BLIMP1 guides the fate of effector B and T cells

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Abstract | B-lymphocyte-induced maturation protein 1 (BLIMP1) is a transcriptional repressor, and its importance in controlling the terminal differentiation of antibody-secreting cells (ASCs) is well established. However, as we discuss in this Progress article, it has now become evident that the ASC programme consists of a discrete BLIMP1-independent initiation phase, followed by a second step in which BLIMP1 is absolutely required for the differentiation of fully mature ASCs. In addition, an important role for BLIMP1 in maintaining the homeostasis of effector T cells is emerging, suggesting intriguing parallels between the control of effector-cell fates in both B and T cells.

The acquisition of effector functions during an immune response is a hallmark of the terminal differentiation of lymphocytes. Activated B cells can either differentiate into antibody-secreting cells (ASCs), which comprise rapidly proliferating plasmablasts and post-mitotic plasma cells, or develop into memory B cells (FIG. 1). Plasma-cell differentiation is an essential arm of the adaptive immune response, generating ASCs that are capable of producing large quantities of natural and antigen-specific immunoglobulins that provide long-term immunity[1]. Memory B cells do not secrete antibody, but on antigen re-exposure they can rapidly differentiate into ASCs. Activated T cells can differentiate into effector cells that acquire the ability to secrete large quantities of cytokines, they can become cytotoxic killer cells or they can develop into memory T cells. Whereas effector T cells are generally short lived, memory T cells can persist for many years in the body and, similar to memory B cells, rapidly differentiate into effector T cells on antigen re-encounter[2].

The transcriptional repressor BLIMP1 (B-lymphocyte-induced maturation protein 1; also known as PRDI-BF1 or PRDM1) has a pivotal role in lymphocyte terminal differentiation (reviewed in REFS 3,4). Whereas the functions of BLIMP1 in T cells are only now emerging, several recent papers have examined its role in ASC development in great detail. Interestingly, recent studies have also uncovered a function of BLIMP1 as a potential tumour suppressor, suggesting a direct role for BLIMP1 in controlling human malignancies that derive from late stages of B-cell development (BOX 1). In this Progress article, we highlight some new and surprising results concerning the role of BLIMP1 in the final stages of lymphocyte maturation.

BLIMP1 regulates ASC differentiation

The finding that enforced expression of BLIMP1 in B-cell lines or in primary splenocytes drives the differentiation of mature B cells to the plasma-cell fate first highlighted the pre-eminent role of BLIMP1 in ASC differentiation[5,6]. Knockout studies have further demonstrated that BLIMP1 is also required for the formation and maintenance of mature plasma cells[7–10]. Therefore, BLIMP1 is considered to be a master regulator of terminal B-cell differentiation.

The evidence so far suggests that BLIMP1 functions predominantly as a sequence-specific transcriptional repressor that recruits co-repressors and histone-modifying enzymes (reviewed in REF. 4). Although the relevance of these interactions in primary B cells is unknown, it is likely that they are important in the permanent establishment of the transcriptional programme that is associated with the plasma-cell stage and immunoglobulin secretion. In keeping with this global role in gene regulation, expression-profiling studies that compare wild-type and BLIMP1-deficient B cells cultured under conditions that favour plasma-cell development have identified hundreds of genes that are deregulated in the absence of BLIMP1, some of which have been shown to be direct BLIMP1 targets[11,12]. Several of these BLIMP1 targets, including *Pax5* (paired box protein 5), *Bcl6* (B-cell lymphoma 6), *Myc*, *Ciita* (MHC class II transactivator) and *SpiB* (SPIB transcription factor) are important for the function of mature B cells, suggesting that BLIMP1 promotes ASC differentiation by silencing the B-cell programme (reviewed in REF. 3). The repression of *Bcl6* (REF. 13) and *Pax5* (REF. 14) by BLIMP1 in B cells is particularly noteworthy as BCL-6 is essential for the germinal-centre reaction and PAX5 is required to maintain B-cell identity (reviewed in REFS 3,15). PAX5 itself directly represses components of the ASC pathway such as immunoglobulin J (*Igj*)[16] and X-box-binding protein 1 (*Xbp1*)[17] that are crucial for immunoglobulin secretion and plasma-cell development[12,18].

In addition to XBP1 and BLIMP1, interferon-regulatory factor 4 (IRF4) is essential for ASC formation. However, the relationship between IRF4 and BLIMP1 at present is unclear as there are conflicting data as to whether BLIMP1 is normally expressed in differentiating *Irf4*$^{-/-}$ B cells[19,20].

The initiation of ASC differentiation is BLIMP1 independent. The importance of BLIMP1 in the differentiation of ASCs has been demonstrated in mice with a B-cell-specific deletion of *Blimp1*, which lack a defined plasma-cell compartment and have severely reduced serum immunoglobulin titres[7]. This was in keeping with the widely accepted notion that BLIMP1 is essential for plasma-cell development. Residual serum antibody in these mice was attributed to incomplete deletion of BLIMP1 or to a putative ASC population that is less dependent on BLIMP1 (REF. 7). One study suggested that B-1 B cells, a distinct subset of B cells with a restricted B-cell-receptor repertoire that resides predominantly in the peritoneal cavity, could secrete immunoglobulin without stimulation and without detectable

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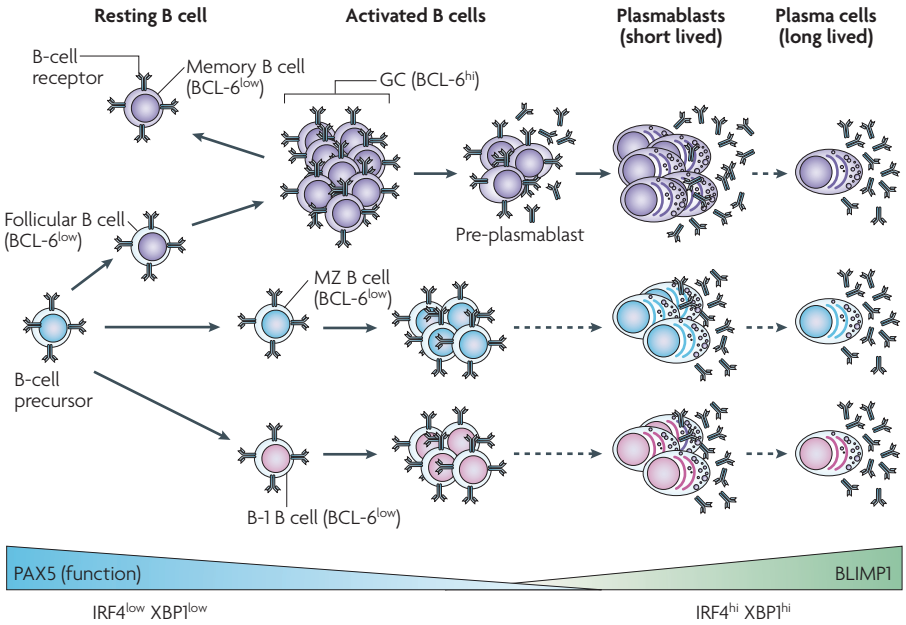

Figure 1 | **The transcriptional control of late B-cell differentiation.** All B-cell subsets derive from bone-marrow or fetal-liver precursors, express paired box protein 5 (PAX5) and have the ability to develop into B-lymphocyte-induced maturation protein 1 (BLIMP1)-positive antibody-secreting cells (ASCs), including plasmablasts and plasma cells, in the periphery. Whereas naive and memory B cells express low amounts of B-cell lymphoma 6 (BCL-6) protein, follicular B cells upregulate BCL-6 during the germinal centre (GC) reaction, which is thought to prevent early differentiation and *BLIMP1* expression. Importantly, GC B cells down-modulate PAX5 activity, which is a crucial step in the initiation of ASC differentiation. Marginal zone (MZ) and B-1 B cells, because of their low BCL-6 expression and PAX5 activity, are poised to differentiate rapidly into ASCs. The expression of BLIMP1 is initiated in pre-plasmablasts that secrete immunoglobulin but are formed independently of BLIMP1 function. Plasmablasts express intermediate levels of BLIMP1, proliferate rapidly and secrete immunoglobulin, whereas plasma cells have high BLIMP1 expression, are long-lived, post-mitotic and produce large quantities of immunoglobulin. It remains unknown whether plasma cells derive from plasmablasts or directly from an earlier stage, and the degree to which MZ and B-1 B cells contribute to the long-lived plasma-cell compartment. Levels of PAX5 function as well as BLIMP1, BCL-6, interferon-regulatory factor 4 (IRF4) and X-box-binding protein 1 (XBP1) expression are indicated.

expression of BLIMP1 (REF. 21). However, both the Calame group[9] and our laboratory[22] have recently demonstrated that B-1 B cells require BLIMP1 in order to develop into ASCs, confirming that BLIMP1 is an essential regulator of ASCs that are derived from all B-cell subsets.

A recent detailed analysis of the earliest steps of ASC differentiation performed in our laboratory made use of a knock-in allele, *Blimp1*^{GFP}, which expresses a truncated, DNA-binding-deficient BLIMP1 molecule and green fluorescent protein (GFP), thereby generating a reporter for an active *Blimp1* locus[10,23]. Recombination-activating gene 1 (*Rag1*)$^{-/-}$ mice reconstituted with fetal liver cells homozygous for *Blimp1*^{GFP} recapitulate the phenotype of mice with the B-cell-specific deletion of BLIMP1 in that they lack plasma cells and have reduced, but detectable, titres of all immunoglobulin isotypes. *In vitro* and *in vivo* analysis of *Blimp1*$^{GFP/GFP}$ B cells revealed that in the absence of BLIMP1 function, GFP-positive B cells can be detected and that these cells show the characteristics of an early stage of plasma-cell differentiation, including decreased *Pax5* expression, activation of plasma-cell-associated genes, such as *Igj* and *Xbp1,* and low immunoglobulin secretion[10]. Therefore, BLIMP1-deficiency leads to a specific block at a stage of differentiation that we term pre-plasmablast, indicating that BLIMP1 is not required for the initiation of antibody secretion, but is essential for the subsequent high-level immunoglobulin production that accompanies terminal ASC differentiation.

These findings raise an important question: what are the molecular processes that are required to initiate ASC differentiation? The analysis of B cells with normal BLIMP1 function identified a phase before the onset of BLIMP1 expression in which PAX5 activity was inhibited[10]. This inhibition resulted in the altered expression of multiple PAX5 target genes, including *Flt3* (FMS-like tyrosine kinase 3), *Emb* (Embigin), *Cd79a* and *Blnk* (B-cell linker). Interestingly, this diminished PAX5 activity was not the result of reduced PAX5 protein levels and, at least in the case of *Flt3*, appeared not to be mediated by differential binding to regulatory sequences, suggesting that another protein or a modification of PAX5 itself suppresses PAX5 function[4,10]. Overall, these data support a multistep model whereby ASC differentiation is initiated by the inhibition of PAX5 function followed by the induction of low-level immunoglobulin secretion and *Blimp1* transcription (FIG. 1). Only subsequently does BLIMP1 drive the terminal-differentiation programme by silencing *Pax5* transcription, thereby promoting high-level immunoglobulin secretion and plasma-cell maturation. This model now provides a framework to expand our understanding of the genetic networks that govern late B-cell differentiation to incorporate the roles of other essential transcription factors including BCL-6, OBF1 (octamer-binding transcription-factor-binding factor 1), BACH2 (BTB and CNC homology 1, basic leucine zipper transciption factor 2) and IRF4 in the process.

It is important to note that different strategies have been employed to mutate the *Blimp1* locus. The loss of BLIMP1 results in embryonic lethality at E10.5 (embryonic day 10.5), probably because of placental insufficiency[24]. By contrast, most *Blimp1*$^{GFP/GFP}$ embryos die between E13.5 and E16.5. This difference in lethality may be the result of distinct genetic manipulations of the *Blimp1* locus, as, whereas the conditional allele completely removes exons 6–8, the *Blimp1*^{GFP} allele results in a truncation of the *Blimp1* transcript after exon 6, but retains the DNA sequences coding for exons 7 and 8. Hence, it is possible that low-level full-length BLIMP1 provides support for the continued development seen in *Blimp1*$^{GFP/GFP}$ embryos. Importantly, we have failed to find any accumulation of wild-type BLIMP1 in *Blimp1*$^{GFP/GFP}$ lymphocytes, which display a similar phenotype to the lymphocytes in mice in which the conditional *Blimp1* allele has been deleted[23,25]. Both mouse strains are also expected to produce a truncated BLIMP1 protein that lacks the zinc-finger proteins encoded by exons 6–8 in one case[7] and exons 7–8 in the other[23]. Both truncations lack the DNA-binding domain and have not been shown to encode a functional BLIMP1 protein.

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Box 1 | **A role for BLIMP1 as a tumour suppressor?**

Many studies have demonstrated that B-lymphocyte-induced maturation protein 1 (BLIMP1 also known as PRDM1), is expressed in cells from patients with multiple myeloma, a cancer that derives from plasma cells. Recently, it was revealed that the human *BLIMP1* gene is mutated in diffuse large B-cell lymphoma (DLBCL), which is the most frequent type of B-cell non-Hodgkin lymphoma[41,42]. *BLIMP1* mutations were restricted to the activated B-cell-like (ABC) subtype of DLBCL that derives from cells that are undergoing the early stages of plasma-cell differentiation. Whereas *BLIMP1* mutations occurred in 25% of ABC-DLBCL biopsies, and were associated with the epigenetic silencing or loss of the second allele, most other cases lacked BLIMP1 protein. This was despite the presence of detectable mRNA and despite high expression of interferon-regulatory factor 4 (IRF4), another transcription factor that is co-expressed with BLIMP1 in normal plasma cells, suggesting that additional mechanisms inhibit BLIMP1 translation or stability[41]. As B-cell lymphoma 6 (*BCL6*) translocations were never found in *BLIMP1*-mutated ABC-DLBCL cases, it is possible that *BCL6* deregulation and *BLIMP1* inactivation are alternative pathogenetic mechanisms that lead to lymphomagenesis[41]. A subsequent study confirmed the discordance between BLIMP1 mRNA and protein expression, but failed to detect mutations in the *BLIMP1* gene and instead found that the expression of the BLIMP1β isoform, that derives from an internal promoter, correlated with short survival times[43].

A role for BLIMP1 as a tumour suppressor is in line with the functions of other members of the PRDM gene family, *PRDM2* (also known as *RIZ*) and *PRDM3* (also known as *MDS-EVI1*), which have been implicated in leukemogenesis[44,45]. Whereas the studies discussed above provide evidence for the recurrent inactivation of *BLIMP1* in ABC-DLBCL, which implies a role for this gene as a tumour suppressor, this remains to be formally demonstrated. It will also be of interest to determine if *BLIMP1* is mutated in other types of B- and T-cell lymphomas.

Distinct regulation of BLIMP1 in B-cell subsets. It is well established that some B-cell subsets can differentiate rapidly in response to antigen. In particular, peritoneal B-1 and splenic marginal-zone B cells can quickly be induced to secrete antibody in response to Toll-like receptor (TLR) stimulation, thereby providing a first line of defence against microbial pathogens[26]. Interestingly, we and others found that, whereas all B-cell subsets were able to differentiate into ASCs in response to various stimuli (including lipopolysaccharide, mediated by TLR4 and CD40-specific antibody in the presence of interleukin-4 (IL-4) and IL-5), B-1 and marginal-zone B cells were able to induce BLIMP1 and immunoglobulin secretion much more rapidly than follicular B cells[22,27]. An exception was stimulation with CpG-containing DNA — a TLR9 ligand — which resulted in significant BLIMP1-induction and immunoglobulin secretion only in B-1 B cells[22]. In line with these findings, B-1 and marginal-zone B cells were found to display a transcriptional-factor profile different from naive follicular B cells, with elevated levels of *Blimp1* and lower expression of *Bcl6, Mta3* and *Pax5* (REFS 22,28). Moreover, a comparison of PAX5 target-gene expression in B-1 and marginal-zone B cells showed that these populations display constitutively inhibited PAX5 activity that is similar to activated follicular B cells[10]. This, combined with the distinct transcription-factor profile, renders these cells poised to differentiate into ASCs (FIG. 1).

Levels of Blimp1 expression define ASC subsets. The analysis of *Blimp1*^{GFP} reporter mice confirmed previous studies that showed a close association between BLIMP1 expression and immunoglobulin secretion[23,29]. These studies also revealed an unexpected heterogeneity of BLIMP1 expression in the ASC compartment[23]. Splenic ASCs can be divided into those that express either intermediate or high levels of BLIMP1, whereas a single population of BLIMP1^{hi} ASCs is found in the bone marrow. Cells that express intermediate levels of BLIMP1 (BLIMP1^{int}) in the spleen retain some expression of the B-cell markers B220 and CD19, both of which are lost on BLIMP1^{hi} cells. Bromodeoxyuridine labelling and immunization experiments demonstrated that intermediate BLIMP1 expression defines short-lived plasmablasts, whereas high BLIMP1 expression marks long-lived plasma cells[23]. The distinction between these two ASC subsets is also evident on a functional level, as only BLIMP1^{int} ASCs are found in the blood of immunized mice, suggesting that these cells are capable of seeding the long-lived plasma-cell compartment in the bone marrow[30]. These data were further supported by a recent study that showed that only BLIMP1^{int} ASCs display a detectable chemotactic response to CXC-chemokine ligand 12 (CXCL12), the ligand for CXC-chemokine receptor 4 (CXCR4)[31]. Importantly, the correlation of BLIMP1 expression levels and maturation state also appears to be present in humans, as tetanus-toxoid-specific bone-marrow ASCs show higher BLIMP1 expression than blood- and tonsil-derived ASCs[32]. Overall, these findings suggest that an intermediate expression level of BLIMP1 is sufficient to support the immunoglobulin secretion programme but still allows for proliferation and migration, whereas high levels of BLIMP1 expression promote exit from the cell cycle and longevity (FIG. 1).

Interestingly, most of the BLIMP1^{int} plasmablasts die during the early phase of the immune reaction. This correlates with the observations that BLIMP1 expression promotes apoptosis[33] and that mice that are deficient for the pro-apoptotic molecule BIM (BCL-2-interacting mediator of cell death)[34] or mice that overexpress BCL-2 (REF. 35) show increased numbers of ASCs. Although it is likely that under normal circumstances only a minority of ASCs become BLIMP1^{hi} long-lived plasma cells, it is unclear how entry into this compartment is regulated (FIG. 1).

BLIMP1 regulates T-cell homeostasis

For many years it was assumed that the function of BLIMP1 in the immune response was B-cell specific, however, it is now clear that BLIMP1 has a crucial role in maintaining the homeostasis of T cells[25,36]. *Blimp1* is most highly expressed in a subset of effector and/or memory T cells of the CD4 and CD8 lineages. Mice with a T-cell-specific deletion[36] and mice reconstituted with BLIMP1-deficient (*Blimp1*$^{GFP/GFP}$) fetal liver cells[25] show a dramatic expansion of the effector T-cell compartment, increased capacity for homeostatic expansion and severe T-cell-mediated immune pathology. As BLIMP1 expression is also readily detected in forkhead box P3 (FOXP3)$^{+}$CD4^{+}CD25^{+} regulatory T (T_{Reg}) cells, it was speculated that this pathology results from a role for BLIMP1 in T_{Reg}-cell functions. Surprisingly, both *in vitro* suppressor assays[25,36] and an *in vivo* model of colitis induced by the transfer of naive CD4^{+} T cells into immune-compromised hosts[36], showed that BLIMP1-deficient T_{Reg} cells were efficient in suppressing the expansion of CD4^{+} T cells and disease. BLIMP1 is, however, likely to have some role in T_{Reg} cells as BLIMP1-deficient T_{Reg} cells had impaired function in a chemically induced colitis model[36] and expressed reduced amounts of *Il10* (REF. 25).

In striking contrast to the B-cell lineage, in which BLIMP1 is directly required for effector function, BLIMP1-deficient naive and effector CD4^{+} T cells cultured in neutral conditions actually have an increased rate of differentiation into IL-2- and

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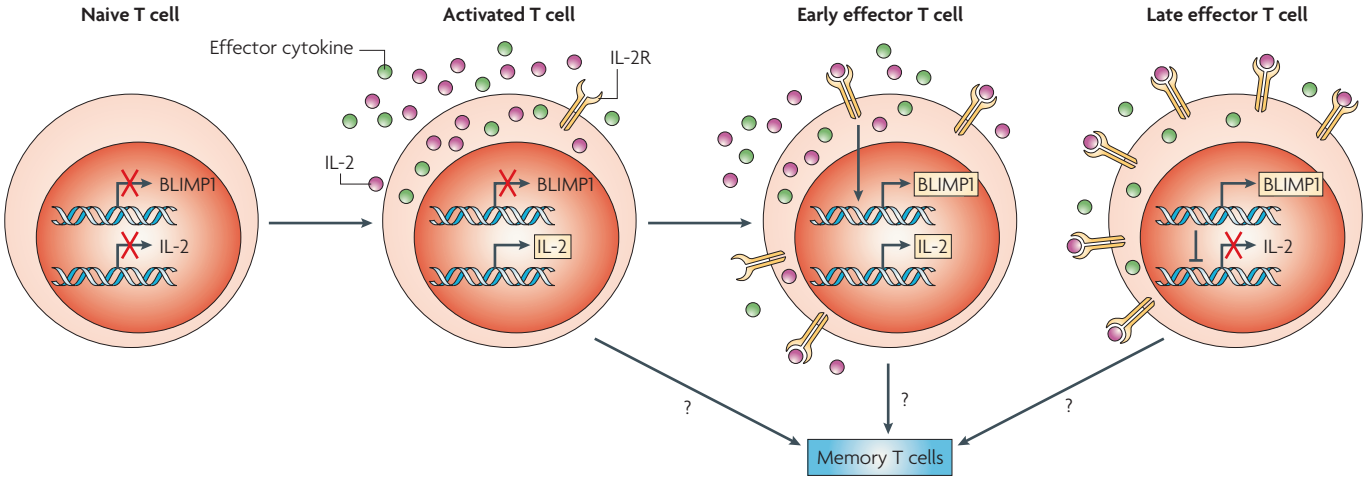

Figure 2 | **Model of the interaction of BLIMP1 and IL-2 in T-cell differentiation.** Naive T cells express neither B-lymphocyte-induced maturation protein 1 (BLIMP1) nor interleukin-2 (IL-2). Following encounter with antigen, activated T cells secrete high quantities of IL-2 and upregulate the IL-2 receptor (IL-2R). Engagement of IL-2R by IL-2 results in *BLIMP1* transcription in early effector cells. BLIMP1 expression increases in late effector cells and represses *Il2* expression through an unknown mechanism. By contrast, most effector cytokines such as interferon-γ or tumour-necrosis factor appear to be unaffected by BLIMP1 expression.

interferon-γ (IFNγ)-secreting cells and a corresponding decrease in IL-10-expressing cells[36]. However, once fully differentiated, BLIMP1-deficient T helper 1 (T_H1) and T_H2 cells secrete comparable quantities of IFNγ or IL-4 (REF. 25). The increased IL-2 production correlates with two recent studies that have identified *Il2* as a target of BLIMP1-mediated suppression[37,38]. IL-2 production by activated $CD4^+$ and $CD8^+$ T cells inversely correlated with BLIMP1 expression levels and ectopic expression of BLIMP1 in activated T cells inhibited *Il2*. This suggests that a negative regulatory feedback loop exists, which ensures that IL-2 limits its own production by inducing the expression of BLIMP1 (REFS 37,38) (FIG. 2). These results also correspond to our observation that $Il2^{-/-}$ T cells activated *in vitro* fail to induce BLIMP1 expression in the absence of exogenous IL-2 (A.K., unpublished observations). Interestingly, BLIMP1-deficient effector T cells are remarkably resistant to activation-induced cell death (AICD), suggesting a role for BLIMP1 in terminating the immune response[25]. Taken together, these data support a model whereby BLIMP1 regulates the terminal differentiation of effector T cells by limiting IL-2 production, increasing IL-10 secretion and promoting AICD. Therefore, effector T cells that lack BLIMP1, despite being able to perform most immediate effector functions, may be 'arrested' in an early stage of differentiation.

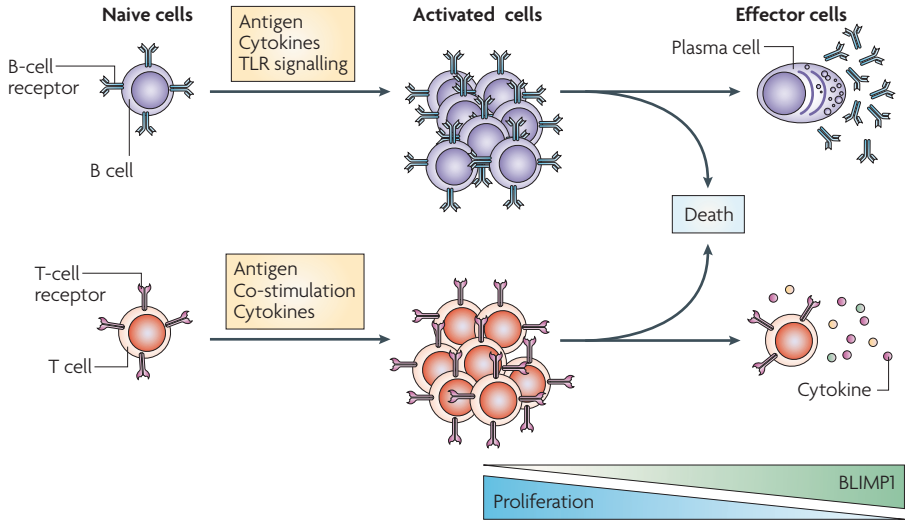

Figure 3 | **Comparison of BLIMP1 functions in B- and T-cell terminal differentiation.** Simplified schematic of lymphocyte terminal differentiation showing the inverse relationship in both lineages between B-lymphocyte-induced maturation protein 1 (BLIMP1) expression and proliferative potential. Activation of naive lymphocytes by antigen, Toll-like receptor (TLR) signals or cytokines promotes proliferation and ultimately results in the induction of BLIMP1 expression and effector function. Most effector cells in either lineage are short-lived and die through apoptosis. The appropriate transition of activated lymphocytes to short and long-lived effector cells requires BLIMP1 function.

It is currently unclear whether BLIMP1 has a role in the generation and maintenance of memory T cells. BLIMP1 expression is found in T cells that have a memory phenotype[36], as well as IL-7 receptor $(IL\text{-}7R)^{low}CD8^+$ T-cell memory precursors after LCMV infection[39]. However, the addition of IL-15 to $CD8^+$ T-cell cultures, which is thought to generate 'memory-like' cells, abolished BLIMP1 expression *in vitro*[37]. This raises the interesting possibility that, in contrast to the B-cell lineage in which memory cells derive from BLIMP1-negative germinal-centre B cells[30], memory T cells derive from effector T cells that have previously expressed BLIMP1 (FIG. 2). *BCL6* is a direct target of BLIMP1 repression in B cells[13] and has been shown to promote memory formation in $CD8^+$ T cells[40]. Indeed, *Bcl6* is modestly upregulated in BLIMP1-deficient T cells, suggesting that the reciprocal regulation of BCL-6 and BLIMP1 may have a role in T cells[36]. Preliminary data from our

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laboratory indicate that effector and memory cells, depending on their phenotype, express different levels of BLIMP1 and it is intriguing to speculate that, as in ASCs, this differential BLIMP1 expression leads to distinct functional properties.

Conclusions

Although it is still early days in our understanding of the function of BLIMP1 in T cells, the surprising finding that BLIMP1 is expressed in a similar manner in the late stages of both T- and B-cell differentiation raises the possibility that its target genes and the molecular process of terminal differentiation are conserved between these lineages. Interestingly, the final differentiation of both T and B cells involves a BLIMP1-independent clonal-expansion phase, followed by the production of short-lived effector cells that require BLIMP1 to complete their developmental programme (FIG. 3). Although the molecular and cellular functions of BLIMP1 in ASCs have come under intense scrutiny and are relatively well defined, the targets of BLIMP1 activity in T cells, beyond *Il2*, are unknown and it is unclear whether BLIMP1 is involved in the production and maintenance of T-cell memory. Whereas it is evident that both ASCs and effector T cells express distinct levels of BLIMP1 at various points in their ontogeny, the impact that these varied levels might have on their distinct biological properties remains to be determined.

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1. Manz, R. A., Hauser, A. E., Hiepe, F. & Radbruch, A. Maintenance of serum antibody levels. *Annu. Rev. Immunol.* **23**, 367–386 (2005).
2. Seder, R. A. & Ahmed, R. Similarities and differences in CD4$^+$ and CD8$^+$ effector and memory T cell generation. *Nature Immunol.* **4**, 835–842 (2003).
3. Shapiro-Shelef, M. & Calame, K. Regulation of plasma-cell development. *Nature Rev. Immunol.* **5**, 230–242 (2005).
4. Kallies, A. & Nutt, S. L. Terminal differentiation of lymphocytes depends on Blimp-1. *Curr. Opin. Immunol.* **19**, 156–162 (2007).
5. Turner, C. A. Jr, Mack, D. H. & Davis, M. M. Blimp-1, a novel zinc finger-containing protein that can drive the maturation of B lymphocytes into immunoglobulin-secreting cells. *Cell* **77**, 297–306 (1994).
6. Schliephake, D. E. & Schimpl, A. Blimp-1 overcomes the block in IgM secretion in lipopolysaccharide/anti-μF(ab')2-co-stimulated B lymphocytes. *Eur. J. Immunol.* **26**, 268–271 (1996).
7. Shapiro-Shelef, M. *et al.* Blimp-1 is required for the formation of immunoglobulin secreting plasma cells and pre-plasma memory B cells. *Immunity* **19**, 607–620 (2003).
8. Shapiro-Shelef, M., Lin, K. I., Savitsky, D., Liao, J. & Calame, K. Blimp-1 is required for maintenance of long-lived plasma cells in the bone marrow. *J. Exp. Med.* **202**, 1471–1476 (2005).
9. Savitsky, D. & Calame, K. B-1 B lymphocytes require Blimp-1 for immunoglobulin secretion. *J. Exp. Med.* **203**, 2305–2314 (2006).
10. Kallies, A. *et al.* Initiation of plasma-cell differentiation is independent of the transcription factor Blimp-1. *Immunity* **26**, 555–566 (2007).
11. Shaffer, A. L. *et al.* Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program. *Immunity* **17**, 51–62 (2002).
12. Shaffer, A. L. *et al.* XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. *Immunity* **21**, 81–93 (2004).
13. Tunyaplin, C. *et al.* Direct repression of prdm1 by Bcl-6 inhibits plasmacytic differentiation. *J. Immunol.* **173**, 1158–1165 (2004).
14. Lin, K. I., Angelin-Duclos, C., Kuo, T. C. & Calame, K. Blimp-1-dependent repression of Pax-5 is required for differentiation of B cells to immunoglobulin M-secreting plasma cells. *Mol. Cell. Biol.* **22**, 4771–4780 (2002).
15. Cobaleda, C., Schebesta, A., Delogu, A. & Busslinger, M. Pax5: the guardian of B cell identity and function. *Nature Immunol.* **8**, 463–470 (2007).
16. Rinkenberger, J. L., Wallin, J. J., Johnson, K. W. & Koshland, M. E. An interleukin-2 signal relieves BSAP (Pax5)-mediated repression of the immunoglobulin J chain gene. *Immunity* **5**, 377–386 (1996).
17. Reimold, A. M. *et al.* Transcription factor B cell lineage-specific activator protein regulates the gene for human X-box binding protein 1. *J. Exp. Med.* **183**, 393–401 (1996).
18. Reimold, A. M. *et al.* Plasma cell differentiation requires the transcription factor XBP-1. *Nature* **412**, 300–307 (2001).
19. Klein, U. *et al.* Transcription factor IRF4 controls plasma cell differentiation and class-switch recombination. *Nature Immunol.* **7**, 773–782 (2006).
20. Sciammas, R. *et al.* Graded expression of interferon regulatory factor-4 coordinates isotype switching with plasma cell differentiation. *Immunity* **25**, 225–236 (2006).
21. Tumang, J. R., Frances, R., Yeo, S. G. & Rothstein, T. L. Spontaneously Ig-secreting B-1 cells violate the accepted paradigm for expression of differentiation-associated transcription factors. *J. Immunol.* **174**, 3173–3177 (2005).
22. Fairfax, K. A. *et al.* Different kinetics of blimp-1 induction in B cell subsets revealed by reporter gene. *J. Immunol.* **178**, 4104–4111 (2007).
23. Kallies, A. *et al.* Plasma cell ontogeny defined by quantitative changes in blimp-1 expression. *J. Exp. Med.* **200**, 967–977 (2004).
24. Vincent, S. D. *et al.* The zinc finger transcriptional repressor Blimp1/Prdm1 is dispensable for early axis formation but is required for specification of primordial germ cells in the mouse. *Development* **132**, 1315–1325 (2005).
25. Kallies, A. *et al.* Transcriptional repressor Blimp-1 is essential for T cell homeostasis and self-tolerance. *Nature Immunol.* **7**, 466–474 (2006).
26. Martin, F., Oliver, A. M. & Kearney, J. F. Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. *Immunity* **14**, 617–629 (2001).
27. Gunn, K. E. & Brewer, J. W. Evidence that marginal zone B cells possess an enhanced secretory apparatus and exhibit superior secretory activity. *J. Immunol.* **177**, 3791–3798 (2006).
28. Genestier, L. *et al.* TLR agonists selectively promote terminal plasma cell differentiation of B cell subsets specialized in thymus-independent responses. *J. Immunol.* **178**, 7779–7786 (2007).
29. Angelin-Duclos, C., Cattoretti, G., Lin, K. I. & Calame, K. Commitment of B lymphocytes to a plasma cell fate is associated with Blimp-1 expression *in vivo*. *J. Immunol.* **165**, 5462–5471 (2000).
30. Blink, E. J. *et al.* Early appearance of germinal center-derived memory B cells and plasma cells in blood after primary immunization. *J. Exp. Med.* **201**, 545–554 (2005).
31. Kabashima, K. *et al.* Plasma cell S1P1 expression determines secondary lymphoid organ retention versus bone marrow tropism. *J. Exp. Med.* **203**, 2683–2690 (2006).
32. Gonzalez-Garcia, I., Ocana, E., Jimenez-Gomez, G., Campos-Caro, A. & Brieva, J. A. Immunization-induced perturbation of human blood plasma cell pool: progressive maturation, IL-6 responsiveness, and high PRDI-BF1/BLIMP1 expression are critical distinctions between antigen-specific and nonspecific plasma cells. *J. Immunol.* **176**, 4042–4050 (2006).
33. Messika, E. J. *et al.* Differential effect of B lymphocyte-induced maturation protein (Blimp-1) expression on cell fate during B cell development. *J. Exp. Med.* **188**, 515–525 (1998).
34. Bouillet, P. *et al.* Proapoptotic Bcl-2 relative Bim required for certain apoptotic responses, leukocyte homeostasis, and to preclude autoimmunity. *Science* **286**, 1735–1738 (1999).
35. Smith, K. G. *et al. bcl-2* transgene expression inhibits apoptosis in the germinal center and reveals differences in the selection of memory B cells and bone marrow antibody-forming cells. *J. Exp. Med.* **191**, 475–484 (2000).
36. Martins, G. A. *et al.* Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. *Nature Immunol.* **7**, 457–465 (2006).
37. Gong, D. & Malek, T. R. Cytokine-dependent Blimp-1 expression in activated T cells inhibits IL-2 production. *J. Immunol.* **178**, 242–252 (2007).
38. Santner-Nanan, B. *et al.* Blimp-1 is expressed in human and mouse T cell subsets and leads to loss of IL-2 production and to defective proliferation. *Signal Transduction* **6**, 268–279 (2006).
39. Intlekofer, A. M. *et al.* Requirement for T-bet in the aberrant differentiation of unhelped memory CD8$^+$ T cells. *J. Exp. Med* **204**, 2015–2021 (2007).
40. Ichii, H. *et al.* Role for Bcl-6 in the generation and maintenance of memory CD8$^+$ T cells. *Nature Immunol.* **3**, 558–563 (2002).
41. Pasqualucci, L. *et al.* Inactivation of the *PRDM1/BLIMP1* gene in diffuse large B cell lymphoma. *J. Exp. Med.* **203**, 311–317 (2006).
42. Tam, W. *et al.* Mutational analysis of PRDM1 indicates a tumor-suppressor role in diffuse large B-cell lymphomas. *Blood.* **107**, 4090–4100 (2006).
43. Liu, Y. Y. *et al.* Rituximab plus CHOP (R-CHOP) overcomes PRDM1-associated resistance to chemotherapy in patients with diffuse large B-cell lymphoma. *Blood* **110**, 339–344 (2007).
44. Steele-Perkins, G. *et al.* Tumor formation and inactivation of RIZ1, an Rb-binding member of a nuclear protein-methyltransferase superfamily. *Genes Dev.* **15**, 2250–2262 (2001).
45. Zeleznik-Le, N. J., Nucifora, G. & Rowley, J. D. The molecular biology of myeloproliferative disorders as revealed by chromosomal abnormalities. *Semin. Hematol.* **32**, 201–219 (1995).

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DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BLIMP1 | *Bcl6* | *Igj* | IRF4 | *Pax5* | *Xbp1*

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