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Effectors and memories: Bcl-6 and Blimp-1 in T and B lymphocyte differentiation

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Abstract

Bcl-6 and Blimp-1 have recently been identified as key transcriptional regulators of effector and memory differentiation in $CD4^+$ T cells and $CD8^+$ T cells. Bcl-6 and Blimp-1 were previously known to be critical regulators of effector and memory differentiation of B lymphocytes. The new findings unexpectedly point to the Bcl-6 and Blimp-1 regulatory axis as a ubiquitous mechanism for controlling effector and memory lymphocyte differentiation and function. Bcl-6 and Blimp-1 are antagonistic transcription factors and can function as a self-reinforcing genetic switch for cell-fate decisions. However, their influences in different lymphocytes are complex. Here we review and examine the commonalities and differences in the functions of these transcription factors in $CD4^+$ follicular helper T_{FH} lymphocytes, effector $CD8^+$ T lymphocytes and B lymphocytes.

$CD4^+$ T cells, $CD8^+$ T cells and B cells are distinct lymphocyte populations with unique, critical roles in adaptive immunity. Each population has been thought to be controlled by quite different transcriptional regulation for its individual effector and memory differentiation programs[1]. Bcl-6 and Blimp-1 (encoded by *Prdm1*) are transcriptional repressors with the ability to block each other's expression (Fig. 1). The recent identification of central roles for Bcl-6 and Blimp-1 in the differentiation of follicular helper $CD4^+$ T cells[2–4] and $CD8^+$ T cell effector and memory differentiation processes[5–7], combined with their well documented roles in B cells, has revealed an unexpected common system used in key fate decisions made by mature $CD4^+$ T cells, $CD8^+$ T cells and B cells.

Bcl-6 and Blimp-1 in B cell differentiation

Bcl6 was first identified as a proto-oncogene frequently expressed in non-Hodgkin's lymphoma as a result of chromosomal translocations[8–12]. Bcl-6 protein was found to be highly expressed in germinal center B cells, which led to the conclusion that many B cell lymphomas begin as germinal center B cells that then acquire dysregulated Bcl-6 expression[11]. The germinal center reaction is the process by which antigen-specific B cells mature into the long-lived plasma cells (antibody-secreting cells) and memory B cells that constitute the cellular components of immunological memory for the B cell lineage[1,13] (Fig. 2). After activation and costimulation, B cells differentiate into either short-lived plasma cells or germinal center B cells[1,14] (Fig. 2).

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Short-lived plasma cells stop proliferating and elaborate a large secretory apparatus for producing antibodies to quickly combat infection[1,14]. In contrast, germinal center B cells have a minimal secretory apparatus and are instead specialized for proliferation and affinity maturation, the exquisitely complex process of rapidly evolving a B cell receptor of higher affinity for the production of high-affinity, isotype-switched antibody[11,15]. This process involves rapid proliferation and substantial amounts of DNA damage (both class-switch recombination and somatic hypermutation, controlled by activation-induced cytidine deaminase (AID)[16]). Bcl-6 is a crucial inducer of germinal center B cell proliferation and a crucial inhibitor of the DNA-damage response[11] (Figs. 1 and 2). Bcl-6-deficient mice have an absence of germinal center B cells and affinity maturation[17–19]. Bcl-6-deficient B cells are nevertheless able to differentiate into plasma cells and secrete antibodies[18,20], although long-term antibody responses in *Bcl6*$^{-/-}$ mice are considerably diminished, as the germinal center reaction is required to produce the majority of long-lived plasma cells[19] (Fig. 2). Constitutive expression of Bcl-6 in B cells *in vivo* results in large germinal centers, which again confirms the central role of Bcl-6 in germinal center B cell differentiation[21].

Plasma cell differentiation, in contrast, critically depends on Blimp-1 ([refs. 22,23]) and the absence of Bcl-6 ([refs. 11,23]). The role of Blimp-1 in B cell development was first demonstrated by the ability of ectopic Blimp-1 expression to induce human B lymphoma cells to differentiate into cells with plasma cell features[24]. Blimp-1 is highly expressed in plasma cells and controls many genes important for plasma cell differentiation[23,25–27], including *Xbp1*, which induces formation of the secretory apparatus necessary for the production of large amounts of antibody[28,29]. Blimp-1 also inhibits genes involved in cellular proliferation, such as *Myc* and *Bcl6*, which thereby allows the terminal differentiation of plasma cells into a post-mitotic state[23,30].

Genetic ablation of Blimp-1 in B cells prevents mature B cells from differentiating into either short-lived or long-lived plasma cells, which results in dramatically reduced antibody titers[22]. Interestingly, germinal centers are enlarged in these mice, and memory B cells are generated[22]. Together with experiments using ectopic expression of Blimp-1, these data suggest that Blimp-1 is a master regulator of plasma cell differentiation with limited or no roles in germinal center B cell and memory B cell differentiation (Fig. 2).

Bcl-6 protein can bind to *Prdm1* and directly repress Blimp-1 expression[20,31,32] (Fig. 1) and thereby induce germinal center differentiation while inhibiting plasma cell differentiation[11]. Conversely, Blimp-1 protein can bind to *Bcl6* and directly repress Bcl-6 production[33] (Fig. 1) and thereby induce plasma cell differentiation while inhibiting germinal center B cell differentiation[23,25]. Although details about the kinetics of the expression of Bcl-6 and Blimp-1 during B cell activation and differentiation *in vivo* still remain to be fully elucidated[25,34], the reciprocal antagonism between Bcl-6 and Blimp-1 clearly provides a powerful mechanism for inducing and then reinforcing bimodal fate ‘decisions’ in B cell effector and memory differentiation.

Bcl-6 and Blimp-1 in CD4$^+$ T cell differentiation

Although Bcl-6 and Blimp-1 have been studied intensively in B cells for some 15 years, the functions of Bcl-6 and Blimp-1 in T lymphocytes remained relatively unexplored until recently[25]. A series of new data has now demonstrated that Bcl-6 is the master regulator of CD4$^+$ follicular helper T cells (T_{FH} cells)[2–4] and that Blimp-1 is a critical antagonist of T_{FH} differentiation[2].

CD4$^+$ T cells can differentiate into at least four different effector lineages (T helper type 1 (T_H1) cells, T_H2 cells, T_H17 cells and regulatory T cells (T_{reg} cells)), which allows them to powerfully tailor the larger immune response to best clear a given infection or control

inflammation[35]. $CD4^+$ T cell help to B cells is essential for the generation of germinal centers, memory B cells and long-lived plasma cells[1]. $CD4^+$ T_H2, T_H1 and T_H17 cells are not required for germinal center formation or B cell help[36–38]. Therefore, it had been proposed, mainly on the basis of gene-expression profiling and *in vitro* T cell help–B cell help assays, that T_{FH} may represent a distinct $CD4^+$ T cell effector lineage specialized for B cell help[39–41]. However, unlike the other effector lineages, until recently T_{FH} cells had no lineage-specifying master regulator transcription factor (such as T-bet, GATA-3, RORγt or Foxp3)[42].

Three new studies have now shown that Bcl-6 is a master regulator of T_{FH} differentiation[2–4]. Constitutive expression of Bcl-6 in $CD4^+$ T cells drives nearly absolute T_{FH} differentiation *in vivo*[2]. These T_{FH} cells induce larger germinal centers and higher antigen-specific antibody titers[2]. In contrast, *Bcl6*$^{-/-}$ $CD4^+$ T cells are unable to differentiate into T_{FH} cells *in vivo*, which demonstrates that Bcl-6 is necessary for T_{FH} differentiation[2–4]. *Bcl6*$^{-/-}$ $CD4^+$ T cells become activated and proliferate in response to protein immunization but are unable to drive germinal center formation[2–4]. These results confirm that T_{FH} cells are a distinct subset of helper $CD4^+$ T cells, reveal that Bcl-6 is a T_{FH} master regulator both necessary and sufficient for T_{FH} differentiation, and demonstrate that T_{FH} cells are uniquely able to drive the germinal center reaction.

Interestingly, although T_{FH} cells have high Bcl-6 expression[42], the remaining antigen-specific $CD4^+$ T cells (non-T_{FH} cells) have high Blimp-1 expression [2,43,44], which indicates that Bcl-6 versus Blimp-1 expression may be a central cell fate decision of differentiating $CD4^+$ T cells. Constitutive expression of Blimp-1 blocks Bcl-6 expression and T_{FH} differentiation but does not block the proliferation and differentiation of non-T_{FH} $CD4^+$ cells[2]. Like *Bcl6*$^{-/-}$ $CD4^+$ T cells, Blimp-1-expressing $CD4^+$ T cells cannot induce germinal center formation, which results in considerably reduced antibody titers[2]. Conversely, Blimp-1-deficient $CD4^+$ T cells preferentially differentiate into T_{FH} cells *in vivo*[2]. Therefore, in $CD4^+$ T cells, Blimp-1 is a physiological regulator of Bcl-6 expression, and vice versa[2].

There are two models for interpreting the Bcl-6 and Blimp-1 results outlined above in the context of $CD4^+$ T cell lineage differentiation (Fig. 3a,b). The simplest model proposes that T_{FH} differentiation occurs via a fully independent differentiation pathway controlled by Bcl-6, analogous to the differentiation pathways for T_H1, T_H2, T_H17 and inducible T_{reg} (iT_{reg}) cells[37] (model 1; Fig. 3a). A second model posits that T_{FH} cells are a distinct type of effector $CD4^+$ T cell but that the T_{FH} differentiation pathway is not fully independent of T_H1, T_H2, T_H17 or iT_{reg} differentiation[2,45] (model 2; Fig. 3b). In this second model, a $CD4^+$ T cell is primed by a dendritic cell and acquires early T_H1, T_H2, T_H17, iT_{reg} or unbiased T_H0 cell characteristics (Fig. 3b). The primed $CD4^+$ T cell (early effector) can then further polarize into a Blimp-1^{hi} full effector T_H1 cell[2], T_H2 cell[2,43], T_H17 cell or iT_{reg} cell[46] (Fig. 3b). Alternatively, the primed $CD4^+$ T cell may encounter a B cell—which induces high Bcl-6 expression—and differentiate into a T_{FH} cell (Fig. 3b). In support of model 1, there is evidence that Bcl-6 can inhibit T_H1, T_H2 and/or T_H17 gene expression[3,4,17,47], and this model fits well with conventional helper T cell schematics. However, several lines of evidence indicate that the second model is probably a more accurate representation of the *in vivo* biology. First, T_{FH} cells produce T_H1 cytokines[2,48–50], T_H2 cytokines,[43,48,50–52] or T_H17 cytokines[53]. The production of T_H1, T_H2 or T_H17 cytokines probably enables T_{FH} cells to specify the antibody isotypes produced during the B cell response[50]. Nevertheless, T_{FH} cells produce lower amounts of T_H1, T_H2 or T_H17 cytokines than do non-T_{FH} cells[2,4,43], which express Blimp-1 ([refs. 2, 43]). Therefore, Bcl-6-expressing T_{FH} cells seem to have some T_H1, T_H2 or T_H17 characteristics acquired at the initial dendritic cell priming (Fig. 3b), but those characteristics are partially subdued in the presence of Bcl-6. Second, dendritic cell priming is insufficient for T_{FH} differentiation *in vivo*, as T_{FH} cells are not observed in the absence of cognate B cells[2,54], which indicates that the interaction of a primed $CD4^+$ T cell with a cognate B cell is a key

second signal for the induction of T_{FH} differentiation[2,45,54]. T_{FH} differentiation can be restored in B cell–deficient mice by the expression of Bcl-6 in antigen-specific $CD4^+$ T cells, which suggests that cognate B cells specifically induce Bcl-6 expression in $CD4^+$ T cells[2] (Fig. 3b).

Blimp-1 is expressed late in $CD4^+$ T cell differentiation *in vitro*[25,55]. Blimp-1 expression is therefore associated with highly polarized effector $CD4^+$ T cells, late in differentiation, with a high cytokine-secretion capacity (Fig. 3b). This is intriguingly similar to the role of Blimp-1 in effector $CD8^+$ T cell differentiation (Fig. 3c; discussed below) and similar to (although less extreme than) its role in plasma cells, which have high expression of Blimp-1 and an enormous secretion capacity (Fig. 4). Furthermore, the highly polarized Blimp-1-expressing effector $CD8^+$ T cells or plasma cells have limited or no proliferative capacity, respectively, which suggests that Blimp-1^{hi} effector $CD4^+$ T cells may have similar properties (Fig. 4). Blimp-1-deficient T cells exhibit hyperproliferation *in vivo*, which results in autoimmunity[46,56]. Early $CD4^+$ T cell effector differentiation depends on neither Bcl-6 nor Blimp-1 ([refs. 3,46,56]). Those findings are consistent with our model, in which Blimp-1 is not required for the priming and development of $CD4^+$ T cell effector functions (cytokine secretion) but is critical for full effector cell differentiation and inhibition of the proliferation of those effector cells (Fig. 3b).

Although Bcl-6 and Blimp-1 are clearly central to effector $CD4^+$ T cell differentiation (and possibly memory, as discussed below), many aspects of their involvement remain unclear. In particular, how Bcl-6 controls T_{FH} differentiation is an area of intensive study. Initial reports have indicated that Bcl-6 can regulate key cytokine receptors (such as the interleukin 6 receptor (IL-6R) or IL-21R)[3] and suppress an important cluster of microRNAs[4], as well as suppress T_H1, T_H2 and T_H17 gene expression[3,4,44]. The specific roles of Blimp-1 in $CD4^+$ T cell effector differentiation remain to be extensively explored.

Bcl-6 and Blimp-1 in $CD8^+$ T cell differentiation

Naive $CD8^+$ T cells differentiate into cytotoxic effectors (cytotoxic T lymphocytes) that are critical for the control and clearance of intracellular pathogens. Recent studies have shown that Blimp-1 is expressed in effector and memory $CD8^+$ T cells[46,56,57] and that the absence of Blimp-1 can result in excessive proliferation and increased numbers of memory $CD8^+$ T cells[56]. Recent data have now convincingly demonstrated that Blimp-1 is an important regulator of effector $CD8^+$ T cell function, proliferation and conversion into memory cells[5–7]. Virus-specific Blimp-1-deficient $CD8^+$ T cells fail to differentiate into KLRG1^{hi}IL-$7R^{lo}$ cells[6,7], also known as short-lived effector cells because of their effector functions and limited ability to survive and convert into memory cells[58]. Instead, Blimp-1-deficient $CD8^+$ T cells preferentially differentiate into KLRG1^{lo}IL-$7R^{hi}$ memory precursor effector cells[6,7], which exhibit better survival than short-lived effector cells and have the potential to convert into memory $CD8^+$ T cells[58] (Fig. 3c). Blimp-1-deficient $CD8^+$ T cells have lower expression of effector molecules important for cytotoxicity, such as granzyme B[5–7]. Nonetheless, Blimp-1-deficient $CD8^+$ T cells have sufficient effector functions to control and clear acute infection with lymphocytic choriomeningitis virus or influenza virus[6,7]. Together these studies elegantly demonstrate that Blimp-1 expression is required for the terminal differentiation of effector $CD8^+$ T cells[6,7].

Blimp-1-deficient $CD8^+$ T cells express more Bcl-6 than do wild-type $CD8^+$ T cells[6,7]. Constitutive Bcl-6 expression suppresses granzyme B expression[59]. Conversely, *Bcl6*$^{-/-}$ $CD8^+$ T cells express more granzyme B[59]. Bcl-6 and Blimp-1 are therefore probably reciprocal regulators of $CD8^+$ T cell effector differentiation.

Certain commonalities can be gleaned from the $CD8^+$ and $CD4^+$ T cell studies about how Blimp-1 and Bcl-6 regulate these cell types. In both $CD8^+$ and $CD4^+$ T cells, Blimp-1 is critical for most terminal effector cell differentiation (Fig. 3b,c). Terminal differentiation is

characterized by low proliferative potential and high effector molecule secretion (Fig. 4). Blimp-1-deficient $CD8^+$ T cells are diverted to a memory-precursor differentiation pathway with enhanced proliferative potential and have lower effector molecule production (Figs. 3 and 4). Blimp-1-deficient $CD4^+$ T cells are diverted away from terminal T_H1 or T_H2 differentiation and toward T_{FH} differentiation[2] (Fig. 3) and exhibit greater proliferative potential[46,56]. These proliferation and secretion commonalities of Blimp-1-expressing T cells are again shared with the B cell lineage, in which B cells with high Blimp-1 expression are terminally differentiated effectors (plasma cells) with low proliferative potential and high effector molecule production (Fig. 4).

Regulation of T and B cell memory by Bcl-6 and Blimp-1

Blimp-1-deficient $CD8^+$ T cells preferentially differentiate into memory $CD8^+$ T cells[6,7,56], and Bcl-6 is upregulated in memory $CD8^+$ T cells[60]. Blimp-1 is also expressed differently by the two main memory $CD8^+$ T cell subsets[6,7]. Effector memory T cells, which are functionally potent memory $CD8^+$ T cells that patrol the periphery but proliferate poorly[58,61], have relatively high Blimp-1 expression. In contrast, central memory T cells have relatively low Blimp-1 expression[6,7] (Fig. 4) and are characterized by lower immediate effector functions and high proliferative potential[58,61].

Bcl-6-deficient $CD8^+$ T cells proliferate poorly and are less able to acquire a memory-like phenotype[62]. Conversely, $CD8^+$ T cells overexpressing Bcl-6 generate a larger memory cell population[63]. There is also some limited evidence that Bcl-6 has a role in memory $CD4^+$ T cells. Bcl-6-deficient $CD4^+$ T cells have an impaired ability to persist as memory cells after immunization[64]. Consistent with that idea, Blimp-1 expression is lower in memory $CD4^+$ T cells than in effector $CD4^+$ T cells[46]. Given that Bcl-6 promotes proliferation, Bcl-6 expression may be a key attribute of $CD8^+$ and $CD4^+$ T cell memory differentiation that Blimp-1 inhibits to direct cells toward terminal effector differentiation.

A simple model is that expression of Bcl-6 and Blimp-1 is a bimodal, self-reinforcing switch between effector and memory T cell differentiation, which is conserved between $CD8^+$ and $CD4^+$ T cells. However, this is an oversimplification, because among effector $CD4^+$ T cells, only T_{FH} cells depend on Bcl-6 expression[2–4] and the absence of Blimp-1 (ref. 2). Furthermore, effector $CD8^+$ T cells have a substantial amount of functionality in the absence of Blimp-1 (refs. 5–7,56). A somewhat more sophisticated model (Fig. 3b,c) incorporates the multiple stages of these $CD4^+$ and $CD8^+$ T cell differentiation pathways and highlights possible parallels in the activities of Bcl-6 and Blimp-1 in each lineage. Of course, many other proteins are also important participants in $CD4^+$ and $CD8^+$ T cell differentiation and functionality, but here we are focusing only on the contributions of Bcl-6 and Blimp-1.

The parallels between the functions of Blimp-1 and Bcl-6 in $CD4^+$ and $CD8^+$ T cells also raise a challenging question about the relationship between memory $CD4^+$ T cells and the T_{FH} and non-T_{FH} effector $CD4^+$ T cell lineages (Fig. 3b,c). Do Bcl-6^{hi}Blimp-1^{lo} T_{FH} cells convert more readily into memory cells than do Bcl-6^{lo}Blimp-1^{hi} effector $CD4^+$ T cells? Additional studies of the mechanistic role of Bcl-6 in $CD8^+$ and $CD4^+$ T cell memory differentiation are much needed.

The role of Bcl-6 in memory B cell differentiation is controversial[13,65,66]. Bcl-6 is generally considered crucial for the generation of B cell memory, as long-lived plasma cells and memory B cells are mainly products of germinal centers (Fig. 2). It has been proposed that Bcl-6 expression is necessary to prevent germinal center B cells from differentiating into plasma cells, allowing them to differentiate into memory B cells instead[65,67]. Human memory B cells do not express Blimp-1 (refs. 66,68). It has also been shown that Bcl-6 expression can enhance

B cell survival and thus may regulate memory B cell self-renewal[19,69]. However, Bcl-6 mRNA expression is not correlated with memory B cell differentiation in mice[70] or humans[66], and some memory B cells can develop in Bcl-6-deficient mice in the absence of germinal centers[19]. High Bcl-6 expression sustains a germinal center B cell phenotype and inhibits human memory B cell differentiation *in vitro*[66]. It remains to be determined what transcription factor induces memory B cell differentiation from Bcl-6-expressing germinal center B cells.

Blimp-1 in exhausted CD8$^+$ T cells

Effector CD8$^+$ T cells can become exhausted by persistent antigen presentation during chronic viral infection[71,72]. Chronic viral infections associated with T cell exhaustion, such as infection with human immunodeficiency virus or hepatitis C virus, are the cause of enormous human suffering and loss of life[73]. Exhausted CD8$^+$ T cells are functionally impotent and proliferate poorly[72], but when exhaustion is reversed in mice by therapeutic treatment, proliferation and effector functions are impressively restored[73–77]. Exhausted CD8$^+$ T cells in mice chronically infected with lymphocytic choriomeningitis virus have abnormally high Blimp-1 expression[5]. In contrast, Blimp-1-deficient CD8$^+$ T cells resist exhaustion and exhibit improved cell numbers[5]. Despite this less exhausted state, mice with conditional knockout of Blimp-1 are unable to efficiently clear the virus[5]. This is probably because Blimp-1 is necessary for effector functions and terminal differentiation, as has been shown in mice with CD8$^+$ T cells heterozygous for *Prdm1* deletion, which clear virus more rapidly than do wild-type mice[5].

Mechanisms of action

Although Bcl-6 and Blimp-1 are clearly powerful regulators of effector and memory cell fate decisions by CD4$^+$ T cells, CD8$^+$ T cells and B cells, it is less clear how Bcl-6 and Blimp-1 accomplish these functions at the level of transcriptional repression. It is also unclear to what extent the gene targets of Bcl-6 and Blimp-1 remain constant across different types of lymphocytes.

Bcl-6 targets are best understood in B cells. Bcl-6 suppresses a collection of DNA-damage–response genes and inducers of apoptosis and cell cycle arrest (p53, cyclin D2 and ATR) while facilitating AID expression in germinal center B cells[11] (Fig. 1). AID induces class-switch recombination and somatic hypermutation[16], which would result in cell cycle arrest and apoptosis if these normal DNA-damage responses were not suppressed by Bcl-6 (ref. 11). These Bcl-6 targets are B cell specific and are not shared by CD4$^+$ or CD8$^+$ T cells (although, curiously, some AID expression is observed in T_{FH} CD4$^+$ T cells[2] and Blimp-deficient CD8$^+$ T cells[6]).

A key aspect of Bcl-6 biology is that Bcl-6 dimers repress transcription only in combination with corepressors, and there are many corepressors that Bcl-6 can partner with. Most corepressors bind to or near the Bcl-6 bric-a-bric, tramtrack, broad complex–poxvirus zinc-finger domain, including BCoR[78,79], N-CoR[80,81], SMRT[80,81], CtBP[31], BAZF[82], PLZF[83], MIZ1 (encoded by *Zbtb17*)[84] and others. At least some of these partners can also form mixed complexes[31,83]. The corepressor MTA3 binds to a second domain of the Bcl-6 protein called RDII (refs. 32,85). The corepressor ETO (encoded by *Runx1t1*) binds to the zinc-finger domain of Bcl-6[86]. The use of these many different corepressors allows combinatorial targeting of Bcl-6 to different collections of genes in different cell types at different times. For example, Bcl-6 inhibits Blimp-1 via interactions with MTA3 (refs. 32,87; Fig. 1) and AP-1 (ref. 88). Bcl-6 protein inhibition of the *Bcl6* gene instead depends on CtBP[31] (Fig. 1). Whole-genome chromatin immunoprecipitation plus micrarray analysis has revealed that Bcl-6 regulates a very different set of genes in primary germinal center B cells than in a diffuse large B cell lymphoma[33]. Of 3,345 genes bound by Bcl-6, less than half of those targets are bound in both

cell types[33], which indicates that differences in corepressor availability probably have considerable effects on Bcl-6 gene targeting in different lymphocyte types at different differentiation stages.

There are only a smattering of obvious gene-expression changes conserved between Bcl-6-expressing T_{FH} $CD4^+$ T cells and Bcl-6-expressing germinal center B cells, beyond Blimp-1 inhibition[2,89]. This indicates that different Bcl-6 corepressors are present in T_{FH} cells and germinal center B cells, which act together to suppress different constellations of genes in the two cell types. There are also only limited similarities in the gene-expression changes in Bcl-6-expressing T_{FH} $CD4^+$ T cells and Blimp-1-deficient $CD8^+$ T cells (which have higher expression of Bcl-6)[2,6], which again suggests that the specific gene-expression changes controlled by the Bcl-6–Blimp1 regulatory axis are more different than similar in B cells, $CD4^+$ T cells and $CD8^+$ T cells and are therefore probably highly influenced by the available corepressors. The present understanding of the genes and gene networks controlled by Bcl-6 remains limited, particularly in T cells, and this is an area that now needs extensive examination, given the importance of Bcl-6 in T cell functions.

It is also important to note that Bcl-6 mRNA quantities are a poor indicator of Bcl-6 protein expression[90] and a poor indicator of Bcl-6 function, as Bcl-6 is controlled by a wide array of post-transcriptional regulatory mechanisms, including absence of translation at the mRNA level[90], as well as protein phosphorylation[91], acetylation[92] and cofactor-mediated degradation[93]. This allows intense signal integration by Bcl-6, as the functional amount of Bcl-6 protein in a cell can be heavily influenced by many transcriptional and post-transcriptional activities, in combination with changes in the availability of corepressors.

The inhibition of Blimp-1 by Bcl-6 is a common feature in germinal center B cells and $CD4^+$ T_{FH} cells[2,20,31] and probably in differentiating $CD8^+$ T cells[6,7]. Because Bcl-6 and Blimp-1 are reciprocal antagonists, it is challenging to disentangle their direct effects versus their effects achieved via inhibition of each other. How much of the effect of Bcl-6 expression in a given cell type is via inhibition of Blimp-1 and vice versa? These and related questions need to be addressed.

Like Bcl-6 target genes, Blimp-1 target genes are best characterized in B cells. Blimp-1 targets in B cells can be placed into three functional categories: inhibition of proliferation (c-Myc[30,94] and E2F1 ([ref. 27])), induction of secretory machinery (XBP-1 ([ref. 27])), and inhibition of the germinal center B cell program (Bcl-6 ([ref. 27]), Pax5 ([ref. 95]) and CIITA[96,97]). Inhibition of proliferation is a common feature of B cells, $CD4^+$ T cells and $CD8^+$ T cells with high expression of Blimp-1 (it is important to note that the antiproliferative effects of Blimp-1 are dose dependent[2,26,55]). The gene encoding Id3, a pro-proliferation transcription factor[98] expressed in T_{FH} cells[2], germinal center B cells[27] and Blimp-1-deficient $CD8^+$ T cells[6], seems to be one common Blimp-1 target in both B cells and T cells and may be a key component of the antiproliferative effects of Blimp-1.

Induction of the secretory apparatus by Blimp-1 (via XBP-1 and possibly other mechanisms) is most dramatic for plasma cells[23] but also occurs in T cells[99], as terminally differentiated effector T cells are specialized producers of cytokines and other secreted products. In both plasma cells and terminally differentiated effector T cells, the cellular metabolism is optimized for protein production and secretion instead of DNA synthesis and proliferation (Fig. 4).

One of the most interesting targets of Blimp-1 that has been characterized in T cells is the gene encoding IL-2 ([refs. 25,55,100]), a cytokine critical for T cell and B cell proliferation and differentiation. T_{FH} cells have been observed to produce more IL-2 than do non-T_{FH} cells[2,4], consistent with the smaller amount of Blimp-1 in T_{FH} cells[2]. Blimp-1-deficient $CD8^+$ T cells also exhibit greater IL-2 production[6,7]. Memory $CD8^+$ T cells are also frequently characterized

by their ability to produce large amounts of IL-2. Given the importance of IL-2 for T cell function and memory differentiation, *Il2* is a key Blimp-1 target gene.

Concluding remarks

Transcription factors drive B lymphocytes and T lymphocytes to differentiate into a variety of different effector and memory cells. Bcl-6 and Blimp-1 are unusual in that they are not unique to one lineage but are common to B cells, $CD4^+$ T cells and $CD8^+$ T cells. Although the roles of Bcl-6 and Blimp-1 in these cell lineage programs share general features—Bcl-6 frequently sustains proliferative potential but not terminal effector function, Blimp-1 enables secretion and effector functions but inhibits proliferation, and the two genes serve as a bimodal self-reinforcing genetic switch—the genes regulated by Bcl-6 and Blimp-1 to produce those phenotypes seem to be predominantly distinct in B cells, $CD4^+$ T cells and $CD8^+$ T cells, which highlights the complexity of the gene programs involved and the importance of additional layers of gene-expression regulation.

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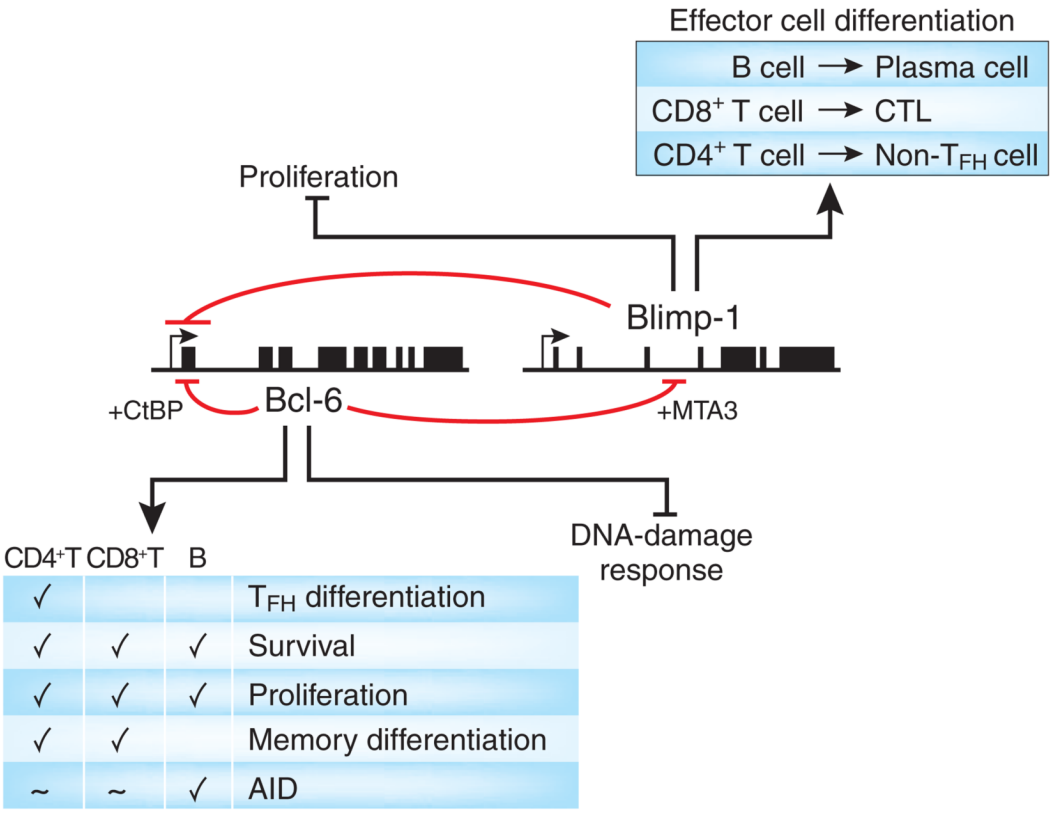

Figure 1.
Bcl-6 and Blimp-1 are reciprocally antagonistic transcription factors. Mechanisms of Bcl-6 and Blimp-1 antagonism and their broad influences on lymphocyte differentiation and function. CTL, cytotoxic T lymphocyte.

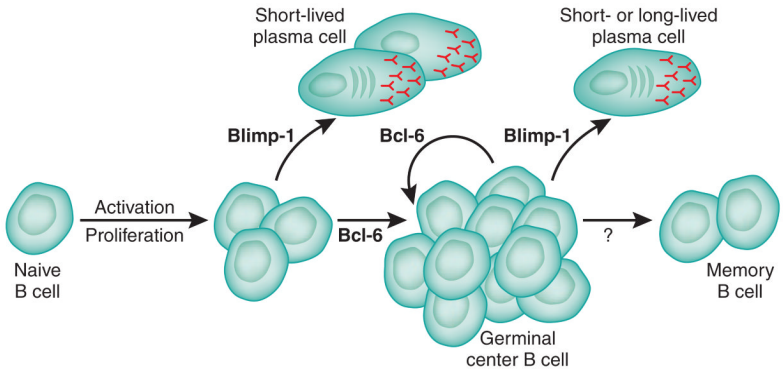

Figure 2.
Roles of Bcl-6 and Blimp-1 in B cell differentiation. Bcl-6 and Blimp-1 are required at various steps of B cell differentiation (as indicated by arrow labels).

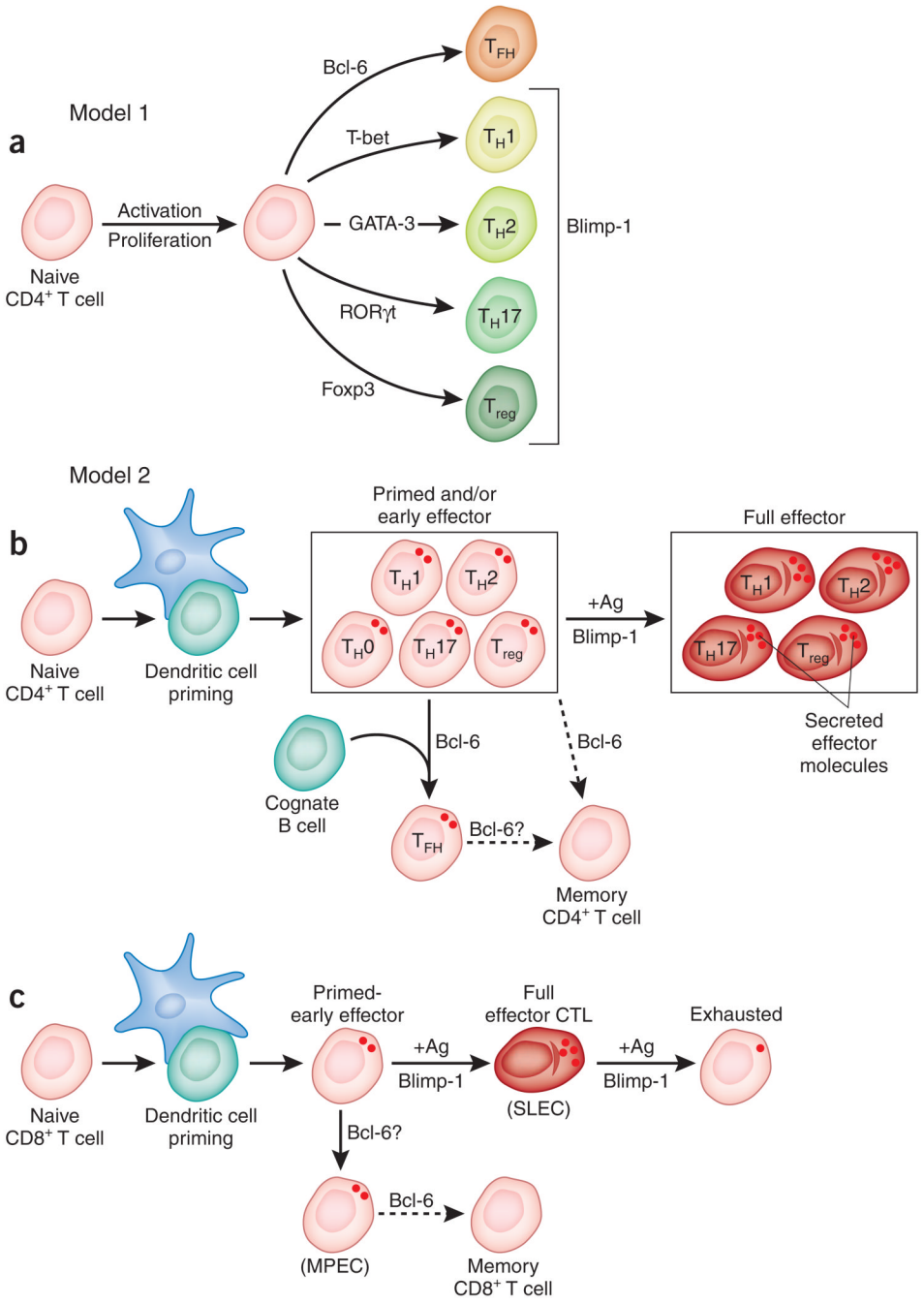

Figure 3.

Roles of Bcl-6 and Blimp-1 in T cell differentiation. (**a,b**) Two proposed models of effector $CD4^+$ T cell differentiation: model 1 (**a**) and model 2 (**b**). in **b**, the partial T_H1, T_H2, T_{reg} and T_H17 characteristics of T_{FH} cells are not shown, for simplicity. (**c**) A model of $CD8^+$ T cell effector and memory differentiation highlighting the similarities to $CD4^+$ T cells. Dotted lines and question marks indicate uncertainty. +Ag, antigen stimulation; SLeC, short-lived effector cell; MPeC, memory precursor effector cell.

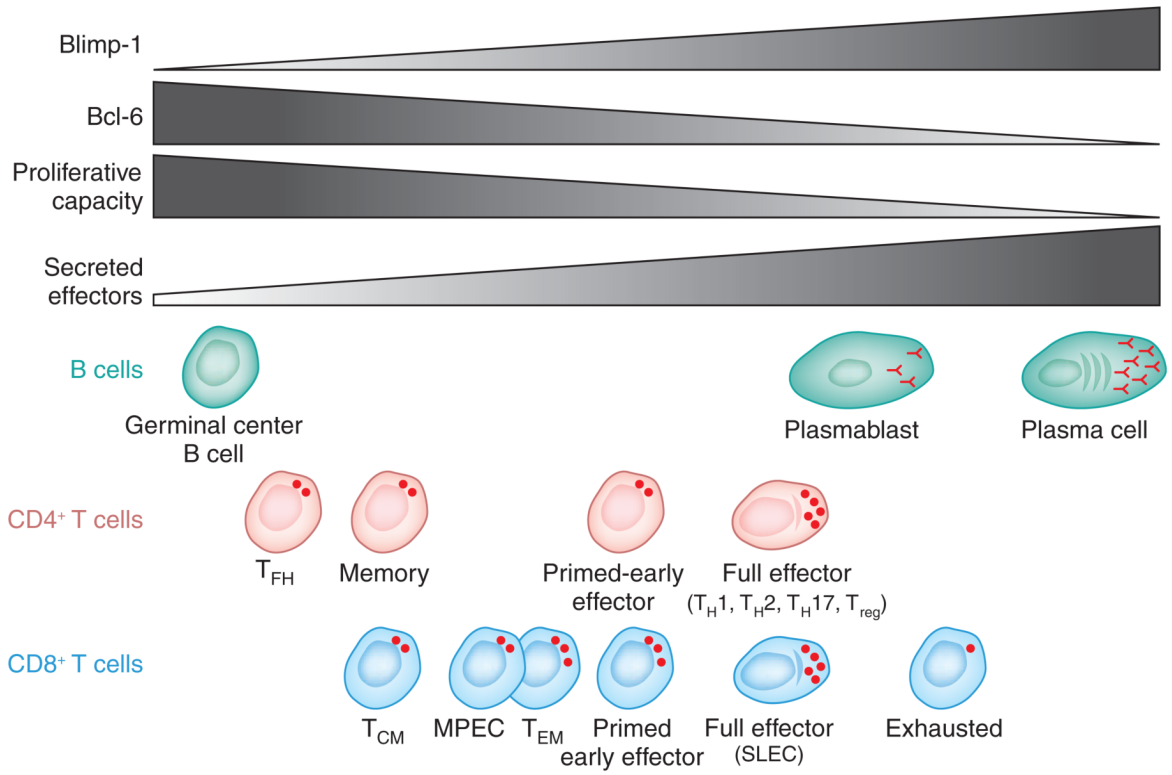

Figure 4.

Functional effects of different amounts of Bcl-6 and Blimp-1 expression. The amount of Bcl-6 and Blimp-1 expression is balanced differently in different lymphocytes at distinct differentiation stages. Lymphocytes with higher expression of Bcl-6 exhibit greater proliferative capacity but less secretory capacity. Lymphocytes with higher expression of Blimp-1 exhibit lower proliferative capacity and greater secretory capacity. Although exhausted $CD8^+$ T cells have large amounts of Blimp-1 and lower proliferative capacity, they do not have more secreted effectors. T_{CM}, central memory T cell; T_{EM}, effector memory T cell.