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Editorial

Travelling with the BAFF/BLyS family: Are we there yet?

The development, maturation and activation of B-lymphocytes is a perilous odyssey, starting in the bone marrow and finishing in the peripheral lymphoid organs. This journey is characterised by a constant struggle for survival and a need to "clear" multiple checkpoints that neutralise potentially harmful self-reactive B cells and selectively favour useful clonotypes. Until recently, B cell receptor (BCR) specificity was considered the prime, if not sole, determinant of survival among developing and primary B cells. However, characterisation of the TNF-like ligand BAFF/BLyS has fundamentally changed this notion. BAFF is now appreciated as central to the survival of peripheral B cells, since without it neither the maturation nor survival of primary B cells is possible. Moreover, BAFF over-expression leads to the development of autoimmune disorders, and elevated BAFF levels are associated with autoimmune diseases such as Systemic Lupus Erythematosus, rheumatoid arthritis and Sjögren's syndrome. As a result, BAFF and its corresponding receptors have become major targets in the development of therapeutics for these diseases, and several promising reagents are presently in clinical trials.

Despite the broad conceptual and clinical importance already evident, readers of this *Seminars in Immunology* volume will learn that the BAFF saga is still far from complete. Numerous exciting new concepts and functions are emerging, and intriguing mysteries remain to be solved. This assembly of contributions provides the latest views and ideas of many experts, and will hopefully serve as the basis for future work on BAFF and related molecules.

BAFF mediates survival signals via its receptor (BAFF-R, BR3) but also binds to two other receptors, TACI and BCMA, which are shared with another TNF-related ligand, APRIL. Bossen and Schneider refine this picture with the characterisation of a splice variant of BAFF that, when combined with full-length BAFF subunits, can create inactive heterotrimeric ligands, perhaps serving as negative regulators. They also find that APRIL can be expressed as a shorter variant that weakly binds BAFF-R. Finally, APRIL interacts with proteoglycan structures expressed on T cells and non-lymphoid cells. Clearly, our knowledge of the ligand/receptor relationships in this system is far from complete and future additional findings are likely to color interpretations of observed biological effects.

Since BAFF over-expression is linked to B cell-mediated autoimmunity, considerable effort has focused on how BAFF corrupts B cell tolerance. Robert Brink provides his views on this important question, based on data obtained using the powerful anti-hen egg lysozyme (HEL) BCR transgenic systems. This work showed that excessive BAFF production would not prevent elimination of high-affinity self-reactive B cells, presumably because they are deleted prior to expression of sufficient BAFF-R. In contrast, low-affinity self-reactive B cells that fail transitional differentiation at normal physiologic BAFF levels, benefit from excessive BAFF and accumulate. Thus, whether the rescue of weakly self-reactive B cells via such mechanisms drives autoimmune etiology is a key remaining question.

BAFF and APRIL may also influence T cell functions. In their contribution, Mackay and Leung combine their findings with those of others, showing direct and indirect effects of BAFF on the makeup of the T cell compartment and T cell functions. Excess BAFF induces changes of the B cell compartment, which in turn increase the number of effector T cells, possibly via the antigen-presenting cell (APC) function of B cells, particularly marginal zone (MZ) B cells. Thus, BAFF-mediated autoimmune disorders may reflect combined pathogenic effects involving both B and T cells. This section also highlights a possible role for BAFF as a negative regulator of T cell activation in some inflammatory settings and the expression of BAFF-R on regulatory T cells.

While the function of BAFF-R as a survival receptor is now well characterised, functions through TACI and BCMA are not fully understood, an aspect complicated by the fact that both BAFF and APRIL can activate these receptors. In her contribution, Susan Kalled describes BAFF/APRIL-mediated functions which are BAFF-R-independent, such as BAFF-mediated up-regulation of CD23 and CD21 on B cells, maturation of follicular dendritic cells in germinal centers (GCs), isotype switching and plasma cell survival, the latter possibly relying on APRIL binding to BCMA.

In a similar vein, the Cancro laboratory (Treml/Crowley) presents data suggesting that the spectrum of BLyS receptors expressed among antigen activated B cells is characteristic of their likely differentiative fate. In general, AFC differentiation is associated with marked TACI up-regulation, whereas

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GC B cells remain high for BAFF-R (BR3), and memory B cells appear to have shifted to a BCMA–APRIL axis for their survival.

Stuart Tangye provides a complete overview of what we know about BAFF and APRIL in the human immune system and human diseases. This contribution highlights a number of dissimilarities between mice and humans. This is particularly true in the case of TACI, where deletion leads to B cell hyperplasia, autoreactivity and lymphomas in mice, yet dominant mutations of the *taci* gene in humans are associated with immunodeficiency. An emerging aspect of the BAFF/APRIL system is its function as survival support for some lymphoid cancers, an aspect likely to extend the use of BAFF/APRIL inhibitors to cancer indications and which potentially offers an alternative to treat a subset of lymphoid cancers un-responsive to current B cell-depleting therapies.

Finally, understanding the signalling pathways via each BAFF/APRIL receptor is still an ongoing effort with new models emerging. Early work has identified the alternative NF-κB pathway as the dominant pathway triggered via BAFF-R and essential for B cell survival. Recently, however, a new study (Sasaki et al. Immunity 2006;24:729–39) suggests that the BAFF-R-induced canonical NF-κB pathway is equally important for B cell survival and, in some respects reconciles observations that mutations disabling the alternative NF-κB pathway do not entirely mimic BAFF-R mutations. In addition, Woodland and Thompson herein propose a novel mechanism promoting B cell survival via BAFF-R. Their work shows that BAFF-R signalling activates Akt and Pim-2, which leads to increased Mcl1 expression, a known inhibitor of the pro-apoptotic oncogene Bim. Another interesting new concept introduced by these authors is the role of BAFF as a stimulator of cellular metabolic activity in B cells, an aspect which may contribute to improved cell survival. Despite these emerging insights regarding the downstream mediators of BAFF–BAFF-R interactions, the signalling mechanisms triggered via TACI and BCMA remain largely unexplored.

Together, the new clues provided by these contributors offer a blueprint of the challenges ahead. We now know that both BCR and BAFF signals are required for B cell survival, maturation and immune tolerance, yet we still understand little about how these two signals balance and interact. Similarly, the exact contribution of B cells and T cells in BAFF-mediated autoimmune disorders and the role of BAFF in inflammation and viral infection remain to be fully elucidated. More work is also required to understand the role of new molecules in this system such as BAFF/APRIL heterotrimers, BAFF splice variants and APRIL binding proteoglycan structures. Understanding of the signalling mechanisms via BAFF/APRIL receptors is rapidly progressing and a clearer picture is likely to emerge very soon. Finally, recent comparison between APRIL/BAFF receptor expression and function in mice and humans has revealed differences, highlighting limitations of animal models as predictors of human immunobiology. Indeed, this may represent the most significant gap in current knowledge, as this information will greatly impact design and test strategies for new therapeutics targeting the BAFF/BLyS family, as well as reveal exciting unforseen therapeutic possibilities.

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