BLIMP1 α , the master regulator of plasma cell differentiation is a tumor suppressor gene in B cell lymphomas

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Aims. The aim of this review was to summarize recent knowledge of the structure and function of a transcriptional repressor, B lymphocyte induced maturation protein 1 (BLIMP1) and its participation in the pathogenesis of B lymphomas.

Methods and results. This review summarizes the structure and function of BLIMP1, its major target genes and its role as a tumour suppressor in B cell lymphomas. We review our recent data implicating the loss of BLIMP1 α as an important step in the pathogenesis of the Epstein-Barr virus (EBV) associated B cell lymphomas.

Conclusions. BLIMP1 is a transcriptional repressor essential for the differentiation of germinal centre (GC) B cells to plasma cells. The loss of BLIMP1 in GC B cells could contribute to the pathogenesis of EBV-associated lymphomas by preventing plasma cell differentiation and viral replication.

Key words: BLIMP1, Epstein-Barr virus, DLBCL, review

Received: August 29, 2011; Accepted: January 3, 2012; Available online: January 31, 2012
<http://dx.doi.org/10.5507/bp.2012.003>

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INTRODUCTION

BLIMP1 is a transcriptional repressor encoded by the *PRDM1* gene and is often described as the ‘master regulator’ of plasma cell differentiation. BLIMP1 was originally identified as a silencer of the human β -interferon gene1 that bound to the positive regulatory domain I (PRDI) of the β -interferon promoter and was therefore designated ‘positive regulatory domain I-binding factor 1’ (PRDIBF1). Davis et al. isolated a murine cDNA that was induced following the cytokine-dependent differentiation of the mouse lymphoma cell line, BCL1, and named this, B lymphocyte induced maturation protein 1 (BLIMP1) (ref.^{2,3}). The same group also demonstrated that ectopically expressed BLIMP1 was sufficient to drive plasma cell differentiation in BCL1 cells². Definitive proof of the indispensable role of BLIMP1 in plasma cell differentiation and Ig secretion was provided by the Calame group using a conditional knock-out of BLIMP1 in mice⁴.

GENE ORGANIZATION AND PROTEIN DOMAINS OF BLIMP1

The human *PRDM1* gene is located on chromosome 6q21-q22.1 (ref.⁵) and encodes two major isoforms, designated BLIMP1 α and BLIMP1 β , which arise from alternate promoters⁶. The full-length BLIMP1 α protein is responsible for plasma cell differentiation^{4,7}. In contrast, BLIMP1 β is transcribed from a novel promoter and new exon, 1 β , located upstream of exon 4 of the full-length gene⁶ (Fig. 1). The BLIMP1 β protein lacks the first 101 amino acids of BLIMP1 α and instead contains 3 novel

amino acids fused to amino acids 102-789 of BLIMP1 α . Since BLIMP1 β contains the DNA-binding domain but bears a disrupted regulatory domain, it has been suggested that it might inhibit BLIMP1 α functions⁶. In normal B cells, BLIMP1 β mRNA levels are substantially lower relative to the full-length form⁶.

In mice, alternative splicing of exon 7 of *PRDM1* leads to production of the BLIMP1 Δ 7 protein which lacks the first 3 zinc fingers and is therefore predicted to be non-functional⁸. Despite having impaired DNA binding activity, the BLIMP1 Δ 7 form was shown to negatively regulate proliferation and cell survival when expressed in an immature B cell line and to interfere with the activity of full-length BLIMP1 α , presumably by forming non-functional heterodimers⁹. The BLIMP1 Δ 7 isoform is preferentially expressed in naïve B cells where it might regulate the levels of BLIMP1 α (ref.⁹). A similar alternatively spliced form of the human protein was described (BLIMP1 Δ 6) (ref.¹⁰).

BLIMP1 protein has a PR domain, so-called after it was identified in both the BLIMP1 (PRDIBF1) and the Rb-binding protein RIZ1 proteins^{1,11} (Fig. 2). The PR domain is a subclass of the SET domain of histone methyl transferases (HMT) (ref.¹²). BLIMP1 also contains five Krüppel-type zinc finger DNA-binding domains located near its C-terminus; however, only the first two finger motifs appear to be required for binding to target loci¹³. The consensus-binding site for BLIMP1, the PRDI site, is an 11-bp sequence (A/C)AG(T/C)GAAAG(T/C)(G/T) and is similar to the binding sites for IFN regulatory factor (IRF)1 and IRF2 (ref.¹⁴). BLIMP1 further contains a proline-rich region and two acidic regions (one each at the N and C termini). The proline-rich region and the

first two zinc fingers of BLIMP1 are required for transcriptional repression.

MECHANISMS OF BLIMP1-MEDIATED REPRESSION OF TARGET GENES

BLIMP1 uses different mechanisms to silence its target genes in a context-dependent manner. Individual domains of the BLIMP1 protein recruit specific co-repressor complexes or chromatin modifying enzymes to mediate transcriptional repression.

The proline-rich region and the zinc finger domains are involved in the recruitment of transcriptional co-repressors of the Groucho family¹⁵. BLIMP1 complexes with the G9a histone methyltransferase through the first 2 zinc fingers resulting in methylation of lysine 9 on histone H3 (H3K9) and repression of the interferon- β promoter¹⁶. The proline-rich region and the zinc finger domains also interact with histone deacetylases (HDAC)s 1/2 to deacetylate histone H3 (ref.¹⁷) as well as with a lysine-specific demethylase, LSD1 (ref.¹⁸), that demethylates mono- or di-methyl groups on H3K4 (ref.¹⁹). It has been proposed that recruitment of HDACs 1/2 and LSD1 is a prerequisite for H3K9 methylation and for the silencing of mature B cell gene expression program during plasma cell differentiation¹⁸. Thus, BLIMP1 serves as a scaffold to recruit proteins or co-repressor complexes that modify histones (by deacetylation, H3K9 methylation, and arginine methylation) and in doing so assembles silent chromatin over the target loci. However, it remains to be determined how exactly chromatin is modified at specific BLIMP1 target genes and whether chromatin modification is the only mechanism by which BLIMP1 represses transcription.

BLIMP1 IS REQUIRED FOR PLASMA CELL DIFFERENTIATION

BLIMP1 expression is essential and sufficient for plasma cell differentiation^{4,20}. The first indication of the importance of BLIMP1 in plasma cell differentiation was provided by the demonstration that ectopic expression of BLIMP1 in mouse B cell lines or in mouse primary splenocytes promoted a plasma cell-like phenotype^{2,21}. Knock-out mice with a conditional deletion in mature B cells of all five zinc finger domains of BLIMP1, showed normal B cell development and number⁴. However, following challenge with both T-independent and T-dependent antigens, these mice showed a virtual absence of plasma cells and diminished immunoglobulin (Ig) secretion. Moreover, mice lacking BLIMP1 in the B cell lineage generated normal numbers of peripheral B cell subsets which were capable of self-renewal, but in which the secretion of all Ig isotypes was severely reduced. Germinal centres (GC) in these mice were enlarged, suggesting a developmental block at the late/post-GC stages²⁰.

The initial step of plasma cell differentiation is BLIMP1-independent and occurs as a result of the func-

tional inactivation of paired box gene 5 (PAX5) in mature B cells by a so far unidentified stimulus²². PAX5 is a transcription factor that is essential for the commitment of lymphoid progenitors to the B cell lineage and for the maintenance of 'B-cell identity' (ref.²³). The experimentally induced down-regulation of PAX5 in mature B cells results in the establishment of a 'pre-plasmablast' stage characterised by the secretion of low amounts of antibodies²². The production of antibodies is mediated by the induction and splicing of X-box binding protein 1 (XBP1), which activates multiple genes which regulate Ig production, the ER stress response (the unfolded protein response), changes in cell size and protein synthesis^{24,26}. The induction of BLIMP1 in pre-plasmablasts is necessary to stabilize and maintain the plasma cell differentiation program^{4,22}. Pre-plasmablasts are precursors of immature short-lived plasma cells, known as plasmablasts which have intermediate levels of BLIMP1, express Igs, and have a high rate of proliferation²⁷ and apoptosis²⁸. Expression of interferon regulatory factor 4 (IRF4), another transcriptional factor essential for plasma cell differentiation, is induced in plasmablasts in response to NF- κ B-mediated CD40 signalling or calcium-dependent activation of nuclear factor of activated T cells (NFAT) transcription factors^{29,34}. The differentiation of plasmablasts to long-lived, post-mitotic plasma cells producing large amounts of antibodies is associated with a further increase in BLIMP1 expression²⁷.

BLIMP1 TARGET GENES

BLIMP1 target genes have been identified in transformed human B cell lines³⁵ and in murine M12 cells³⁶ following their transfection with BLIMP1; and in BCL1 cells following their cytokine-induced differentiation³⁶.

BLIMP1 TARGET GENES CONTROLLING MATURE B CELL FUNCTIONS AND AFFINITY MATURATION

BLIMP1 silences genes which specify B cell identity, these include: surface B cell markers (*CD19*, *CD20*, *CD22*, *CD45*); B cell activation markers (*CD69*, *MIP-1 β* , *A1*); B cell-associated transcription factors (*BCL6*, *PAX5*, *SPIB*, *OCT-2*, *STAT6*, *EBF*); BCR signalling components (*BLNK*, *CD79A*, *SYK*, *BTk*, *PKC β* , *LYN*); and, genes induced by BCR signalling (*A1*, *MIP-1 β* , *CD69*, *CD83*, and *SPI-1/PU.1*) (ref.³⁵). BLIMP1 also inhibits class switch recombination (CSR) by silencing genes essential for CSR and/or somatic hypermutation (SHM) (e.g. *KU70*, *KU86*, *DNA-PKCs* and *AID*) (ref.^{37-39,35}). *CIITA* is also repressed by BLIMP1 (ref.^{40,35}), which leads to the down-regulation of MHC class II genes and antigen presentation in plasma cells⁴¹.

BLIMP1 TARGET GENES CONTROLLING CELL CYCLE AND APOPTOSIS

BLIMP1 also down-regulates genes involved in cell proliferation, partly by directly repressing *C-MYC* expression^{35,42}. Accordingly, many *C-MYC* target genes are also regulated by BLIMP1 (e.g. *RCL*, *ODC*, *LDH-A*, and *DHFR*) (ref.^{35,43,44}). BLIMP1 also down-regulates genes involved in DNA synthesis and repair (*PCNA*, *PMS4*, *KU70*, *KU86*, *MCM2*, *primase*) and cell cycle progression (*PLK*, *aurora kinase*, *CKSHS1*, *CKSHS2*, *CDC2*, *CDK2*, *E2F-1*), perhaps as an indirect consequence of the cell cycle arrest due to the loss of *C-MYC* (ref.³⁵). Although the repression of *C-MYC* transcription is necessary for the exit of B cells from the cell cycle and terminal differentiation of B cells, the removal of *C-MYC* activity is not sufficient to trigger plasma cell differentiation⁴⁵.

The expression of BLIMP1 in B cell lymphomas representative of immature or partially activated B cells induces cell cycle arrest and apoptosis, in part by repressing the expression of *C-MYC* and of the anti-apoptotic *BCL2* family member *A1* (*BCL2A1*). In contrast, in fully activated B cells BLIMP1 expression promotes differentiation^{28,46}. This has led to suggestion that BLIMP1 expression induces growth arrest and cell death at earlier stages of B cell development but promotes maturation and Ig secretion at later stages of B cell differentiation.

BLIMP1 TARGET GENES CONTROLLING IMMUNOGLOBULIN SECRETION AND PLASMA CELL FUNCTIONS

BLIMP1 activates genes involved in antibody production and the stress response³⁵. This induction is in part mediated by the inactivation of *PAX5* and de-repression of down-stream targets of *PAX5* including *XBPI* (ref.^{24,36,47}), *J chain*⁴⁸ and *IgH* chain gene⁴⁹. Accordingly, BLIMP1-expressing cells exhibit a dramatic increase in both total *Ig* mRNA as well as individual *Ig* mRNA isoforms³⁶. BLIMP1 also up-regulates the expression of *CXCR4* and the integrin receptor *VLA4* (ref.³⁶), both of which have been shown to participate in the migration of plasma cells to specialized niches in the bone marrow⁵⁰.

BLIMP1 IS A TUMOUR SUPPRESSOR GENE

The region encompassing the *PRDM1* gene (6q21–q22.1) is frequently deleted in B cell lymphomas^{51,52}. Inactivation of the *PRDM1* gene was found in a subset of diffuse large B cell lymphoma (DLBCL) of the activated B-cell type (ABC) and is believed to contribute to lymphomagenesis by blocking post-GC B cell differentiation^{53–55}. Although *PRDM1* mutations occur in only 25% of ABC-DLBCL biopsies; the majority of other cases of this subtype lack BLIMP1 protein, suggesting that additional mechanisms may inhibit BLIMP1 translation or stability⁵⁴. For example, a role for the microRNA let-7

family in mediating the translational down-regulation of BLIMP1 in DLBCL has been proposed⁵⁶. Alternatively, reciprocal translocations resulting in aberrant expression of *BCL6* could contribute to the pathogenesis of DLBCL (ref.⁵⁴). The malignant Hodgkin/Reed–Sternberg (HRS) cells of classical Hodgkin lymphoma (cHL) have BLIMP1 mRNA (ref.⁵⁷). However, several studies show that in most cases BLIMP1 protein is only weakly expressed by HRS cells^{57–60}. This could indicate that plasma cell differentiation is initiated in a fraction of HRS cells but remains abortive⁵⁸. The absence of BLIMP1 protein in HRS cells could be due to the overexpression of miR-9 and let-7a miRNA (ref.⁶¹). The malignant lymphoplasmacytic cells found in patients with Waldenstrom's macroglobulinemia also express lower levels of BLIMP1 compared to normal plasma cells⁶². Deleterious mutations of *PRDM1* associated with loss of BLIMP1 protein have also been reported in primary central nervous system lymphoma⁶³. Finally, ETS-1, the transcription factor, which is amplified in certain leukemias, interacts with BLIMP1 leading to a block in BLIMP1 DNA binding activity and a reduction in the ability of BLIMP1 to repress target genes^{64–68}.

In contrast, the over-expression of the BLIMP1 β isoform has been reported in multiple myeloma, DLBCL and in some T cell lymphomas^{6,69–71}. BLIMP1 β over-expression is associated with advanced Ann Arbor stage and a high-risk International Prognostic Index in T cell lymphomas and with a shorter patient survival in both DLBCL and T cell lymphoma patients^{70,71}. In both B and T cell lymphomas, BLIMP1 β expression is also associated with *in vitro* resistance to chemotherapeutic agents^{70,71}. Interestingly, the up-regulation of the BLIMP1 β isoform in T cell lymphomas was associated with high *C-MYC* levels⁷¹. A recent study by Zhang et al. demonstrated that the up-regulation of the PRDM1 β isoform was associated with hypomethylation of the PRDM1 β specific promoter in a subset of DLBCL with aggressive behaviour⁷².

REGULATION OF BLIMP1 BY THE EPSTEIN-BARR VIRUS

Recently, we have shown that BLIMP1 α is down-regulated in primary human germinal centre (GC) B cells following expression of the Epstein-Barr virus (EBV) oncogene, latent membrane protein (LMP1) (ref.⁷³). This is important because EBV is found in a substantial fraction of GC-derived lymphomas, including Hodgkin's lymphoma (HL), Burkitt's lymphoma (BL) and in a subset of DLBCL (ref.⁷⁴). We also showed that the re-expression of BLIMP1 α in EBV-infected B cells induced the virus lytic cycle, an event which can ultimately lead to virus replication and cell death. Our observations suggest that the loss of BLIMP1 α expression could contribute to EBV-induced lymphomagenesis not only by suppressing plasma cell differentiation by also by preventing induction of the viral lytic cycle.

Although we have shown that EBV can down-regulate BLIMP1, it is not known if BLIMP1 α is involved in the early stages of B cell immortalization and consequently in

Fig. 1. Schematic of the genomic structure and α , β and Δ mRNAs of human BLIMP1. BLIMP1 β lacks the first 3 exons and the amino-terminal 101 amino acids of BLIMP1 α and has a new exon, 1 β . BLIMP1 β transcripts initiate from an alternative promoter between exons 3 and 4. Numbered open boxes represent the exons. BLIMP1 Δ 6 lacks exon 6 and the first 3 zinc fingers (modified from Hangaishi and Kurokawa, 2010) (ref.⁷⁵)

Fig. 2. Domain structures of BLIMP1. The BLIMP1 protein harbors five zinc fingers involved in DNA binding and protein-protein interactions, two acidic regions, a PR domain and a proline rich region (modified from John and Garrett-Sinha, 2009) (ref.⁷⁶).

the establishment of primary infection. In preliminary experiments, we have shown that the infection of peripheral blood B cells with EBV is followed in the first few days of infection by the transient up-regulation of BLIMP1 α mRNA which is followed soon after by its down-regulation (Vrzalikova et al. unpublished observations). It is tempting to speculate that the up-regulation of BLIMP1 α in newly infected B cells might contribute to the induction of the viral lytic cycle which has been shown to be important for efficient EBV-induced transformation.

Our microarray studies have revealed that while the transcriptional programs of LMP1 and BLIMP1 α show a surprising overlap, an important subset of genes are repressed by BLIMP1 α but induced by LMP1. These included *C-MYC*, the suppression of which is essential for plasma cell differentiation. We have proposed that LMP1 drives a reciprocal regulatory loop involving BLIMP1 α and *C-MYC*, which ultimately leads to the activation of *C-MYC* and the repression of BLIMP1 α . Taken together our findings suggest that while LMP1 might be capable of driving post-GC B-cell differentiation, it appears to disrupt plasma cell differentiation. Our model has implications for the treatment of EBV-associated lymphomas since small molecule inhibitors of *C-MYC* might be expected to induce BLIMP1 α expression potentially resulting in differentiation and cell cycle exit.

ABBREVIATIONS

ABC-DLBCL, Diffuse large B cell lymphoma of the activated B-cell type; BCL2A1, BCL2 family member A1; BLIMP1, B lymphocyte induced maturation protein 1; cHL, Classical Hodgkin lymphoma; EBV, Epstein-Barr virus; GCs; Germinal centres; HDACs, Histone deacetylases; HMT, Histone methyl transferases; HRS, Hodgkin/Reed-Sternberg; IRF, IFN regulatory factor; Ig, Immunoglobulin; LMP1, Latent membrane protein; NFAT, Nuclear factor of activated T cells; PAX5, Paired box gene 5; PRDI, Positive regulatory domain I; PRDIBF1, Positive regulatory domain I-binding factor 1; XBP1, X-box binding protein 1.

ACKNOWLEDGEMENT

This work was supported by the Leukaemia and Lymphoma Research Fund, in part by European Union (infrastructure support CZ.1.05/2.1.00/01.0030 and CZ.1.07/2.3.00/20.0019).

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