Mini-review
Mechanism of BLyS action in B cell immunity
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Abstract
The B lymphocyte stimulator (BLyS), also known as BAFF, THANK, TALL-1 and zTNF4, is the most recent addition to the tumor necrosis factor family (TNF) ligands and has a unique role in B cell immunity. Its requirement for the humoral immune response is evident in mice lacking BLyS, which exhibit profound deficiencies in peripheral B cell development and maturation. It regulates the antibody response, as shown in mice overexpressing BLyS, which develop autoimmune manifestations resulting from peripheral B cell expansion and differentiation. Attenuation of apoptosis appears to underlie BLyS action in B cells. However, elucidation of the mechanism of BLyS has proven to be more challenging, because BLyS binds three different TNF receptors (TACI/BCMA/BAFF-R) and shares overlapping functions with a related TNF ligand, APRIL. The unique role of BLyS in B cell development and differentiation and the pathogenesis of autoimmune diseases, systemic lupus erythematosus (SLE) in particular, makes the study of BLyS and its downstream targets attractive in the development of novel therapies. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Autoimmunity; Humoral immune response; Apoptosis; TNF; NF-kappaB

1. BLyS, a TNF family ligand

The B lymphocyte stimulator (BLyS), also known as BAFF, THANK, TALL-1 and zTNF4, is a recently discovered tumor necrosis factor (TNF) family ligand that is important in B cell immunity (Table 1). The extracellular domain of BLyS shows highest sequence homology with APRIL, and lesser homology with TNFs, TRAIL, RANKL, and LT-α. BLyS and APRIL have been shown to specifically bind two TNF family receptors, TACI and BCMA with similar sub-nanomolar affinities [2–6] (Fig. 1). BLyS is now found to also bind a third TNF family receptor referred to as BAFF-R [7]. The significance of these receptors will be discussed below.

The expression of BLyS protein is restricted to cells of myeloid origin, including macrophages and dendritic cells [1,8]. It is up-regulated mainly by interferon-γ, and to a lesser extent, interleukin-10 [9]. BLyS exist as a type II membrane protein as well as a soluble protein derived from the membrane-bound form by cleavage with a putative furin family protease [8]. The soluble form consisting of the extracellular domain trimerizes and is biologically active [1,8]. APRIL is expressed in peripheral blood lymphocytes, monocytes and macrophages at the mRNA level [10], although its protein expression profile is currently unknown.

2. B cells are targets of BLyS action

Early attempts to elucidate the biological role of BLyS immediately revealed its remarkable B cell specificity. Mature B cells in the periphery were able to bind a biotinylated form of soluble BLyS [1]. Moreover, BLyS functioned as a potent co-stimulator with anti-Ig stimulation during B cell activation and expansion in vitro, and administration of BLyS intraperitoneally led to elevated serum IgM and IgA antibody titers [1]. Thus, BLyS enhances B cell responsive-}

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Cytokine & Growth Factor Reviews 13 (2002) 19–25

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2. B cells are targets of BLyS action

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The formation of antibody secreting plasma cells during B cell terminal differentiation in most cases begins with the help of T cells, in a T cell dependent response (TD). However, some antigens can elicit an antibody response in the absence of T cells, and are termed T independent (TI). One of the best characterized TD antigens is NP–CGG, which consists of the hapten nitrophenol (NP) conjugated to chicken gamma-globulin (CGG), a protein carrier. Other antigens, such as Pneumovax, composed of polysaccharides derived from different strains of Streptococcus pneumoniae, induce an antibody response independent of T cells. It was
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soon uncovered that BLyS enhanced both TD (NP–CGG) and TI (Pneumovax) antibody responses [11]. BLyS must target a number of different peripheral B cell subsets. However, the precise B cells on which BLyS acts was not immediately evident.

Several lines of evidence point to the possibility that there may be overlapping functions between BLyS and APRIL, a highly related TNF family protein, in B cell immunity. APRIL was initially identified as a tumor cell proliferation ligand [12]. It was later found to bind both cultured B and T cell lines, and enhance the proliferation of primary B and T cells in co-stimulation assays [13]. Intraperitoneal administration of APRIL led to enlargement of the spleen, accompanied by a disproportionate increase in B cells relative to T cells [13].

The expression and regulation of APRIL, however, remains poorly understood.

### 3. The BLyS receptors

The search for BLyS receptors has been intense and extensive. It initially revealed two previously cloned TNF receptor family genes, TACI and BCMA [5] (Table 2). TACI was expressed on the surface of B cells as well as immotylin and phorbol ester-activated T cell [14] whereas, BCMA was an orphan TNF receptor family protein expressed exclusively on B cells [15]. Soon thereafter, APRIL was found to bind the same receptors with similar affinities [4], and at least one report suggests that BLyS can bind activated T cells as well [6], presumably through TACI [14]. Collectively, these findings strengthen the notion that BLyS and APRIL may share the same role in immunity, primarily affecting B cells and to a lesser extent T cells.

Most recently, a third BLyS-specific receptor was unveiled and referred to as BAFF-R [7]. Importantly, BAFF-R does not bind to APRIL, as do TACI and BCMA. APRIL alone potentially binds a third receptor found on tumor cells [16]. Thus, while BLyS and APRIL share two receptors, TACI and BCMA, they are distinguishable in the context of ligand–receptor interaction and cell type expression (Fig. 1).

While it was clear that exogenous BLyS and APRIL enhanced the B cell immune response, their physiological role was not immediately evident. Several groups addressed this question by using recombinant decoy receptors composed of the soluble versions of the extracellular domains of TACI or BCMA fused to an immunoglobulin Fc portion. Both TACI-Fc and BCMA-Fc are effective in reducing the antibody responses to a TI antigen (Pneumovax) and TD antigens (NP–CGG, KLH) [3,13]. TACI-Fc can also block the activation and priming of T cells in vivo [17], although it is unclear whether this is secondary to inhibition of B cells. However, since these decoy receptors can bind APRIL and BLyS equally, the relative importance of BLyS compared to APRIL in B cell and T cell biology in vivo was not resolved by these studies.

### 4. The physiologic function of BLyS and autoimmunity

#### 4.1. The BLyS transgenic mice

To probe the BLyS function in vivo, three different transgenic mice were generated with each group using a
different strategy for BLyS overexpression: Mackay et al. used a liver-specific alpha-1 anti-trypsin promoter and APO E enhancer [18], while Khar et al. used a β-actin promoter [19]. Thus, both relied on the systemic action of released soluble BLyS. Gross et al. employed a lymphoid-specific Vav promoter and Eμ enhancer, providing paracrine BLyS action limited to B cell receptor bearing cells [5]. Nevertheless, all three groups reported similar phenotypes: increased mature B cells in the periphery, enlarged lymphoid organs and spleens, and hypergammaglobulinemia with autoimmune-like manifestations, including anti-DNA antibodies and Ig-deposition in the kidneys leading to glomerulonephritis. No changes were observed in the bone marrow, consistent with a restricted role of BLyS in the peripheral B cell compartment.

In addition, Mackay et al. reported a disproportional increase in the marginal zone B cells, and detected the presence of rheumatoid factors. Furthermore, numerous large germinal centers and plasmacytoid cells (syndecan-1 positive) were found in the enlarged lymphoid organs even in the absence of immunization [18]. Several differences were noted among these groups, perhaps reflecting differences in the control of BLyS expression: a two-fold increase in total T cell numbers [18] and elevated splenic B1-a cells (CD5 + the control of BLyS expression: a two-fold increase in total T cell receptor bearing cells [5]. Nevertheless, all three groups reported similar phenotypes: increased mature B cells in the periphery, enlarged lymphoid organs and spleens, and hypergammaglobulinemia with autoimmune-like manifestations, including anti-DNA antibodies and Ig-deposition in the kidneys leading to glomerulonephritis. No changes were observed in the bone marrow, consistent with a restricted role of BLyS in the peripheral B cell compartment.

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4.2. Mice deficient in BLyS or its receptors

The potential functional redundancy BLyS has with other TNF family proteins, in particular APRIL, has presented a challenge of defining the precise physiologic role of BLyS. To address this issue, mice deficient in BLyS receptors as well as BLyS itself have been generated (Table 3). As we will discuss below, BLyS appears to play a unique role in B cell development which is not compensated by APRIL, while BAFF-R appears to be the main receptor through which BLyS exerts its action.

Table 3: Mouse models for BLyS and BLyS receptors

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLyS</td>
<td>Transgenic</td>
<td>Enlarged lymphoid organs, increased B cell numbers, SLE-like autoimmunity. [5,18,51]</td>
<td></td>
</tr>
<tr>
<td>BLyS</td>
<td>Deficient</td>
<td>Reduced peripheral mature B cells, block at TI immature B cell stage. No B1-B cell or bone marrow abnormalities. [26,27]</td>
<td></td>
</tr>
<tr>
<td>BCMA</td>
<td>Deficient</td>
<td>No abnormalities [23]</td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>Deficient</td>
<td>Slightly enlarged lymphoid organs and elevated B cell numbers, deficient TI antigen response. [24,25]</td>
<td></td>
</tr>
<tr>
<td>TACI Ig</td>
<td>Transgenic</td>
<td>Similar but milder phenotype than BLyS deficient mice, and reduced B1-B cell numbers. [26]</td>
<td></td>
</tr>
<tr>
<td>BAFF-R</td>
<td>Mutation</td>
<td>Similar but milder than BLyS deficient mice. Impaired TD response. [7]</td>
<td></td>
</tr>
</tbody>
</table>

* A/WySnJ mice have a possible deletion of exon 3 in BAFF-R (see text).
The phenotype of mice lacking BLyS was much more dramatic, revealing that BLyS is essential for the development of mature B cells [26]. The number of peripheral B cells in the spleen and lymph nodes were reduced by over two-fold. Upon closer inspection, B cell development appeared to be blocked at the stage of immature transitional type 1 B cells exiting the bone marrow (T1 B cells) (Fig. 2). T1 B cells precede T2 B cells, which then differentiate into mature follicular (IgMδ, IgD+, CD21int, CD1hi) or marginal zone (IgMhi, IgD−, CD21hi) B cells. Hence, virtually no T2, follicular or marginal zone B cells were found in the BLyS−/− mice. In addition, as expected of a restricted role for BLyS in maintaining the peripheral conventional B2 cells, there were no changes in the bone marrow except for the absence of mature recirculating B cells, and the peripheral B1 cell population remained intact. Similar results were obtained in an independent study of BLyS deficient mice [27]. Moreover, these mice were severely impaired in antibody response to both TI and TD antigens. Thus, while the possibility exists that the absence of T2 B cells is a consequence of rapid apoptosis in the BLyS−/− mice, BLyS seems to be critical for B cell development beyond the T1 stage or the maintenance of B2 cells in the periphery.

5. Mechanism of BLyS action

While an essential role for BLyS in B cell immunity is now established, there has been some confusion over the precise mechanism of BLyS action. Initially, it was suggested that BLyS functioned to enhance B cell proliferation following anti-IgM stimulation [8]. A role for BLyS in controlling cell survival was also proposed, as B cells isolated from BLyS transgenic mice had elevated Bcl-2 levels [18], and survived longer than wild type B cells [19]. However, BLyS was also reported to directly enhance B cell proliferation in the same study [19]. BLyS was also believed to enhance immunoglobulin secretion [4]. A dissection of BLyS action on B cells is not possible in vivo, and difficult in heterogeneous cultures. Moreover, BLyS binds three receptors, which may lead to divergent signaling pathways. Our own studies of BLyS action in primary mouse splenic B cells indicate that BLyS does not induce cell cycling on its own, but acts primarily on a proliferative signal such as CD40L, Bcl-2 levels [18], and survived longer than wild type B cells [19]. However, BLyS was also reported to directly enhance B cell proliferation in the same study [19]. BLyS was also believed to enhance immunoglobulin secretion [4]. A dissection of BLyS action on B cells is not possible in vivo, and difficult in heterogeneous cultures. Moreover, BLyS binds three receptors, which may lead to divergent signaling pathways. Our own studies of BLyS action in primary mouse splenic B cells indicate that BLyS does not induce cell cycling on its own, but acts primarily on a proliferative signal such as CD40L, Bcl-2 levels [18], and survived longer than wild type B cells [19]. However, BLyS was also reported to directly enhance B cell proliferation in the same study [19]. BLyS was also believed to enhance immunoglobulin secretion [4]. A dissection of BLyS action on B cells is not possible in vivo, and difficult in heterogeneous cultures. Moreover, BLyS binds three receptors, which may lead to divergent signaling pathways. Our own studies of BLyS action in primary mouse splenic B cells indicate that BLyS does not induce cell cycling on its own, but acts primarily on a proliferative signal such as CD40L, Bcl-2 levels [18], and survived longer than wild type B cells [19].
Table 4
Signal transduction downstream of BLyS

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Downstream signaling</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human myeloid cell line</td>
<td>NF-κB and JNK</td>
<td>[50]</td>
</tr>
<tr>
<td>293 cells overexpressing BCMA and TACI</td>
<td>NF-κB</td>
<td>[4]</td>
</tr>
<tr>
<td>A20 B cell line</td>
<td>NF-κB and JNK</td>
<td>[6]</td>
</tr>
<tr>
<td>293 cells overexpressing BCMA</td>
<td>NF-κB, Elk-1, p38 MAPK and JNK</td>
<td>[48]</td>
</tr>
<tr>
<td>293 cells overexpressing BCMA</td>
<td>NF-κB</td>
<td>[49]</td>
</tr>
<tr>
<td>Mouse splenic B cells</td>
<td>NF-κB, p50/p50 and p50ReIB</td>
<td>[11]</td>
</tr>
<tr>
<td>Human tonsil B cells</td>
<td>NF-κB, Elk-1</td>
<td>[30]</td>
</tr>
</tbody>
</table>

phenotypes observed above, including those in BLyS transgenic mice, as apoptosis is recognized to play an important role in immune tolerance and the development of autoimmunity [28]. Although B cells are direct targets of BLyS action, the exact range of BLyS action in the B lineage has not been completely defined (Fig. 2). Our findings indicate that BLyS attenuates apoptosis in mature B cells before and after they are activated by CD40L [11]. Whether the BLyS response is maintained once activated B cells differentiate to plasma cells or memory cells is not known. Even as BLyS binds a number of different targets, its action may not be uniform throughout. In fact, there is also evidence that BLyS attenuates apoptosis of immature transitional T2 and marginal-zone (IgMhi, IgD−)) B cells, at least when cultured in vitro [29]. B cells residing in the marginal zone, which include isotype-switched memory B cells, are believed to play a role in TI antibody responses in addition to TD response (Fig. 2). The T2 B cells represent B cells at an earlier stage of development, between B cells leaving the bone marrow and mature B cells populating the lymphoid organs. The authors pointed out that these observations were carried out in vitro, and might not reflect the in vivo scenario given the expansion of all peripheral B cell populations in BLyS transgenic mice. Nevertheless, these findings implicate that BLyS may be more critical for the survival of certain B cell subsets. They also suggest an alternative explanation for the apparent absence of T2 B cells in BLyS−/− mice [26], a lack of T2 cell survival, instead of or in addition to a block of development of T1 to T2 B cells. The mechanism of BLyS action, therefore, requires careful investigation in each cell type.

6. BLyS signal transduction

An analysis of the signaling events downstream of BLyS may further our understanding of its mechanism of action. BLyS and at least two of its receptors were reported to signal activation of NF-κB by TACI and BCMA is not surprising since most TNF-family receptors signal at least in part through this family of transcription factors. While it remains to be confirmed, activation of NF-κB by BAFF-R would also be expected. The activation of NF-κB is consistent with an anti-apoptotic role for BLyS, since NF-κB enhances the transcription of a number of cell survival genes, including A1/Bfl-1 and Bcl-xL of the Bcl-2 family [31–34], and cIAP2 [35] and cFLIP [36–37]. Somewhat surprisingly, our findings indicate that BLyS enhances the protein level of Bcl-2, but not that of Bcl-xL [11]. The relative contribution of these proteins to BLyS-mediated attenuation of apoptosis thus remains to be determined.

Different members of the NF-κB transcription family are believed to have distinct functions in B cell survival. Overexpression of c-Rel in WEHI 231 immature B-lymphoma cells protects them from anti-IgM induced apoptosis [38]. Studies of primary B cells isolated from NF-κB mutant mice further indicate that p50, but not c-Rel, is important for the survival of quiescent B cells, whereas both are important for the survival of mitogen-activated B cells [39]. It is, therefore, noteworthy that BLyS specifically activates NF-κB dimers p50/p50 and p50/ReIB in resting and CD40L-activated primary B cells alike [11]. As for ReIB, studies of deficient mice indicated that ReIB seems to be required for B cell proliferation [40] and appears to promote the antigen-presentation function of B cells [41].

While many TNF-family proteins signals protein through NF-κB, the outcome is contingent on the cellular milieu and the specific dimers activated. It this context, it is of particular interest that p50 deficiency results in a greater defect in marginal zone B cells than p65 or c-Rel deficiency [42]; these same cells are expanded in BLyS transgenic mice [18], and their survival are preferentially enhanced by BLyS in vitro [29]. Whether preferential activation of NF-κB dimers p50/p50 and p50/ReIB modulates specific anti-apoptotic genes is, therefore, an important question that remains to be addressed.

Stimulation of B cells by CD40L induces cell survival in addition to cell proliferation, in part through activation of NF-κB and its downstream targets, A1 and Bcl-xL. The addition of BLyS, however, does not induce Bcl-xL, despite the activation of NF-κB [11]. Instead, BLyS elevates Bcl-2 protein levels, consistent with the increases in Bcl-2 protein in B cells isolated from BLyS transgenic mice [18]. This

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anti-apoptotic gene is not a recognized target of NF-κB, but is known to play an important role in B cell survival. The Bcl-2 deficient mice are reduced in B and T cells in lymphoid compartments including the bone marrow by 4 weeks of age [43]. Conversely, Bcl-2 transgenic mice display increased B cells and plasma cells [44] and seem to sustain B cell memory [45]. Not surprisingly, inappropriate Bcl-2 expression in the germinal center inhibits B cell apoptosis [46] and abrogates negative selection of lower affinity memory B cells [47]. Moreover, the Bcl-2 transgenic mice have provided the first experimental evidence that inhibition of cell death could lead to autoimmunity [44]. Thus, the ability of BLYS to up-regulate Bcl-2 protein levels could perhaps explain its ability to breakdown tolerance in the BLYS transgenic mouse. Whether BLYS activates Adi/Adi-1, another known target of NF-κB, to further disrupt the B cell selection process remains to be determined.

Little is known about the BLYS signaling upstream of NF-κB, except for the activation of TNF-receptor associated factors (TRAFs) by TACI and BCMA. In a yeast two-hybrid screening of a B cell library, TACI interacted with TRAF2, TRAF5, and TRAF6 through a conserved region found between murine and human TACI [6]. The characterization of TRAF activation by BCMA is currently unclear, one group found association of TRAF1, TRAF2, and TRAF3 with BCMA by co-immunoprecipitation [48], while another group found TRAF5 and TRAF6, but not TRAF2 association by a similar method [49]. Both groups used dominant negative forms of their respective TRAFs to inhibit NF-κB activation by BCMA overexpressed in 293 cells. As these studies are performed in cell lines with varying expression of transfected genes, the specific TRAFs that function to mediate the physiologic signals of these receptors and BAFF-R, requires further studies. The BLYS signaling pathway may also extend to activation of JNK and several other MAP kinase pathways, at least in some cell lines (Table 4). The relevance of activation of JNK by BLYS in B cell function, however, also remains to be clarified.

7. Summary

TNF-family proteins play a critical role in immunity, regulating proliferation, differentiation and survival of a number of cell types. BLYS is a novel member of this family, joining CD40L, Fas and many others to modulate B cell immune responses. BLYS is distinct, however, in its remarkable B cell specificity and could, therefore, be a more attractive target for B cell-mediated diseases. This cytokine appears to bind a number of peripheral B cell subsets and enhance the humoral immune response through attenuation of apoptosis. As BLYS is expressed and released from macrophages and dendritic cells, it could link the innate and adaptive immune response. Its expression must be carefully regulated, as overexpression can lead to a breakdown in tolerance and autoimmunity. The development of decoy receptors based on TACI, BCMA, and BAFF-R, or antibodies directed against BLYS, are thus potential tools against B cell-mediated autoimmune diseases. The role of BLYS in B cell malignancies has been largely unexplored, but could also be another target for novel cancer therapies. Finally, the precise mechanism by which BLYS enhances B cell survival and the extent of BLYS action throughout the B cell lineage remain to be addressed.

Acknowledgements

We thank Josie Ursini-Siegel, Eunice Hatada and Lee Kiang for a critical reading of this manuscript. This work was supported by the Cornell-Rockefeller University-Sloan Kettering Institute Tri-Institutional National Institutes of Health Medical Scientist Training Grant (5T32GM07393) to R.K.G. Do, and grants from The National Institutes of Health (AR44580 and CA80204) and a Specialized Center of Research grant from The Leukemia and Lymphoma Society of America to S. Chen-Kiang.

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