Role of BAFF in B cell Biology and Autoimmunity

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B cell development in health and disease:

B-lymphocytes or B cells, and the antibodies they produce, are crucial mediators of humoral immunity, providing significant protection against a wide range of pathogens. B cells develop from hematopoietic precursors that originate in the bone marrow and progress through a series of tightly regulated selection and maturation processes to form immature B cells. Immature B cells enter the spleen as transitional B cells, which subsequently undergo the developmental steps required for production of mature B cells and functional adaptive immunity (Pieper, Grimbacher et al. 2013).

In healthy individuals, B cell development and maturation is tightly regulated, however this delicate balance is disrupted in autoimmune disease, where B cell dysfunction can lead to a loss of self-tolerance. Disrupted B-cell maturation and function and is implicated in several autoimmune diseases, including system lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), Sjögren's Syndrome (SS), and Graves' Disease, and as a result significant research has focused on understanding the mechanisms governing B-cell maturation (Pillai, Mattoo et al. 2011, Bluml, McKeever et al. 2013).

Signaling via BAFF and its receptors - an introduction:

B cell activating factor (BAFF) and its receptors on B cells have been identified as critical players orchestrating the developmental steps required for production of mature B cells and functional adaptive immunity. Since its discovery in 1999, much attention has focused on studying BAFF and the downstream pathways it stimulates. BAFF, also termed TALL-1, THANK, BlyS and zTNF4 belongs to the Tumor Necrosis Factor (TNF) family of ligands and is produced by cells of the myeloid lineage such as monocytes and dendritic cells. BAFF is initially expressed as a Type II transmembrane protein, which is then typically processed by proteases and secreted as a soluble ligand. BAFF binds with similar affinity to BCMA (B cell maturation antigen), TACI (transmembrane activator and CAML-interactor), and BAFF-R, three cell surface members of the TNF receptor superfamily and provides the necessary signals for survival and maturation of B cells (Rolink and Melchers 2002, Melchers 2003, Sasaki, Derudder et al. 2006, Krivosikova, Dallos et al. 2009).

Each of the three BAFF receptors has different patterns of expression and mediates distinct roles in B cell homeostasis. Unlike BAFF-R however, neither BCMA nor TACI are mandatory for B cell survival or maturation. The precise signal transduction pathways engaged by BAFF and its receptors are still poorly characterized and current research indicates a prominent role for the NF-κb family of transcription factors (Sasaki, Derudder et al. 2006).

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BAFF as a target in autoimmune disease:

Given its critical role in B cell homeostasis, it is not surprising that de-regulated BAFF signaling is associated with autoimmunity. Though the exact mechanisms are as yet unknown, several animal studies have demonstrated a role for the BAFF axis in autoimmune diseases. For instance, BAFF transgenic mice develop SLE/SS-like phenotypes, including enlarged B cell compartment and lymphoid organs, high titers of anti-double stranded DNA (dsDNA) antibodies and rheumatoid factor, hypergammaglobulinemima, and circulating immune complexes. Human studies provide further evidence for a role of BAFF signaling in autoimmunity with one study demonstrating elevated serum levels of BAFF and a related factor, APRIL, in a subset of patients suffering from SLE, RA, SS and other disorders of the immune system. In another study on lupus patients a positive correlation between BAFF levels and anti-dsDNA antibody levels was also identified (Rottman and Willis 2010, Morais, Vilas-Boas et al. 2015).

Animal studies provided the first indication that BAFF could be a target for therapeutic intervention. Several strategies were developed to block BAFF, including using a decoy soluble BAFF-R or BAFF inhibitory antibodies. BAFF-blockade delays disease onset in most models of SLE, though significant strain-specific variance was reported. For example, the Davidson group at the Feinstein Institute for Medical Research reported a thirty-week delay in time to death in NZB/W F1 mice treated with BAFF-blockade. In comparison, the same group reported significantly longer survival in NZM2410 mice in response to an identical treatment regimen (Liu and Davidson 2011, Davidson 2012).

Clinical development of BAFF targeted agents:

The animal studies provided the impetus for evaluation of BAFF-inhibitors in the clinic and several biologic drugs were developed including belimumab, tabalumab, atacicept, and blisibimod. Of these drugs belimumab, a fully human monoclonal antibody that antagonizes BAFF signaling by binding to the soluble form of BAFF, is now licensed by the US Food and Drug Administration (FDA) for SLE treatment (Vincent, Morand et al. 2014). Belimumab was the first biologic therapeutic to be approved for SLE in nearly fifty years and pivotal phase III trials with belimumab (BLISS-52 and BLISS-76) demonstrated a significant clinical response in patients with active, autoantibody-positive SLE who were receiving standard therapy (Figure 1) (Liu and Davidson 2011).

However, clinical development of BAFF antagonists has also faced challenges. For instance, tabalumab, a human monoclonal Ab against soluble and membrane-bound BAFF failed in two Phase III trials for lupus, leading to the termination of its development program. Furthermore, enthusiasm for belilumab has also been limited despite its approval, owing to weak efficacy and concerns that its immunosuppressive mechanism may aggravate infections. Recent research suggests that targeting BAFF-receptor, TACI, instead of the BAFF ligand itself, may provide greater therapeutic benefit; Figgett et al. showed that deleting the BAFF receptor TACI in mice protected against SLE-like symptoms without extensive reduction of B cell numbers (an issue faced by BAFF-targeted therapies like belilumab) (Liu and Davidson 2011).

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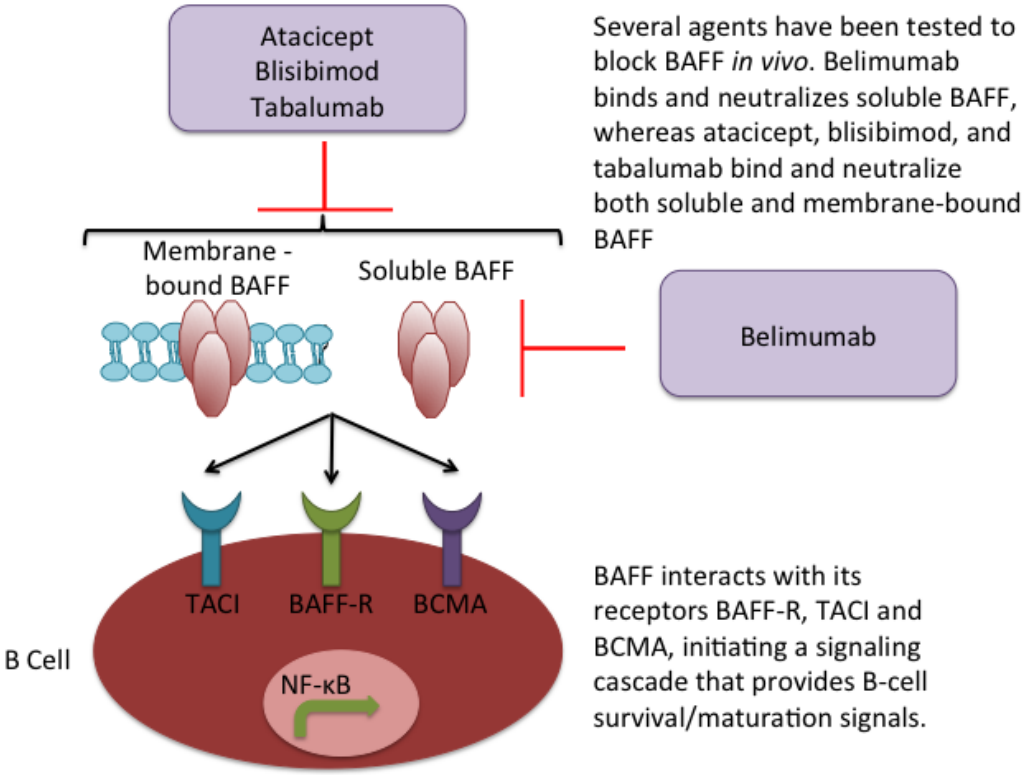
Figure 1: BAFF Signaling Cascade as a Therapeutic Target



Conclusions:

B cells can contribute to autoimmune diseases through different mechanisms including autoantibody production, antigen presentation, and cytokine production. The BAFF-BAFF-R signaling pathway is clearly an important player in the orchestration of this pathology and future research will continue to shine new light on the precise mechanisms at play. Intriguingly, recent evidence suggests that deregulated BAFF-BAFF-R signaling may also have an impact beyond autoimmune diseases, and may be involved in infections and cancer. Specifically, BAFF is emerging as a critical factor in various hematological and lymphoid cancers. Thus, investigating the role of BAFF-BAFF-R signaling in these other diseases may shed additional light on the precise biological functions of the molecule and ways in which it can be targeted for therapeutic benefit (Vincent, Saulep-Easton et al. 2013).

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