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Mini review

New roles for the BLyS/BAFF family in antigen-experienced B cell niches

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ABSTRACT

BLyS family members govern selection and survival of cells in the pre-immune B cell compartment, and emerging evidence suggests similar roles in antigen-experienced B cell pools. We review the features of this family, with particular emphasis on recent findings of how BLyS influences affinity maturation in germinal centers, which lie at the intersection of the pre-immune and antigen-experienced B cell compartments. We propose a model whereby tolerogenic selection at the transitional stage and affinity maturation in the germinal center employ the same BLyS driven mechanism.

1. Introduction to the BLyS family of cytokines and receptors

B cells are the effectors of humoral immunity. Quiescent, pre-immune B cells are generated throughout life from hematopoietic stem cells and, when activated by antigen exposure, expand and further differentiate into antibody-forming plasma cells (PCs) or memory B cells (Bmem) that mediate long-term immunity. Members of the B lymphocyte stimulator (BLyS, a.k.a. B cell activating factor of the TNF family, BAFF) family of ligands and receptors play unique, lineage-specific roles in B cell development, selection, persistence, and function. Much research and speculation to date has focused on how members of this family govern the size and composition of pre-immune B cell pools. However, more recent evidence reveals roles for this molecular family in dictating the differentiation, selection and persistence of activated and antibody secreting effector cells of the B lineage. Accordingly, we herein briefly overview the basic features of BLyS family members and their roles in pre-immune B cell selection and homeostasis. We then provide a more forward thinking and detailed consideration of recently appreciated influences on other B lineage subsets, with emphasis on the selective processes acting on germinal center (GC) B cells.

1.1. BLyS family ligands: BLyS (BAFF) and APRIL

The BLyS family is a subset of the tumor necrosis factor (TNF) superfamily, and includes two ligands (reviewed in detail in [1,2]). A proliferation inducing ligand (APRIL, TNFSF13a) was the first to be described, and is also termed TALL-2 (TNF- and ApoL-related Leukocyte-expressed Ligand 2) or TRDL-1 (TNF-related death ligand-1a). Subsequently, several laboratories simultaneously reported B lymphocyte stimulator (BLyS; TNFSF13b), which also appears in the literature as BAFF (B cell activating factor of the TNF superfamily), THANK (a TNF homologue that activates apoptosis, nuclear factor-kappaB, and c-Jun NH2-terminal kinase), TALL-1 (TNF- and ApoL-related leukocyte-expressed ligand 1) and zTNF4. While these two ligands share only ~25% identity with the conserved carboxy-terminal regions of other TNF family members, they share 33% amino acid and 48% DNA homology with each other. Moreover, amino acid sequence homologies for each cytokine between mammals range from 80% to 97%.

Both APRIL and BLyS are type II transmembrane proteins that are cleaved into soluble forms by protein convertases ([3,4]; reviewed in [2]). Their active forms are composed of homotrimers and, while heterotrimers have been demonstrated, the biological relevance of such hybrid molecules is not yet understood. Nevertheless, heterotrimers are active in vitro and are elevated in the serum of some autoimmune patients (for example, [5]). BLyS can also assemble into 60mers, which exhibit distinct binding and signaling characteristics [6]. Finally, membrane-bound forms of BLyS have been observed which might reflect incomplete cleavage of the membrane form or the expression of an alternative splice form known as deltaBAFF, which lacks the stalk region and

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consequently cannot be cleaved [7]. Unlike BLyS, APRIL is cleaved in the Golgi prior to secretion, precluding expression as a membrane-bound form [4]. Nonetheless, it can bind heparan sulfated proteoglycans (HSPG) via its amino terminus, allowing oligomerization and presentation on cell surfaces [8].

BLyS and APRIL are produced by cells of non-hematopoietic and hematopoietic origin (reviewed in [9,10]). Radioresistant stromal cells maintain systemic BLyS levels, with apparently minimal contribution from cells of hematopoietic origin [11]. Similar assessments have not yet been made for APRIL. Tumor cell lines derived from non-hematopoietic tissues as well as astrocytes are enriched for APRIL production [12,13], but the extent of the contribution of these sources to overall APRIL production has not yet been determined. Among hematopoietic cells, myeloid cells/cell lines such as monocytes, eosinophils, osteoclasts, and neutrophils produce both cytokines, albeit with a generally greater propensity to produce APRIL than BLyS [10]. Macrophages and dendritic cells express membrane-bound BLyS, and expression levels can be augmented or depressed by cytokines such as IFNγ or IL-4, respectively [3,14]. Further, compared to macrophages and B-1 B cells, resting splenic B-2 cells in mice express neither BLyS nor APRIL message [15]. However, TLR agonists or surrogate BCR cross-linking in vitro may induce transcripts for both cytokines [15,16]. Similarly, quiescent T cells express no BLyS or APRIL, although expression can be induced by TCR-driven activation in some circumstances [4,15,17]. Curiously, in autoimmune-prone mice, depletion of CD4 T cells significantly reduces circulating levels of BLyS. Whether this is due to the absence of T cell-derived cytokines (such as IFNγ) that augment BLyS secretion by myeloid cells, or to a significant contribution of BLyS from excessive activated CD4 T cells themselves, is not yet known. Among activated CD4 T effectors, antigen-specific follicular helper T cells (T_{FH}) are enriched for BLyS mRNA expression and express BLyS protein in the germinal center [18], as discussed further in Section 3 below.

1.2. BLyS family receptors: BR3/BAFFR, TACI, and BCMA

BLyS and APRIL can interact with three receptors, BR3 (BLyS Receptor 3, also termed BAFFR), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) or BCMA (B cell maturation antigen). These interactions are extensively reviewed elsewhere, for both mice and humans [1,2,10,19], and briefly addressed here. These receptors possess characteristic canonical cysteine rich domains (CRDs) that are composed of 6 cysteine residues, and transduce TNF receptor associated factor (TRAF)-mediated signals. However, unlike other TNF receptors that express 3–6 CRDs, BR3 has only a partial CRD, BCMA has one CRD, and TACI has two. These atypical structures confer exquisite specificity for BLyS and APRIL, but not for other TNF ligands [20,21]. As noted above, APRIL can passively bind to proteoglycans, though whether such interaction induces downstream signaling events is not yet known [8,22]. Finally, TWE-PRIL, a fusion protein between the intracellular, transmembrane and stalk region of TWEAK (TNF Weak inducer of apoptosis) coupled to the extracellular receptor-binding part of APRIL, recognizes BCMA and TACI [19].

BLyS binds with much higher affinity to BR3 than to BCMA, whereas APRIL has a greater affinity for BCMA and little or no binding capacity for BR3 [23]. Moreover, BLyS has a higher affinity for TACI compared to BCMA, and the converse is true for APRIL [21]. Nonetheless, BLyS binds to BR3- or TACI-transfected cells with similar strength, and TACI has ~25-fold higher affinity for BLyS than for APRIL [24,25]. Therefore, it is conceivable that under steady state conditions, BLyS is largely bound to TACI. Indeed, reagents that detect pre-bound BLyS on B cells in mice have revealed that TACI is the key receptor involved in binding of BLyS to mature naïve B cells [18]. Consistent with the inefficient binding of BLyS to TACI-deficient B cells, elevated levels of circulating BLyS are observed in TACI knockouts [18]. Additionally, BLyS 60mers bind to TACI with much higher affinity than BLyS trimers, and thus are readily detectable in the circulation of TACI-deficient mice [26].

1.3. BLyS family members govern B lineage homeostasis and selection

Homeostasis in the various functional B cell compartments is achieved by regulating generation rates, selection thresholds, and cellular lifespan. Steadily accumulating evidence over the last decade has revealed that BLyS family members play critical and non-redundant roles in all of these processes. A key feature of the BLyS family is that it includes multiple receptors and ligands with different binding preferences. We and others have posited that differential expression of the three BLyS family receptors affords coexisting, yet distinct and independently regulated, homeostatic niches for mature naïve, antibody-secreting, and memory B cell subsets [27]. Consistent with this idea, the various pre-immune and antigen-experienced B cell subsets express different combinations of BLyS receptors at varying levels (reviewed in [28,29]), and display differential reliance on the two cytokines (summarized in Table 1). The following sections expand on this theme, and review evidence supporting this idea for resting, activated, and antibody secreting B cell populations. Moreover, we propose a model based on recent findings that suggests transitional (TR) and germinal center (GC) B cell selection proceed via the same, BLyS-mediated, mechanism.

Table 1
BLyS family receptor expression patterns and cytokine dependence for developing, pre-immune, and antigen-experienced murine B cell pools.

Differentiation stage	Receptor expression[a]			Cytokine dependence[b]	
	BR3	TACI	BCMA	BLyS	APRIL
Developing and pre-immune pools					
Bone marrow Pro-B and Pre-B	–	–	–	N	N
Bone marrow immature	+	±	–	Y (?)	N
Transitional	+	+	–	Y	N
Follicular	+	+	–	Y	N
Marginal zone	+	++	–	Y	N
Antigen-experienced pools					
Germinal center	+	↓	–	Y	N
Short-lived plasma cell	↓	↑	–	N (?)	Y
Long-lived plasma cell	↓	↓	↑	Y	Y
Memory B cell	↓	+	↑	N (?)	N (?)

[a] No expression (–), relative expression level (++, ± or +), downregulation (↓), or upregulation (↑) compared to pre-immune pools.
[b] Y, yes; N, no evidence/not known.