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Regulatory Roles of the Tumor Necrosis Factor Receptor BCMA

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Abstract

B cell maturation antigen (BCMA) is a tumor necrosis family receptor (TNFR) member that is predominantly expressed on terminally differentiated B cells and, upon binding to its ligands B cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL), delivers pro-survival cell signals. Thus, BCMA is most known for its functional activity in mediating the survival of plasma cells that maintain long-term humoral immunity. The expression of BCMA has been also linked to a number of cancers, autoimmune disorders, and infectious diseases that suggest additional roles for BCMA activity. Despite the recent advances in our understanding of the roles for the related TNFR members BAFF-R and transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), the signaling pathway used by BCMA for mediating plasma cell survival as well as its putative function in certain disease states are not well understood. By examining the expression, regulation, and signaling targets of BCMA we may gain further insight into this receptor and how it operates within cells in both health and disease. This information is important for identifying new therapeutic targets that may be relevant in treating diseases that involve the BAFF/APRIL cytokine network.

Keywords

BCMA; BAFF; APRIL; B cells; plasma cells; autoimmunity

I. INTRODUCTION

We produce billions of B cells as part of normal immune homeostasis every day.¹ Only a few of these newly generated B cells survive and are considered fit enough to mature further to provide humoral immunity while the rest undergo cell death. Members of the tumor necrosis factor receptor (TNFR) superfamily and their ligands play a critical role in regulating the immune system and, in particular, controlling proliferation, differentiation, and apoptosis of B cells.² These include death receptors (CD95, TNFR1, DR4, DR5) that trigger apoptosis and receptors lacking a death domain (CD30, CD40, TNFR2), which promote cell proliferation, differentiation, and survival.³ Over the past two decades, the TNF family members belonging to the B cell activating factor (BAFF; also named zTNF4, BLyS, TALL-1, THANK, TNFSF13B) ligand-receptor network have been closely linked to the homeostasis of B cells.^{4, 5} Failure of B cells to receive signals mediated by BAFF dramatically impairs B cell maturation and the maintenance of mature B cell populations. In contrast, excess BAFF signaling of B cells significantly increases the numbers of peripheral

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B cells and has been linked to chronic inflammatory disorders, autoimmune diseases, and certain malignancies.

Enormous strides have been made toward understanding the mechanisms by which the BAFF ligand-receptor network controls the properties of B cells. BAFF can be recognized by the receptors BAFF-R (also named BR3), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), and B cell maturation (BCMA) antigen; these BAFF receptors are expressed predominantly on B cells in a temporal and maturation stage-specific fashion; BAFF signaling through each of these receptors mediates multiple functions of B cells; and lastly, abnormal production of BAFF and its receptors disrupts B cell proliferation, terminal differentiation into effector cells, and survival.^{4, 5} In recent years, several excellent reviews have discussed the signaling pathways through BAFF-R and TACI that historically are the best defined among the three BAFF receptors.^{2, 6-8} This review specifically covers the early characterization of the BCMA receptor, its physiologic significance in B cells, and the recent discoveries of how BCMA is distinct from other BAFF receptors.

II. IDENTIFICATION OF B CELL MATURATION (BCMA) ANTIGEN

Tsapis and colleagues first identified BCMA through molecular analysis of a t(4;16) (q26;p13) translocation found in a human intestinal T cell lymphoma.⁹ This translocation juxtaposed the IL-2 gene on chromosome 4 with a novel coding sequence on chromosome 16 that did not have homology with any known sequences. Subsequent screening of a cDNA library from tumor cells using an IL-2 gene-specific probe demonstrated a chimeric gene containing the first three exons of IL-2 followed by an in-frame sequence that mapped to the 16p13.1 chromosome band. To determine the normal tissue expression of mRNA transcripts homologous to the 16p13.1 chromosome band sequence, Northern blot analysis of human organs was initially performed using probes representative of the sequence juxtaposed to IL-2 sequences in the rearranged fragments.⁹ This analysis produced negative results; however, further analysis using a variety of hematopoietic cell lines revealed positive RNA signals from those of B cell lineage. RNA signals were measured in mitogen-activated primary human B cells, B lymphoblast cell lines (Daudi, BL31, 167), and human plasmacytic cell lines (RPMI8226, U266). In contrast, RNA was not detected in cell lines representative of pre-B cells (NALM-6, JEA, REH, KM3) and resting primary human mature B cells.⁹ RNase protection assays confirmed that BCMA mRNA is predominantly expressed in terminally differentiating B cell lines.^{10, 11} These results were the first to suggest that the RNA homologous to the sequence contained within the 16p13.1 chromosome band, and the corresponding gene, is expressed in mature B cells associated with terminal differentiation properties and was named BCMA for B Cell Maturation.

Cloning of normal human BCMA cDNA demonstrated an open reading frame of 552 bp that encodes a 184 amino acid polypeptide.⁹ The Tsapis group subsequently showed that the BCMA gene is organized into three exons that are separated by two introns, each flanked by GT donor and AG acceptor consensus splicing sites, and codes for a transcript of 1.2 kb.¹⁰ Early computational analysis of the structure of BCMA protein showed no homology with previously characterized proteins and predicted an integral transmembrane protein based on a central 24 amino acid hydrophobic region in an α -helix structure. Initial biochemical characterization of human BCMA protein expression using U266 plasmacytic cells and BCMA-specific rabbit polyclonal sera demonstrated that BCMA is not expressed at detectable levels on the cell surface, but is located on the Golgi apparatus.¹¹ Interestingly, BCMA is the first Golgi resident protein identified whose expression is linked to a specific cell lineage (B cells) and whose amount of expression is proportional to the stage of cellular differentiation (highest in plasma cells). Since the Golgi system is larger and more numerous

in plasma cells and is integral in modifying, sorting, and packaging proteins for cell secretion, Gras et al. hypothesized that BCMA may play an important role in facilitating antibody secretion.¹¹ This hypothesis remains to be directly tested.

Cloning and characterization of the murine homolog of the BCMA gene demonstrated that the murine BCMA gene, located on chromosome 16 syntenic to the human 16p13 region, also consists of three exons that are separated by two introns and encodes a 185 amino acid protein.¹² Analysis using a variety of murine hematopoietic cell lines demonstrated that murine BCMA mRNA was expressed as a 404 bp transcript at the highest levels in plasmacytoma cells (J558) and at modest levels in the A20 B cell lymphoma line. Interestingly, murine BCMA mRNA transcripts were also detected at low levels in T cell lymphoma (EL4, BW5147) and dendritic cell (CB1D6, D2SC1) lines in contrast to human cell lines of T cell and dendritic cell origin. The murine BCMA cDNA sequence has 69.3% nucleotide identity with the human BCMA cDNA sequence and slightly higher identity (73.7%) when comparing the coding regions between these two cDNA sequences. Mouse BCMA protein is 62% identical to human BCMA protein and, like human BCMA, contains a single hydrophobic region suggestive of an internal transmembrane segment.¹² Sequence analysis of the N-terminal 40 amino acid domain of both murine and human BCMA protein revealed six conserved cysteine residues, consistent with the formation of a cysteine repeat motif found in the extracellular domain of TNFRs. Similar to members of the TNFR superfamily, BCMA protein contains a conserved aromatic residue four to six residues C-terminal from the first cysteine.¹³ Based on these findings, BCMA was identified as a new TNFR member and assigned the gene nomenclature TNFRSF17.

III. THE BAFF-BCMA CONNECTION

BAFF (zTNF4) was identified as a member of the TNF ligand superfamily through analysis of a human-granulocyte-derived cDNA library,¹⁴ and was found to be a potent co-stimulator of B cell activation and antibody production *in vitro* and *in vivo*.^{15, 16} In early 2000, several groups determined that BCMA was a receptor for BAFF. Gross et al. identified BCMA, along with TACI, as receptors for BAFF through analysis of zTNF binding to COS7 cells transfected with a cDNA library prepared from the B lymphoblastoid RPMI 1788 cell line.¹⁷ Soluble forms of TACI and BCMA were demonstrated to bind zTNF4 and inhibit the co-stimulatory activity of zTNF4 on both human and murine B cells *in vitro*. Equally important, this group was among the first to show that there was a strong association between the amounts of soluble BAFF protein in sera of the lupus-prone New Zealand black/white mouse model and disease severity. Treatment of New Zealand black/white mice with soluble TACI reduced disease pathogenesis. These results were consistent with studies by two independent groups who observed the spontaneous development of a lupus-like disease in transgenic mice engineered to overexpress BAFF.^{18, 19} These groups demonstrated that BAFF transgenic mice develop abnormally high numbers of mature B cells in the spleen, spontaneous germinal centers, autoantibody production, and immune complex deposition in kidneys.

Two other groups also used a soluble BCMA-Ig-Fc fusion protein to determine that BCMA is a receptor for BAFF and could bind to both soluble and membrane forms of BAFF.^{20, 21} Rennert et al. further demonstrated that soluble BCMA could also bind the BAFF homologue, a proliferation-inducing ligand (APRIL), whose interaction is of higher affinity compared to BCMA-BAFF interactions.²¹ A subsequent report also demonstrated that BCMA has a higher affinity for APRIL than for BAFF,²² which is due to the Tyr13 and Arg27 residues within the cysteine rich domain of BCMA that are essential for APRIL binding but are dispensable for BAFF binding.^{22, 23} Following *in vivo* administration of soluble BCMA, the APRIL-BCMA-mediated growth of human adenocarcinoma and lung

carcinoma cell lines in nude mice was inhibited.²¹ These findings suggested early on an important role for BAFF and APRIL in tumorigenesis and, in particular, tumors that express BCMA. In addition, a profound biological activity of BAFF on normal B cell effector function was also demonstrated by reduced antigen-specific antibody responses and decreased germinal center formation in the spleens of mice treated with soluble TACI after antigenic challenge.²¹

Using soluble forms of BCMA and TACI, Marsters et al. confirmed that these receptors interact with both BAFF and APRIL, and were further validated in transfection studies of COS7 cells with expression vectors encoding the full-length receptors.²⁴ Interestingly, BCMA localized to the cell surface and bound to soluble BAFF and APRIL in transfected cells, suggesting that BCMA can be membrane-anchored in addition to its localization in the Golgi complex as previously described. The notion that BCMA could be expressed on the cell surface and, thus, interact with cell-extrinsic ligand was confirmed by Thompson et al. through flow cytometric analysis of transfected 293 cells and, importantly, primary human tonsillar B cells using an anti-BCMA antibody.²⁵ Detection of murine BCMA on the cell surface has been more challenging. We and others have detected no BCMA on the cell surface of normal mature murine B cells and modest levels on the surface of murine plasma cells.^{26–29} Differences in the cell surface expression of BCMA between mouse and human B cell populations could arise from natural variation in expression patterns and/or the detection reagents available for measuring protein levels. Thus, most analyses of mouse BCMA expression have been derived from measuring mRNA transcript levels. In addition to the cell types discussed previously, a summary of all human and mouse cell types reported to express BCMA mRNA transcript and protein levels is provided in Table 1.

Together, the studies described above revealed a dual ligand-receptor system that plays a critical role in humoral immunity and set the stage for developing therapeutic strategies that interrupt BAFF (and APRIL) activity for treating autoimmune diseases and cancer.

IV. BCMA-MEDIATED SIGNALING PATHWAYS

The Ashkenazi group was among the first to establish the signaling mechanisms by which BCMA delivers its co-stimulatory activity to B cells for IgM production;²⁴ interaction of BCMA (as well as TACI) with APRIL or BAFF induces the activation of NF- κ B.^{17, 30–32} Biochemical analysis of BCMA-mediated activation of the NF- κ B pathway further identified multiple downstream signal transducers. Transfection studies using 293 cells that overexpress BCMA and dominant negative mutants of the signaling proteins TNFR-associated factor 2 (TRAF2), TRAF5, TRAF6, NF- κ B-inducing kinase, IKK α , and IKK β inhibited BCMA-mediated activation of the NF- κ B pathway.³⁰ Consistent with these findings, BCMA was found to physically interact with TRAF2, TRAF5, and TRAF6 as demonstrated from co-immunoprecipitation experiments.³⁰ TRAF1 and TRAF3 were also determined to physically interact with BCMA, but their functional role in BCMA-mediated NF- κ B activation is unknown.³² Activation of the NF- κ B pathway through BCMA signaling was confirmed using an agonistic anti-BCMA antibody to membrane-expressed BCMA on the human macrophage-like cell line THP-1,³³ and using the H929 B cell lymphoma line when stimulated with APRIL.³⁴ However, BAFF stimulation of B cell lymphoma cells demonstrated that BCMA did not interact with TRAF3 in contrast to BAFF-R and TACI, which both interacted with TRAF3 following stimulation.³⁵ Analysis of the intracytoplasmic domain of BCMA revealed that a 25 amino acid segment (position 119–143) is critical for its interaction with the TRAFs and the activation of NF- κ B.³⁰ This segment was also found to be important for the activation of Elk-1, a substrate for JNK, p38, and ERK. Activation of JNK and p38 were also determined in human adipose-derived stem cells when stimulated with BAFF and APRIL; however, since both TACI and BCMA are

expressed by these stem cells the relative contribution of TACI and BCMA to MAPK activation is unknown.³⁶ These studies indicate that when BCMA is expressed in multiple cell types it can deliver downstream signals that activate the NF- κ B pathway, but suggest that the signal transducers involved may be specific to the stimuli and cell type.

V. REGULATION OF BCMA EXPRESSION

Following the identification of the murine BCMA gene, analysis of the expression of murine BCMA mRNA revealed an alternate splice form in addition to the full-length transcript.¹² PCR amplification of murine BCMA mRNA transcripts from J558 cells resulted in two sequences, one corresponding to the normal BCMA mRNA sequence, and the other to a truncated sequence of 145 bp corresponding to a splice variant that lacks exon 2 encoding the transmembrane domain.¹² This finding has potential biological significance because it suggests that a soluble form of the BCMA receptor can be produced which could act as a natural decoy receptor. Interestingly, four splice variants of human BCMA mRNA transcripts have been found in CD19⁺ PBMCs of which one variant also lacks exon 2, similar to the mouse splice variant.^{12, 37} The remaining human BCMA mRNA splice variants have truncations in exon 1 that could alter receptor binding to BAFF/APRIL and one with a potential cryptic exon within intron 2 that may alter the intracellular domain and, thus, signaling capacity.³⁷ It remains to be determined whether these splice variants are biologically active receptors and, if so, the potential roles they may have in regulating BAFF/APRIL signals.

Interestingly, a natural antisense BCMA RNA that is transcribed from the opposite strand of the BCMA gene, encoding a putative 115 amino acid protein, was identified in several human B cell lines (RPMI 8226, U266B1, 167, Daudi, BL36, Raji, REH).¹⁰ Transfection studies further demonstrated that overexpression of antisense BCMA RNA in cell lines that express BCMA decreased both BCMA-mediated NF- κ B activation and BCMA protein expression.³⁸ So far, there have been no reports of antisense BCMA RNA transcripts present in murine B cells. These observations suggest that BCMA expression in primary B cells may be controlled by mechanisms involving natural antisense transcripts. Thus, antisense BCMA RNA may regulate BCMA expression in terminally differentiating B cells and/or bind to sense RNA, masking the splice sites and thereby changing the balances between splice variants. These are important issues to also consider for how BCMA expression and, thus, signaling is abnormally regulated in autoimmunity and BCMA-expressing cancers.

Little is known about how BCMA expression is regulated. Analysis of the human BCMA gene revealed a TATA box located upstream of the transcription initiation site,¹⁰ suggesting a role for transcription factors. Examination of the nucleotide sequence upstream of the transcription initiation site in the mouse BCMA gene indicated that it did not contain a typical TATA box, but showed evidence for several high consensus sites of transcription factors.³⁹ These sites include the transcription factors Oct-1, GATA-1, c-myb, Pbx1b, Bcd, cdxA, HSF, CRE-BP, and AP-1. In addition, the transcription factors POU2AF1, RUNX3, and Blimp-1 have specific binding sites in the 5' region,⁴⁰ or within the BCMA promoter,^{39, 41} and have been shown to induce the expression of BCMA. Interestingly, overexpression of Blimp-1 in J558L plasma cells increased promoter activity of the mouse BCMA gene while shRNA knockdown of Blimp-1 mRNA decreased expression of BCMA mRNA transcript and protein levels.³⁹ Using myeloma cell lines, Shaffer et al. demonstrated that BCMA co-immunoprecipitates with IRF-4,⁴² a transcription factor important for controlling plasma cell differentiation and class switch recombination,⁴³ suggesting that BCMA is a direct target of IRF-4. Given that BCMA is predominantly expressed in terminally differentiated plasma cells these observations suggest that Blimp-1 and IRF-4 are positive regulators of the murine BCMA gene and are important for maintaining BAFF/

APRIL-BCMA-mediated survival of plasma cells. Further work is needed to confirm whether Blimp-1 and IRF-4 control BCMA expression in human B-lineage cells.

Several cytokines and B cell co-stimulatory molecules have been identified that lead to BCMA transcription. Stimulation of primary murine B cells with IL-4 and IL-6 upregulates the expression of BCMA mRNA transcript levels,³¹ which are further increased when cells are exposed to BAFF and an agonistic anti-CD40 antibody.²⁹ In addition, it has been demonstrated that the expression of BCMA increases in B-1 cells but not in splenic B-2 (conventional) cells when stimulated with the TLR9 agonist, CpG.²⁸ Finally, post-translational modification of BCMA could also regulate the expression and activity of BCMA protein. BCMA contains several post-translational modification sites, with only 4 shared between mouse and human.¹² These include a PKC phosphorylation site in the N-terminus, a PKC phosphorylation site in the C-terminus, and two CKII phosphorylation sites in the C-terminus. The impact of these modification sites on both the expression and function of BCMA remains to be determined.

VI. BCMA DOES NOT MAINTAIN NORMAL B CELL HOMEOSTASIS BUT MEDIATES THE SURVIVAL OF LONG-LIVED PLASMA CELLS

Because the predominant expression of BCMA is in B lineage cells and BAFF can drive B cell proliferation and antibody production, it was anticipated that a deficiency in the BCMA gene would greatly influence B cell responses. However, analysis of BCMA deficient (BCMA^{-/-}) mice revealed no overt differences in the steady-state frequencies or composition of peripheral B cell subsets (immature, marginal zone, follicular, B1) compared to wild type mice.⁴⁴ These observations were consistent with BCMA^{-/-} mice showing normal B cell development in the bone marrow (pre-B, immature) compared to control animals, albeit based on limited analysis. Moreover, there were no differences in basal circulating antibody titers between naïve BCMA^{-/-} and wild type mice. Antigen-specific B cell responses to both T cell-independent and T cell-dependent antigens, including the formation of germinal centers, were also found to be equivalent between BCMA^{-/-} mice and controls.⁴⁴ These observations were mirrored in a separate study using a different approach. Schneider et al. generated transgenic mice that produced a soluble form of TACI or a soluble form of BCMA that bind to endogenously produced APRIL and BAFF, acting as inhibitory decoy receptors.⁴⁵ Mice transgenic for soluble BCMA had no detectable differences in their B cell phenotype compared to control animals. In contrast, mice transgenic for soluble TACI had significantly reduced frequencies of peripheral transitional T2 B cells, marginal zone B cells, and mature follicular B cells. These studies indicated that B cell development and the homeostasis of peripheral mature B cells were not controlled through a BCMA signaling pathway. Equally important, the developmental block of B cell maturation when BAFF and APRIL were inactivated by soluble TACI, together with abnormal homeostasis of peripheral B cells in mice transgenic for BAFF expression,^{18, 19} demonstrated a critical role for these ligands in controlling B cell physiology and humoral immunity, and implicated a role for another receptor.

We now know that BAFF is a critical factor for B cell maturation, tolerance, and the survival of peripheral B cells through the binding of its receptor BAFF-R.^{46, 47} BAFF-R is first expressed on transitional B cells at the T2 stage and increases its expression throughout B cell maturation, with the highest levels of BAFF-R expression on B cells in the lymphoid follicle and the marginal zone of the spleen.^{48, 49} BAFF-R-deficient mice resemble the phenotype of BAFF-deficient mice, showing impaired B cell maturation at the transitional stage and the loss of mature B cell populations.^{45, 50} The signaling pathway through BAFF-R is the best defined among the three BAFF receptors. When BAFF binds to BAFF-R, the adaptor protein TRAF3 is recruited to the receptor, preventing the degradation of NF- κ B-

inducing kinase.^{35, 51, 52} In turn, NF- κ B-inducing kinase processes the classical NF- κ B pathway substrate, p100, to generate the alternative NF- κ B2 substrate, p52. Translocation of p52 into the nucleus promotes cell survival by inducing the anti-apoptotic protein Mcl-1 and the serine-threonine kinase Pim2.^{51, 53} Mcl-1 and Pim2 promote B cell survival by inhibiting transcription of the pro-apoptotic genes *Bad* and *Bim*, respectively. This B cell survival pathway is both mediated and limited to low amounts of BAFF present in the periphery under normal physiologic conditions and is critical for maintaining non-autoreactive B cells.

The role for BAFF-BAFF-R interactions in controlling B cell survival involves additional signals; cross talk between BAFF-R signaling and B cell receptor signaling pathways is important for regulating B cell homeostasis in the periphery.^{2, 4, 48, 49} Since B cells undergo apoptosis in the absence of B cell receptor or BAFF-R signaling, signals delivered through both receptors appear to be required for the survival of mature B cells.^{50, 54} Under normal physiologic conditions, signaling through BAFF-R alone would eventually exhaust intracellular stores of p100 to generate p52 and curtail B cell survival. Thus, reserves of p100 are needed to support the survival of B cells. Low-level tonic B cell receptor signals trigger the classical NF- κ B pathway, leading to the upregulation of p100 transcription that replenishes p100 stores. Interestingly, autoreactive B cells are more dependent than other B cells for BAFF-mediated survival.^{55, 56} The increased dependency for BAFF-mediated survival of autoreactive B cells could result from increased occupancy of BAFF-R, or other BAFF receptors such as BCMA that we discuss below. Thus, when the availability of BAFF is limited in normal physiologic conditions, healthy mature B cells preferentially survive while autoreactive B cells die by apoptosis.

Although BCMA^{-/-} mice did not demonstrate detectable changes in B cell development and peripheral B cell immune responses compared to wild type mice, Noelle and colleagues determined that BAFF and APRIL signaling through BCMA sustains the survival of antigen-specific bone marrow-resident plasma cells after antigenic challenge.⁵⁷ This observation is consistent with BCMA being predominantly expressed in terminally differentiated plasma cells in both humans and mice.^{57, 58} BCMA is also expressed on human tonsillar memory B cells and germinal center B cells,⁵⁸ but has not been detected on murine memory B cells and is not required for their survival.²⁷ Together, these findings demonstrate that while BCMA does not play a role in normal murine B cell homeostasis it is critical for the long-term survival of murine bone marrow plasma cells.

VII. ROLE FOR BCMA IN AUTOIMMUNITY

Early evidence quickly demonstrated a close link between BAFF, APRIL, BCMA, and autoimmunity.¹⁷ In lupus-prone mouse models and SLE patients as well as patients with rheumatoid arthritis, circulating amounts of BAFF are abnormally high and correlate with increased numbers of peripheral autoreactive B cells, heightened B cell activation, and autoantibody production.^{17, 59, 60} Pre-clinical studies examining the therapeutic benefit of neutralizing BAFF in lupus-prone mice demonstrated reductions in peripheral B cell numbers as well as reductions in the frequency of plasma cells when both BAFF and APRIL were blocked.^{61, 62} Results from these studies provided the basis for developing BAFF antagonists as potent therapeutics for autoimmune disorders where B cell depletion would be predicted to ameliorate disease activity by reducing the numbers of newly activated B cells that secrete pathogenic IgG autoantibodies. There are several agents currently in development that target and neutralize BAFF activity. These agents and their potential for providing clinical benefit to SLE patients have been recently discussed.^{63–65} In general, the clinical trials using BAFF-targeting agents have shown less promising clinical response rates than anticipated despite effective depletion of peripheral B cells. However, analysis of the human mAb belimumab (Benlysta) that inhibits BAFF demonstrated clinical benefit in adult

patients with active SLE and was approved in 2011 for treatment of active lupus. Collectively, the analyses of BAFF-specific inhibitors raise a question regarding the potential of BAFF antagonists for treating autoantibody-mediated autoimmune disorders in which autoreactive B cells have already differentiated into long-lived effector B cells such as memory and/or long-lived plasma cells. This is an important issue since long-lived autoreactive plasma cells have been shown to accumulate not only in the bone marrow but also in secondary lymphoid organs and inflamed tissues of lupus-prone mice.^{66, 67} Interestingly, in certain lupus-prone mouse strains neither treatment with antagonists to BAFF nor APRIL reduces autoantibody production and immune complex deposition within kidneys,⁶¹ suggesting that terminally differentiated autoreactive plasma cells do not have increased dependency on BAFF/APRIL for survival in contrast to peripheral autoreactive B cells. Therefore, chronic autoantibody production could be maintained through low-level tonic BCMA signals that trigger the survival of long-lived autoreactive plasma cells similar to healthy protective plasma cells. This would suggest that an alternative strategy to deplete autoantibody-secreting plasma cells is through the loss of BCMA-mediated survival signals.

Based on the above observations, we hypothesized that BAFF/APRIL-mediated survival of long-lived plasma cells would be significantly impaired in lupus-prone mice deficient in BCMA and lead to reduced autoantibody production. To test this hypothesis, we analyzed two different lupus-prone mouse models, B6^{lpr} and B6.Nba2 mice, and compared the development of autoimmune traits of these mice to those that were bred onto a BCMA deficient background. Contrary to what we predicted, we found that the loss of BCMA in both lupus-prone strains led to: 1) an accelerated lymphoproliferative disorder, particularly within the mature B cell compartment; 2) increased numbers of short-lived and long-lived plasma cells that are sustained within secondary lymphoid organs; and 3) exacerbated autoimmune traits including heightened levels of serum anti-nuclear IgG antibodies and BAFF, and enhanced immune complex deposition in kidneys.²⁶ These findings revealed a novel regulatory role for BCMA to control B cell homeostasis and self-tolerance in an autoimmune susceptible environment. This work raises at least two important questions. First, what role does BCMA signaling play in regulating B cell responses in lupus susceptible hosts? Second, in the absence of BCMA signaling, do signals through TACI and/or BAFF-R become disease relevant, promoting the abnormal homeostasis of peripheral B cells and their differentiation into plasma cells?

The abnormal homeostasis of peripheral mature B cells in BCMA-deficient lupus-prone mice was unanticipated given that the frequency of peripheral B cells in the parental, nonautoimmune BCMA^{-/-} strain is normal,⁴⁴ and that BCMA expression is undetectable on the surface of B cells from both wild type and lupus-prone mice on a BCMA-sufficient background.²⁶ These observations suggested that signaling through membrane-anchored BCMA on B cells would not likely play a role in maintaining peripheral B cell homeostasis. However, analysis of intracellular expression of BCMA demonstrated higher steady-state levels in mature B cells of B6^{lpr} mice compared to B cells of wild type mice.²⁶ Therefore, it is possible that B cells within autoimmune hosts stably express intracellular BCMA as a means for increasing the dependency of BAFF/APRIL-mediated survival to promote apoptosis of autoreactive B cells. Yet, the capacity of BCMA to stringently eliminate the survival of autoreactive B cells in lupus susceptible hosts is overridden when BAFF is produced at abnormally high levels. This notion is consistent with several reports demonstrating that BCMA expression levels are increased on B cells from SLE patients compared to B cells from healthy donors.^{68–70} Interestingly, Kim et al. demonstrated that BCMA expression on B cells is associated with cellular activation since increased levels of BCMA are measured on activated B cells from both SLE patients and healthy individuals, and are increased further after TLR9 stimulation.⁷⁰ Co-stimulation of TLR9 and BCMA using an agonistic anti-BCMA antibody enhanced B cell proliferation and antibody

production *in vitro* compared to B cells stimulated through TLR9 alone. These observations suggest that TLR9-mediated activation of human B cells positively regulates BCMA expression that can contribute to antibody production, including autoantibodies. Further analysis is required to determine whether BCMA-expressing B cells from lupus-prone mice represent cells of an activated phenotype, if BCMA expression is also upregulated on TLR9-activated murine B cells from nonautoimmune mice, and whether signaling through BCMA influences B cell responses when BAFF-R and TACI are engaged.

BCMA expression has also been demonstrated to be upregulated on PBMCs from mice that develop a Sjogren's-like syndrome,⁷¹ patients with Sjogren's syndrome,⁷² and patients with rheumatoid arthritis.⁷³ Whether the BCMA-expressing cells in these patients represent activated mature B cells will be important to establish. Screening for variations of the human BCMA gene in patients with rheumatoid arthritis, SLE, and common variable immunodeficiency has revealed no evidence for association of mutations with disease,^{60, 74, 75} suggesting that changes in BCMA protein levels on B cells of these patients is controlled by other factors. BCMA expression does not appear to be associated with all autoimmune disorders. Patients with myasthenia gravis, multiple sclerosis, and idiopathic thrombocytopenic purpura do not have any detectable changes in BCMA expression levels on PBMCs compared to healthy controls.^{76, 77}

We propose several possible mechanisms by which BCMA regulates plasma cell differentiation and survival in autoimmunity. First, abrogation of BCMA signaling leads to accelerated B cell differentiation into plasma cells. Evidence to support this hypothesis is provided by our observation that mature B cells from BCMA-deficient lupus-prone mice rapidly proliferated and differentiated into plasma cell after adoptive transfer into nonautoimmune wild type recipient mice compared to B cells from BCMA-sufficient parental strains.²⁶ Second, BCMA regulates the frequencies of BAFF-producing cells through an unknown mechanism. Our studies demonstrated that both BAFF levels and the number of BAFF-producing cells (macrophages, dendritic cells) were increased in BCMA-deficient lupus-prone mice compared to BCMA-sufficient control animals.²⁶ We have further determined that the number of neutrophils, a key source of BAFF and APRIL, is significantly increased in the spleens and lymph nodes of BCMA-deficient lupus-prone mice compared to control strains (C.M. Coquery and L.D. Erickson, unpublished data). We hypothesize that the heightened amounts of BAFF and APRIL produced locally within the secondary lymphoid organs sustain the survival of long-lived plasma cells. This would suggest that BAFF/APRIL-mediated survival of plasma cells is controlled by BAFF-R or TACI in the absence of BCMA. We believe that TACI is the most likely candidate since we have measured detectable levels of TACI but not BAFF-R on plasma cells.²⁶ Lastly, BCMA may be expressed on non-B cells in autoimmunity that, upon engagement with BAFF and APRIL, regulates their biological activity to activate B cells and drive terminal B cell differentiation. We previously demonstrated that splenic dendritic cells are constitutively active in B6.*Nba2* mice and produce copious amounts of IL-6, IL-10, and IFN α that directly promote B cell differentiation into antibody-secreting cells.⁷⁸ Thus, BCMA signaling may affect other immune cell populations, in addition to B cells, that indirectly control B cell responses in autoimmune susceptible hosts. These cell populations would exacerbate B cell responses in the absence of BCMA. A thorough analysis of BCMA expression levels on both B cells and non-B cells in healthy hosts and lupus susceptible hosts will likely reveal important insights into additional cell types that contribute to disease pathogenesis.

VIII. ROLE FOR BCMA IN OTHER DISEASES

1. Cancer

BCMA is expressed on a number of hematologic malignancies. BCMA is expressed in both Hodgkin's and non-Hodgkin's lymphomas.^{79–83} The biological relevance of BCMA in maintaining the viability and proliferation of malignant cells has been demonstrated by Chiu et al.⁷⁹ BCMA expression is also found on both primary tumor cells and cell lines of multiple myeloma.^{81, 84, 85} Interestingly, these tumor cells consistently express BCMA while the expression levels of TACI and BAFF-R vary among myeloma cell lines and primary cells, suggesting that, like healthy plasma cells, signals through BCMA mediate the survival of tumor cells. This hypothesis is supported by several studies that demonstrated a critical role for BCMA in protecting myeloma cells from apoptosis.^{81, 85} Interestingly, Cassinelli et al. measured a substantial decrease in BCMA expression in multiple myeloma cells after treatment with the pan-tyrosine kinase inhibitor RP-1.⁸⁶ Given that the main downstream signaling targets of RP-1 are FGF-R3, Jak2, Akt and Stat3, this finding suggests that these molecules are important for inducing or maintaining BCMA expression. Thus, BCMA-specific antagonists may have significant clinical benefit for BCMA-expressing cancers. Evidence to support this therapeutic strategy is provided by the inhibitory anti-BCMA antibody, SG1, promoting antibody-dependent cell-mediated cytotoxicity of BCMA-expressing multiple myeloma cells.³⁴ Transfection studies of BCMA using HEK 293 cells not only confirmed this observation but also established that SG1 inhibited APRIL binding to the BCMA receptor.³⁴ Interestingly, it has been reported that anti-BCMA antibodies measured in sera of myeloma patients undergoing bone marrow transplantation are able to kill BCMA-expressing multiple myeloma cells *in vitro*.⁸⁷ Individual reports have also shown that BCMA is expressed in other cancers, including leukemia,⁸⁸ Waldenstrom macroglobulinemia,⁸⁹ and glioblastoma/astrocytomas.⁹⁰ Therefore, *in vivo*, SG1 and other BCMA antagonists may be able to function in several capacities by limiting BAFF/APRIL-BCMA-mediated tumor cell survival and by promoting tumor cell lysis.

2. Infection

BCMA has been implicated in the context of both viral and fungal infections.^{91–93} Peripheral blood B cells isolated from HIV+ viremic patients have increased expression levels of BCMA compared to HIV+ aviremic patients and healthy controls.⁹¹ A subsequent report measured increased BCMA expression levels on total cells from lymph node biopsies taken from HIV infected patients in transition from the acute to the asymptomatic stage.⁹³ Whether these differences in BCMA expression patterns reflect the activation state of B cells or the tissue origin is unknown. During fungal infection with *C. neoformans*, Xia et al. found a significant decrease in the expression levels of BCMA on PBMCs isolated from individuals infected compared to healthy controls.⁹² The biological relevance of BCMA expression in the infection process of these pathogens remains to be determined.

3. Mucosal immunity

BCMA has also been linked to mucosal immunity. Using BCMA and TACI double knockout animals, Massacand et al. demonstrated that the ability of Peyer's Patch-derived dendritic cells to drive CD40-independent IgA production required these two receptors.⁹⁴ These findings suggest that BCMA signaling in B cells and non-B cells is important for driving protective IgA responses. Consistent with this finding, the expression of BCMA within the gut has been demonstrated. Work by Barone et al. demonstrated that BCMA was expressed in microdissected tissue sections from the lamina propria of the ileum and colon of healthy individuals.⁹⁵ Abnormal expression or signaling of BCMA in the gut may be relevant to diseases such as irritable bowel disease and ulcerative colitis. Microarray

analysis has identified 4 single nucleotide polymorphisms in the human BCMA gene that individually do not associate with susceptibility to irritable bowel disease and ulcerative colitis, but specific combinations of the 4 single nucleotide polymorphism haplotypes were found to associate significantly with either irritable bowel disease or ulcerative colitis compared to healthy controls.⁹⁶ Whether the role of BCMA in mucosal immunity and disease is related to BCMA expression on B cells or other cell populations within the gut is unknown and warrants investigation.

IX. CONCLUSIONS AND FUTURE DIRECTIONS

BCMA is a member of the TNFR superfamily and is one of three receptors for the cytokine BAFF. Analysis of BCMA expression using both human and murine systems has demonstrated that BCMA is predominantly expressed in B-lineage cells where it is highest within terminally differentiated plasma cells. The binding of BCMA to its ligands BAFF and APRIL leads to the transcription of anti-apoptotic genes important for cell survival. Both *in vitro* and *in vivo* studies have demonstrated that BAFF/APRIL-BCMA interactions promote the survival of long-lived plasma cells and are not involved in regulating either B cell development or the homeostasis of normal mature B cells. This has led to the conclusion that the biological activity of BCMA is most relevant to humoral immunity through supporting plasma cell longevity, particularly those plasma cells that reside within the bone marrow. However, the majority of work to date has analyzed BCMA expression and function using human B-lineage cell lines, primary cells from human plasma cell malignancies, and primary murine B cells from healthy animals leaving open the question of whether BCMA is expressed differently on B cells and non-B immune cell types in certain disease states.

Work performed by our laboratory indicates that BCMA plays a significant role in maintaining homeostasis, tolerance, and terminal differentiation of B cells when analyzed in preclinical lupus-prone mouse models. In the absence of BCMA, lupus-prone mice develop a B cell lymphoproliferative disorder and a more severe autoimmune phenotype, including elevated titers of sera autoantibodies and circulating BAFF as well as heightened numbers of plasma cells that reside within secondary lymphoid organs. These findings provide some of the first evidence that BCMA plays an important role within autoimmunity to curtail B cell responses. We propose that BCMA may be functionally active in both B cells and non-B immune cell types that control the activation, differentiation, and survival of B cells in autoimmune susceptible hosts. Future studies to elucidate the expression, regulation, and signaling pathways of BCMA within immune cells will be important to determine the biological properties of this receptor in both health and disease. This information will provide important insights into how BCMA might be harnessed for devising therapeutic strategies that would be useful in treating antibody-mediated autoimmune disorders, certain infections, and BCMA-expressing malignancies.

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Abbreviations

APRIL	A proliferation inducing ligand
BAFF	B cell activator of the TNF family
BAFF-R	B cell activator of the TNF family receptor

BCMA	B cell maturation antigen
SLE	Systemic lupus erythematosus
TACI	Transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TNF	Tumor necrosis family
TNFR	Tumor necrosis family receptor
TRAF	Tumor necrosis family associated factor

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Table I

BCMA Expression in Tissue and Cellular Sources

Source	Identification Method
<u>Cell Lines:</u>	
Acute Lymphoblastic Leukemia: LBL31 ¹¹	RT-PCR, IP
* Dendritic Cell: D2SC1, ¹² CB1DG ¹²	RT-PCR
* Epithelial Tumor: 167 ¹¹	RT-PCR
Glioma/Astrocytoma: SKMG12, ⁹⁰ T98H, ⁹⁰ SF126, ⁹⁰ U399MG, ⁹⁰ U118MG, ⁹⁰ CB193 ⁹⁰	RT-PCR
Hodgkin: HD-MyZ, ⁷⁹ L428, ⁷⁹ KM-H2, ⁷⁹ L1236 ⁷⁹	RT-PCR, WB
Mantle Cell/Burkitt's Lymphoma ⁸³	RT-PCR, WB, FM
* Myeloma/Carcinoma: U266, ¹¹ HT29, ⁸¹ KAS-6/1, ⁸¹ DP-6, ⁸¹ A20, ¹² RPMI8226, ^{11, 85} KMS11, ⁸⁶ J558L ^{12, 39}	RT-PCR, FC, WB
Non-Hodgkin's Lymphoma: BL36, ¹¹ Raji, ¹¹ Daudi ^{9, 11}	NB, RT-PCR, IP
Precursor B Cell: JEA, ¹¹ DLBCL, ⁸² 207, ⁸⁸ SUP-B15, ⁸⁸ BLIN-1, ⁸⁸ NALM-6 ⁸⁸	RT-PCR, FC
<u>Primary Cells:</u>	
Adipocytes ^{36, 97}	IHC, RT-PCR, FC
* Bone Marrow B Cells ^{27, 58} (Plasma cells, Memory)	FC, RT-PCR
Fibroblast-like Synovial Cells ⁷³	RT-PCR, IHC
Keratinocytes ⁹⁸	FC, IHC
Peripheral Blood Cells ^{36, 37, 68, 76, 77, 81, 91–93, 96, 99–101}	FC, MR, RT-PCR, TP
* Peritoneal B Cells ²⁸	RT-PCR, FC
* Splenic B Cells ^{26, 27, 29, 81, 99, 102} (CD38 ⁺ , Memory)	FC, RT-PCR
Tonsillar B Cells ^{25, 58, 79, 83, 95, 99, 103–105} (Germinal center, Naïve, Memory, Centroblasts, Centrocytes)	FC, FM, IHC
Tumor Cells: Waldenstrom Macroglobulinemia, ⁸⁹ Mantle Cell/Burkitt's Lymphoma, ⁸³ Hibernoma, ⁹⁷ Liposarcoma, ⁹⁷ Multiple Myeloma, ^{81, 84} Chronic Lymphocytic Leukemia, ¹⁰⁶ Squamous Cell Carcinoma ⁹⁸	RT-PCR, WB, FM, FC, IHC
<u>Tissue:</u>	
Adrenals ¹¹	RT-PCR
Ileum/Colon ⁹⁵	RT-PCR
Kidney ⁶⁹	RT-PCR
Liver ¹¹	RT-PCR
Lymph Node ¹¹	RT-PCR
Placenta ^{10, 107}	SB, RT-PCR, IHC
Spleen ^{11, 12}	RT-PCR
* Submandibular gland ^{71, 72}	MR, FM
Thymus ^{11, 12}	RT-PCR

* Denotes data from both human and mouse

FC – Flow Cytometry, MR – Microarray, FM, Fluorescence Microscopy, IHC – Immunohistochemistry, SB – Southern Blot, NB – Northern Blot, WB – Western Blot, IP – Immunoprecipitation, TP – Taqman Probe