup>+</sup> T cells, which allow them to reactivate the program to become cytotoxic-related property. When CD4<sup>+</sup> T cells are transferred into lympho-deficient host mice, a proportion of these cells exposed to gut-specific environmental cues reexpress CD8 $\alpha$  chain and become CD4<sup>+</sup>CD8 $\alpha\alpha$ <sup>+</sup> cells that also express other cytotoxic-related genes (Mucida et al. 2013; Reis et al. 2013). Prior to such a dressing up with cytotoxic features, ThPOK expression is vanishing, while Runx3 expression is induced. Continuous expression of ThPOK using retroviral expression vectors prevents this reprogramming, confirming that ThPOK downregulation is essential for the acquisition of cytotoxic features. Similar to the initial lineage selection in the thymus, the *Thpok* silencer is also involved in erasing *Thpok*

expression in the gut (Mucida et al. 2013). Thus, an antagonistic cross-regulation between ThPOK and Runx3 also regulates the maintenance of CD4 lineage identity in peripheral lymphoid organs.

## ***2.4 MAZR/Patz1: Part of the Transcription Factor Network that Controls CD4/CD8 Lineage Choice***

MAZR (Myc-associated Zn finger related)/Patz1 [POZ (BTB) and AT hook containing ZF 1], encoded by the *Patz1* gene, has been first described as an interacting partner of Bach2 (Kobayashi et al. 2000), which is a B cell-specific transcriptional repressor involved in antibody class switching (Muto et al. 2004) and that has also been shown to function in T cells (Hu and Chen 2013; Roychoudhuri et al. 2013; Tsukumo et al. 2013). In humans, PATZ1 has been identified as a factor interacting with the Ring finger protein RNF4, a mediator of androgen receptor activity (Fedele et al. 2000). It was described that MAZR/Patz1 activates several promoters (Kobayashi et al. 2000; Morii et al. 2002); however, it also functions as a transcriptional repressor (Fedele et al. 2000; Bilic et al. 2006; Sakaguchi et al. 2010; Abramova et al. 2013). This indicates context- and gene loci-dependent transcriptional activation and repression functions of MAZR/Patz1. Mice with a germline deletion of MAZR/Patz1 are embryonic lethal on a C57BL/6 background due to defects in the CNS and in the cardiac outflow tract. The MAZR/Patz1-null mice on a mixed 129 Sv/C57BL/6 background are born at reduced Mendelian ratio and are smaller in size (Sakaguchi et al. 2010; Valentino et al. 2013). This indicates important functions for MAZR/Patz1 during embryonic development, differentiation, and proliferation. Moreover, MAZR/Patz1 is linked with oncogenesis, since MAZR/Patz1-deficient mice develop Bcl6-dependent lymphomas (Pero et al. 2012). Moreover, MAZR/Patz1 is also involved in the regulation of embryonic stem cell identity (Ow et al. 2013). During T cell development it was shown that MAZR/Patz1 interacts in DN thymocytes with several *Cd8 cis*-regulatory elements. MAZR/Patz1 is expressed at high levels in DN thymocytes and downregulated at later stages of developing T cells. MAZR/Patz1, like other BTB-ZF proteins, interacts with the nuclear coreceptor NCoR1 and enforced expression of MAZR/Patz1 during T cell development impairs the activation of CD8 expression in a proportion of DP thymocytes, resulting in a variegated expression of CD8 (Bilic et al. 2006). This indicates that MAZR/Patz1 is part of a transcriptional complex that represses CD8 in DN cells and that downregulation of MAZR/Patz1 is necessary for the proper activation of the *Cd8ab* gene complex during the DN to DP transition.

The generation of MAZR/Patz1-deficient mice combined with *Mazr*<sup>+/+</sup> and *Mazr*<sup>-/-</sup> fetal liver transfer experiments into recipient mice revealed that MAZR/Patz1 is also part of the transcription factor network that controls CD4/CD8 cell fate choice of DP thymocytes (Sakaguchi et al. 2010). In the absence of MAZR/Patz1,

a fraction of MHC class I-signaled DP thymocytes redirects into CD4 lineage T cells instead of developing into the CD8 lineage. A detailed molecular and genetic analysis of MAZR/Patz1-deficient mice revealed that MAZR/Patz1 represses ThPOK, the master commitment factor of CD4 lineage differentiation. As described above, ThPOK expression leads to the development of CD4 lineage cells, while repression of ThPOK is essential for CD8 lineage differentiation. In the absence of MAZR/Patz1, ThPOK is derepressed in a fraction of MHC class I-signaled CD4<sup>+</sup>CD8<sup>lo</sup> thymocytes, leading to the redirection of CD8<sup>+</sup> T cells into the CD4 lineage. Interestingly, MAZR/Patz1 interacts with Runx complexes (Sakaguchi et al. 2010), which are essential for the repression of ThPOK (Setoguchi et al. 2008). This suggests that MAZR/Patz1 and Runx complexes together are required to repress ThPOK expression during CD8 lineage differentiation. Moreover, a fraction of peripheral MAZR/Patz1-null CD8<sup>+</sup> T cells derepressed ThPOK (Sakaguchi et al. 2010), suggesting that MAZR/Patz1 has also a role in regulating peripheral CD8<sup>+</sup> T cell function.

## ***2.5 PLZF: A Key Regulator of NKT Cells and Other Innate-like T Cells***

PLZF (promyelocytic leukemia ZF), encoded by the *Zbtb16* gene, was initially identified as target of chromosomal translocations that lead to the development of acute promyelocytic leukemia (Chen et al. 1993; Suliman et al. 2012). Subsequent studies following the generation of PLZF-deficient mice (Costoya et al. 2004) revealed important functions for PLZF in many biological processes such as renewal of germ stem cell and spermatogenesis, skeletal patterning, and also in the hematopoietic system (Costoya et al. 2004; Suliman et al. 2012). Moreover, a nonsense mutation in the *Zbtb16* gene is the molecular cause of the luxoid phenotype in mice (Buaas et al. 2004).

Several studies have shown that PLZF is important for the development of innate-like T cells, a subset of T cells that is characterized by having a CD44<sup>hi</sup> expression phenotype and by displaying immediate effector functions such as the rapid release of cytokines upon activation (Lee et al. 2011). In contrast to “classical” CD44<sup>hi</sup> effector/memory T cells, innate-like T cells acquired their effector phenotype during their development and not in response to antigen stimulation. Certain innate-like T cells are derived from DP thymocytes and at least some of these cells can be selected on nonclassical MHC class Ib molecules (Rodgers and Cook 2005) via interaction with hematopoietic cells rather than with thymic epithelial cells (Urdahl et al. 2002). Innate-like T cell subsets include, among others, iNKT cells, H2-M3-specific T cells (Colmone and Wang 2006; Mir and Sharma 2013), mucosal-associated invariant T (MAIT) cells (Treiner and Lantz 2006; Le Bourhis et al. 2013), and certain  $\gamma\delta$ TCR<sup>+</sup> T cell subsets. PLZF received a lot of attention in the field of T cell biology when it was shown that PLZF plays an

important role for the development and function of iNKT cells (Kovalovsky et al. 2008; Savage et al. 2008). Although loss of PLZF did not change the development of conventional T cells, loss of PLZF led to severely reduced numbers of iNKT cells in the thymus, spleen, and liver. The PLZF-null iNKT cells that emerged showed impaired effector function and were preferentially redistributed to lymph nodes (Kovalovsky et al. 2008; Savage et al. 2008). In contrast, enforced transgenic expression of PLZF in conventional T cells (which do not express PLZF) induced an effector phenotype (Raberg et al. 2008; Savage et al. 2008; Kovalovsky et al. 2010) and led to a migration of T cells into peripheral tissues such as lung and liver (Savage et al. 2008). This links PLZF expression with the regulation of an effector program and effector function, a process regulated by PLZF in association with the E3 ligase cullin 3 (Mathew et al. 2012), although the molecular details about how PLZF regulates target genes are largely unknown.

PLZF expression has been observed in other innate-like T cell subsets such as  $V\gamma 1.1^+V\delta 6.3^+$  TCR expressing T cells in the mouse (Alonzo et al. 2010; Felices et al. 2009; Kreslavsky et al. 2009) and MAIT cells (Savage et al. 2008) and unconventional  $CD4^+$  T cells that are selected on MHC class II-dependent thymocyte–thymocyte interactions in the human (Lee et al. 2010). A surprising role for PLZF and PLZF-expressing T cell subsets for the proper regulation of T cell development was demonstrated in studies that analyzed several mutant mouse mice that have increased numbers of  $CD8^+$  T cells with innate-like T cell characteristics (Alonzo and Sant'Angelo 2011; Lee et al. 2011). Mice deficient for Itk (Atherly et al. 2006; Broussard et al. 2006), Klf2 (Weinreich et al. 2009; Weinreich et al. 2010), CBP (Fukuyama et al. 2009) or Id3 (Verykokakis et al. 2010) develop large numbers of innate-like  $CD8^+$  T cells. However, these developmental alterations are not intrinsic to the developing innate-like  $CD8^+$  T cells but are caused due to IL-4-producing PLFZ $^+$  T cell subsets including NKT cells and  $\gamma\delta$ TCR $^+$  T cells that are enhanced in the absence of Itk, Klf2, CBP, and Id3 (Weinreich et al. 2010; Verykokakis et al. 2010). In the absence of PLZF or IL-4 signaling, the development of the innate-like T cell phenotype is reverted and Itk-, KLF2-, CBP-null mice (Weinreich et al. 2010), or *Id3* $^{-/-}$  mice (Verykokakis et al. 2010) have a normal appearance of naïve  $CD8^+$  T cells.

## 2.6 ROG/PLZP: Regulating T Cell Activation and Th2 Cytokine Production

The transcription factor ROG (repressor of GATA)/PLZP (PLZF-like zinc finger protein), which is encoded by the *Zbtb32* gene, was isolated in a search for factors that interact with GATA-3 (Miaw et al. 2000), which is a key regulator of early T cell development, the specification of the  $CD4$  T cell lineage and for Th2 cell differentiation (Hosoya et al. 2010). ROG/PLZP, also known as TFZP (Lin et al. 1999) and FAZF (Hoatlin et al. 1999) is expressed, if at all, at very low levels in

the thymus, spleen and in non-stimulated T cells. However, ROG/PLZP is transiently induced within 24 h under Th1 and Th2 polarizing conditions and reinduced upon anti-CD3 restimulation (Miaw et al. 2000, 2004). Early studies showed that enforced expression of ROG/PLZP in established Th2 cell clones inhibits cytokine expression, further indicating a repressive role via GATA-3 inhibition. ROG/PLZP inhibited also IFN $\gamma$  expression in Th1 cell clones (Miaw et al. 2000), thus ROG/PLZP might regulate other transcription factors in addition to GATA-3. Subsequent studies revealed that ROG/PLZP regulates also T cell proliferation upon TCR triggering independent of GATA-3 activity (Kang et al. 2005; Miaw et al. 2004; Piazza et al. 2004). ROG/PLZP has been shown to be a target gene of NFATc2 (Miaw et al. 2004). NFATc2-deficient CD4<sup>+</sup> T cells display a hyperproliferative phenotype with increased production of IL-4 (Xanthoudakis et al. 1996; Hodge et al. 1996). NFATc2-null T cells failed to fully upregulate ROG/PLZP and transgenic expression of ROG/PLZP attenuated the hyperproliferation observed in NFATc2-deficient CD4<sup>+</sup> T cells, while expression of ROG/PLZP in wild-type CD4<sup>+</sup> T cells only modestly interfered with the proliferation upon anti-CD3/anti-CD28 stimulation (Miaw et al. 2004). Thus, ROG/PLZP might be part of a NFATc2-mediated negative feedback mechanism that controls the extent of T cell activation.

The proposed role of ROG/PLZP in T cell proliferation and cytokine production has been confirmed by the generation and analysis of *Zbtb32*<sup>-/-</sup> mice. ROG/PLZP-deficient mice are born at normal Mendelian ratio and show no gross developmental or pathological alterations. ROG/PLZP-null T cells have an increased proliferative response to anti-CD3 stimulation and produce increased levels of IL-2 due to enhanced NF- $\kappa$ B activity (Kang et al. 2005). Surprisingly, ROG/PLZP-deficient T cells differentiated normally into Th1 or Th2 cells in vitro with only a modest elevation of cytokine expression. However, Nakayama and colleagues showed that ROG/PLZP-deficient mice have enhanced allergic airway inflammation accompanied with an increase in Th2 cytokines in the bronchoalveolar lavage, while transgenic mice expressing exogenously ROG in the T cell lineage showed reduced allergic airway inflammation (Hirahara et al. 2008). The effect was intrinsic to T cells, since adoptive transfer of OVA-primed ROG/PLZP-null CD4<sup>+</sup> T cells or of OVA-primed transgenic ROG/PLZP-expressing CD4<sup>+</sup> T cells into OVA-primed wild-type mice enhanced or attenuated eosinophil numbers in the inflamed lung, respectively (Hirahara et al. 2008). Moreover, ROG/PLZP inhibits also type-2 allergic responses in a contact hypersensitivity model (Hirasaki et al. 2011). Together, these studies demonstrate a crucial in vivo role for ROG/PLZP in Th2-type-mediated diseases. Whether ROG/PLZP is also important for Th1 and Th17-type immune responses in vivo is not clear. ROG/PLZP-deficient mice have a similar incidence and clinical score in EAE, indicating that Th1/Th17-mediated immune responses are not severely affected by loss of ROG/PLZP (Kang et al. 2005). Further studies are needed to reveal potential functions of ROG/PLZP beyond Th2-type immune responses.



Of note, ROG/PLZP represses GATA-3-mediated transactivation in Th2 cells by preventing, at least in part, GATA-3 binding to DNA (Miaw et al. 2000). However, ROG/PLZP might also use different cell-type specific mechanisms to repress target genes independently of GATA-3. CD8<sup>+</sup> T cells that are activated under Th2-polarizing conditions (Tc2 cells; Kelso and Groves 1997; Seder et al. 1992) produce Th2-type cytokines such as IL-4, IL-5, and IL-13, although IL-4 expression is lower than in Th2 cells (Croft et al. 1994) and cannot be enhanced by overexpression of GATA-3 (Miaw et al. 2004). ROG/PLZP is expressed at much higher levels in Tc2 cells compared to Th2 cells. ROG/PLZP binds to a so-called ROG responsive element within the 3'-UTR of the *Il13* gene, which is in close proximity upstream to the *Il4* gene locus. This *cis*-regulatory region is also bound by HDAC1 and HDAC2, and binding of ROG/PLZP, HDAC1, and HDAC2 correlated with diminished acetylation of the *Il4* gene locus in Tc2 cells in comparison to Th2 cells (Miaw et al. 2004). This suggests that the recruitment of ROG/PLZP together with HDACs and potentially other components of corepressor complexes in Tc2 cells leads to a weakened expression of IL-4 in Tc2 cells.

Taken together, ROG/PLZP is a crucial factor in the regulation of Th2 immune responses in vivo.

## 2.7 *LRF/Zbtb7a: Controlling ThPOK-Independent Helper Functions*

The transcription factor LRF/Zbtb7a (Leukemia/lymphoma Related Factor; known previously as Pokemon), encoded by the *Zbtb7a* gene, regulates many lineage decisions during hematopoiesis and plays a role in the maturation and differentiation of peripheral B cells. Moreover, LRF/Zbtb7a has important functions during oncogenic transformation (Lunardi et al. 2013). *Zbtb7a*<sup>-/-</sup> mice are embryonic lethal and die around day 16 due to severe anemia (Maeda et al. 2007). The analysis of conditional *Zbtb7a*<sup>fl/fl</sup> mice in which *Zbtb7a* was inducible deleted by Mx-Cre implicated LRF/Zbtb7a in the regulation of B versus T cells choice, since DP thymocytes developed in the BM at the expense of B cells upon deletion of LRF/Zbtb7a (Maeda et al. 2007). This phenotype is reminiscent to the phenotype of mice that expresses a constitutively active form of Notch (Pui et al. 1999), suggesting that LRF/Zbtb7a might antagonize Notch signaling. A later study demonstrated that aberrant T cell development in the BM in the absence of LRF/Zbtb7a is due to the upregulation of Notch ligand Delta-4 on erythroblasts, which leads to a premature differentiation of hematopoietic stem cells toward T cells (Lee et al. 2013a). This indicates that loss of LRF/Zbtb7a indirectly affects B versus T cell choice.

In the T cell lineage, LRF/Zbtb7a is expressed at low levels in DP thymocytes and is upregulated to much higher levels in CD4SP and CD8SP thymocytes and in peripheral T cells (Carpenter et al. 2012). However, deletion of LRF/Zbtb7a using



*Cd4-Cre* did not lead to any alterations during T cell development (Carpenter et al. 2012). A surprising role for LRF/Zbtb7a in the control of Th cell-specific gene expression was identified by Bosselut and colleagues when T-helper immune responses were analyzed in ThPOK-deficient mice (Carpenter et al. 2012). As described above, ThPOK/Zbtb7b, to which LRF/Zbtb7a is closely related, is a key commitment factor for the CD4 T cell lineage. In the absence of ThPOK, MHC class II-restricted thymocytes are redirected into CD8<sup>+</sup> T cells (Keefe et al. 1999) and a fraction of these cells reexpressed CD4 upon activation (Carpenter et al. 2012). Moreover, ThPOK-null mice are able to mount a Th1-type T-helper response upon *Leishmania major* infection (Carpenter et al. 2012). This indicates that ThPOK is not essential for the maintenance of some Th cell functions and that other factors might be responsible for compensating ThPOK function or controlling ThPOK-independent Th functions. The analysis of conditional ThPOK and LRF/Zbtb7a double-deficient mice revealed that ThPOK-independent Th functions are dependent on LRF/Zbtb7a (Carpenter et al. 2012), suggesting that ThPOK/Zbtb7b and LRF/Zbtb7a have in part redundant functions in maintaining Th cell-specific gene expression.

## 2.8 BAZF/Bcl6b: Regulating Memory CD8<sup>+</sup> T Cells

BAZF (Bcl6-associated ZF protein, also known as Bcl6b), encoded by the *Bcl6b* gene, is a transcriptional repressor that was identified due to the very high homology to Bcl6 (Okabe et al. 1998). BAZF/Bcl6b and Bcl6 bind to the same target sequences that partially overlap with the STAT6 binding sites, suggesting that BAZF/Bcl6b and Bcl6 may repress some STAT-mediated transcription by binding to STAT binding sites (Hartatik et al. 2001). Bcl6 and BAZF/Bcl6b are able to bind to each other and this interaction with Bcl6 appears to be essential for the repressive function of BAZF/Bcl6b (Takenaga et al. 2003). BAZF/Bcl6b does not bind directly nuclear corepressor complexes, thereby BAZF/Bcl6b might recruit corepressor complexes via its association with Bcl6 (Takenaga et al. 2003). Whether other BTB-ZF proteins are able to interact with BAZF/Bcl6b has not been reported. BAZF/Bcl6b expression is restricted to heart, lung, and activated splenocytes (Okabe et al. 1998). Later studies showed that BAZF/Bcl6b is expressed in CD4SP and CD8SP thymocytes and in peripheral activated CD4<sup>+</sup> T cells (Takamori et al. 2004) and in memory CD8<sup>+</sup> T cells (Manders et al. 2005). BAZF/Bcl6b is implicated in the regulation of angiogenesis in wound healing (Ohnuki et al. 2012); however, not much is known about the function outside the hematopoietic system.

A hint about the role of BAZF/Bcl6b in T cells was provided with the analysis of BAZF/Bcl6b knockout mice, which were independently generated by three research groups. BAZF/Bcl6b-deficient mice are viable, fertile, and display no gross abnormalities (Takamori et al. 2004; Manders et al. 2005; Broxmeyer et al. 2007). Tokuhisa and colleagues focused on the analysis of CD4<sup>+</sup> T cells. T cell

development is normal in the absence of BAZF/Bcl6b and there is also a normal distribution of peripheral naïve and memory CD4<sup>+</sup> and CD8<sup>+</sup> T cell subsets. However, BAZF/Bcl6b-deficient CD4<sup>+</sup> T cells show reduced proliferation upon anti-CD3 stimulation and impaired IL-2 production. In contrast, transgenic Bcl6b-expressing CD4<sup>+</sup> T cells showed an increase proliferative response upon anti-CD3 stimulation (Takamori et al. 2004). The proliferation of CD44<sup>hi</sup> effector/memory CD4<sup>+</sup> T cells is not affected by gain or loss of BAZF/Bcl6b function, suggesting that BAZF/Bcl6b functions specifically during the activation of naïve T cells (Takamori et al. 2004). Fearon and colleagues analyzed the role of BAZF/Bcl6b during the secondary response of memory CD8<sup>+</sup> T cells, since CD44<sup>hi</sup> CD8<sup>+</sup> T cells expressed higher levels of BAZF/Bcl6b compared to CD44<sup>lo</sup> CD8<sup>+</sup> T cells (Manders et al. 2005). Enforced expression of BAZF/Bcl6b reduced the growth of CD8<sup>+</sup> T cells in response to IL-2 (Manders et al. 2005). Using a vaccinia virus and an influenza infection model it was shown that BAZF/Bcl6b-deficient mice have normal primary CD8<sup>+</sup> T cell responses. However, CD8<sup>+</sup> memory T cells were unable to induce IL-2 and to generate effector cells after in vitro restimulation and the magnitude of the memory response in vivo was reduced (Manders et al. 2005). These data suggest that BAZF/Bcl6b has a nonredundant role in controlling the secondary response of CD8<sup>+</sup> memory T cells. Dent and colleagues generated another strain of BAZF/Bcl6b-deficient mice (Broxmeyer et al. 2007). The authors focused on the role of BAZF/Bcl6b in hematopoiesis and found that the numbers of cycling hematopoietic progenitor cells (HPC) were reduced in the BM of BAZF/Bcl6b-null mice, while the numbers of cycling HPC in the spleen were increased upon loss of BAZF/Bcl6b. Depletion experiments revealed that the enhanced population of HPC in the spleen is due to the presence of BAZF/Bcl6b-null CD8<sup>+</sup> T cells. Thus, it is likely that BAZF/Bcl6b-null CD8<sup>+</sup> T cells produce a cytokine or other soluble factors that interfere with the function of HPC. Further studies are required to understand this in more detail.

## 2.9 *Bcl6: Regulating B and T Lymphocytes*

The proto-oncogene Bcl6 (B cell leukemia/lymphoma 6), encoded by the *Bcl6* gene, has been initially identified as a gene that is frequently translocated in B cell lymphomas (Ye et al. 1993, 1995). Bcl6 has important functions in B cells and is essential for germinal center (GC) B cell formation (Dent et al. 1997; Ye et al. 1997). Bcl6 is expressed at high levels in GC B cells and it represses target genes important for the terminal differentiation of B cells into plasma cells, such as Blimp-1 (Shaffer et al. 2000). Bcl6 represses also p53 in GC B lymphocytes and modulates DNA damage-induced apoptosis in GC B cells (Phan and Dalla-Favera 2004), suggesting that Bcl6 contributes to lymphomagenesis in part by the suppression of p53 (for reviews on the role of Bcl6 in B cells and in B cell lymphomas, see Ci et al. 2008; Basso and Dalla-Favera 2012; Bunting and Melnick 2013).

The analysis of *Bcl6*<sup>-/-</sup> mice indicated that Bcl6 has also important functions in the T cell lineage. Bcl6 is a crucial regulator of the differentiation of follicular helper T cells (Tfh), which are an important T cell subset essential for the generation and function of GC B cells (Vinuesa and Cyster 2011; Crotty 2011). Bcl6 is expressed at high levels in Tfh and Bcl-6-deficient T cells failed to differentiate into Tfh cells (Johnston et al. 2009; Nurieva et al. 2009; Yu et al. 2009; Liu et al. 2012). Further, Bcl6-null CD4<sup>+</sup> T cells failed to induce GC responses (Nurieva et al. 2009; Johnston et al. 2009) and Bcl6-null mice show enhanced differentiation of other Th subsets. In contrast, enforced expression of Bcl6 induces key Tfh molecules such as CXCR5 and PD-1 but inhibits the differentiation of Th1, Th2, and Th17 cells (Yu et al. 2009), although another study suggest that Bcl6 might have a positive role for the generation of Th17 cells (Mondal et al. 2010). More recent data using conditional targeting approaches confirmed the importance of Bcl6 for the generation of Tfh in vivo and indicated also a role for Bcl6 in the regulation of Tfh survival (Hollister et al. 2013).

Bcl6 has also been implicated in regulating Treg function. Bcl6-null Treg cells were able to suppress T cell responses in vitro and in a Th1-type colitis model in vivo. However, *Bcl6*<sup>-/-</sup> Tregs failed to suppress Th2-type immune responses in vivo leading to strong lung inflammation in an allergic airway inflammation model (Sawant et al. 2012). It has been shown that Bcl6 repressed Th2-type genes in Tregs by impairing the transcriptional activity of Gata3. In the absence of Bcl6, Treg acquires certain Th2 effector functions (Sawant et al. 2012). This might contribute to the enhanced Th2 responses and Th2-type inflammation observed in *Bcl6*<sup>-/-</sup> mice, which develop at a high frequency myocarditis and pulmonary vasculitis due to infiltration of eosinophils contributing to the early death of about 50 % of *Bcl6*<sup>-/-</sup> mice (Dent et al. 1997; Ye et al. 1997). However, increased differentiation of Th1, Th2, and Th17 cells as observed in Bcl6-null mice was not observed upon T cell-specific deletion of Bcl6 (Hollister et al. 2013). This indicates that T cell-extrinsic factors might regulate enhanced Th subset differentiation upon germline deletion of Bcl6. In addition, a subset of Bcl6-dependent follicular CXCR5-expressing Foxp3<sup>+</sup> regulatory T cells as well as CXCR5<sup>+</sup> follicular NKT cells have been described and implicated in the regulation of the GC reaction (Chung et al. 2011; Linterman et al. 2011).

Bcl6 also plays a role in the generation and maintenance of CD8<sup>+</sup> memory T cells, in particular central memory T cells (Ichii et al. 2002, 2004). *Bcl6*<sup>-/-</sup> mice display reduced numbers of central memory T cells, while transgenic expression of Bcl6 leads to increased numbers of central memory T cells and Bcl6 transgenic T cells display enhanced proliferation upon restimulation. Moreover, Bcl6 is important for the generation of long-term memory CD4<sup>+</sup> T cells, probably via regulating survival of memory precursor CD4<sup>+</sup> T cells (Ichii et al. 2007). Thus, Bcl6 is an important regulator of both CD4<sup>+</sup> and CD8<sup>+</sup> memory T cell generation and homeostasis.

### 3 Conclusion

Members of the BTB-ZF family have been implicated in the development of human diseases such as B cell lymphomas and promyelocytic leukemia for over 20 years and the crucial role of some of these factors in B cells was soon thereafter established. During the last 10 years, BTB-ZF factors received a lot of immunological attention also from T cell biologists and these studies revealed important roles for BTB-ZF factors in the T cell lineage from early stage T cell progenitors until the formation of memory T cells during an immune response. Several important questions about this gene family remain to be addressed. To comprehensively understand how BTB-ZF factors modulate the immune systems, novel tools such as reporter mice for BTB-ZF factors are required to identify immune cell subsets that potentially might be controlled by these factors. Moreover, at a molecular level, it will be important to characterize protein complexes that together with BTB-ZF factors regulate target gene expression. This will reveal whether some BTB-ZF factors share certain interacting partners and/or whether unique interacting partners exist and also how posttranslational modifications of BTB-ZF factors regulate their activity. A better description of these interacting networks will help to understand why BTB-ZF factors act at certain gene loci as transcriptional repressors, while other genes loci are activated by BTB-ZF factors. Finally, it can be expected that the identification of genome-wide target genes using ChIP-seq and RNA-seq approaches and the functional analysis of pathways regulated by the various members of the BTB-ZF family will provide novel insight into regulatory circuits that control T cell development and function. This will also help to better understand the role of BTB-ZF factors in hematopoietic cells beyond the T cell lineage. Since mutations in ZBTB24 were identified in patients suffering with immunodeficiency, centromeric instability, and facial anomalies syndrome type 2 (ICF2) (de Greef et al. 2011; Chouery et al. 2012; Nitta et al. 2013), this might also provide insight into the molecular cause of human immunodeficiencies.

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