Commentary
SLE

Systemic lupus erythematosus: a BLySful, yet BAFFling, disorder

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Abstract

BLyS/BAFF (B-lymphocyte stimulator/B-cell activating factor) is a vital B-cell survival factor. Overexpression of BLyS in mice may lead to systemic-lupus-erythematosus-like (SLE-like) disease, and BLyS overexpression is common in human SLE. Treatment of SLE-prone mice with a BLyS antagonist ameliorates disease progression and enhances survival, making BLyS an attractive therapeutic target in human disease. However, several unresolved issues remain, including what is the contributory role of APRIL (a tumor-necrosis-factor superfamily member related to BLyS) in the 'autoimmunogenic' effects of BLyS, identification of the 'optimal' BLyS antagonist, and identification of those SLE patients most likely to benefit from BLyS antagonist therapy.

Keywords: APRIL, B cells, biologic antagonists, BLyS/BAFF, SLE

Introduction

BLyS (B-lymphocyte stimulator), also commonly known as BAFF (B-cell activating factor), is a 285-amino-acid member of the TNF- (tumor necrosis factor)-ligand superfamily [1–5]. (Because the two names are both so common, I use them interchangeably throughout this commentary.) It is a vital B-cell survival factor [6–8], and mice genetically deficient in BAFF display profound global reductions in mature B cells and in circulating immunoglobulin levels [9,10]. Conversely, constitutive overexpression of BAFF in BAFF-transgenic mice leads to expanded B-cell populations and polyclonal hypergammaglobulinemia [5,11,12]. This association between elevated circulating levels of BLyS and polyclonal hypergammaglobulinemia extends to humans as well, inasmuch as increased serum and/or plasma levels of BLyS have been documented in human systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and HIV infection [13–16], all conditions associated with polyclonal hypergammaglobulinemia.

Therapeutic antagonism of BLyS/BAFF

Of paramount importance to human autoimmune diseases associated with pathogenic autoantibodies (especially SLE), constitutive overproduction of BAFF in mice not only leads to B-cell expansion and polyclonal hypergammaglobulinemia, but also often leads to elevated circulating titers of multiple autoantibodies (including anti-dsDNA), circulating immune complexes, and immunoglobulin deposits in the kidneys [5,11,12]. Moreover, SLE-prone NZB × NZW F1 and MRL-*lpr*/*lpr* mice harbor elevated circulating BAFF levels, and treatment of these mice with a BAFF antagonist ameliorates progression of disease and improves survival [5,17]. Although humans are not simply large mice, it does not take a great leap of faith to postulate that elevations in circulating BAFF levels contribute to development and/or maintenance of SLE in humans and that blockade of BAFF activity could be therapeutically beneficial.

Borrowing from the successful clinical experience with TNF antagonism in rheumatoid arthritis and Crohn's disease, anti-BLyS monoclonal antibody and/or fusion proteins between any of the three known BLyS receptors (BCMA; TACI; BAFFR) and the Fc portion of IgG could bind and neutralize circulating BLyS. Although BLyS receptor fusion proteins are still undergoing preclinical evaluation, a phase-I clinical trial in SLE with a fully human

APRIL = a proliferation-inducing ligand; BAFF = B-cell activating factor; BAFFR = BAFF receptor; BAHTs = BLyS/APRIL heterotrimers; BLyS = B-lymphocyte stimulator; BLyS/BAFF = B-lymphocyte stimulator/B-cell activating factor belonging to the TNF family; Fc = crystallizable fragment; mAb = monoclonal antibody; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

antihuman BLyS monoclonal antibody was initiated in early 2002. All the patients had received their test drug (or placebo control) by the end of 2002. Post-treatment follow-up of these patients should be complete by mid-2003, with safety and pharmacokinetic data emerging shortly thereafter.

Biologic antagonists directed against BLyS and/or its receptors need not be limited to monoclonal antibody or receptor fusion proteins. Other attractive candidate biologic antagonists include BLyS analogues that competitively bind to BAFFR (the BLyS receptor absolutely essential to the BLyS-driven biologic effects on B cells [18,19]) but cannot trigger signaling. Alternatively, BAFFR-blocking agents that render the receptor inaccessible to BLyS binding could also be clinically efficacious. Indeed, there is no a priori reason that such antagonists must necessarily be biologic. They could be low-molecular-weight synthetic compounds as well. In any case, development of appropriate BLyS analogues and/or BAFFR blockers will require more detailed studies of BLyS/BAFFR interactions and how (whether) other cell-surface structures affect such interactions.

APRIL: the wild-card factor

APRIL (a proliferation-inducing ligand) is a member of the TNF-ligand superfamily related to, but distinct from, BLyS. APRIL binds to two of the three known BLyS receptors (BCMA and TACI) [20–23] but not to BAFFR [18]. Given its inability to bind to BAFFR, it has been believed that APRIL has little (if any) effects on B-cell biology. Indeed, constitutive overexpression of APRIL in APRIL-transgenic mice does *not* lead to overt B-cell abnormalities or serologic or clinical autoimmunity [24]. However, APRIL and BLyS can form BLyS/APRIL heterotrimers (BAHTs), which *do* have 'BLyS-like' biologic activity *in vitro* and which *do* circulate *in vivo* [25]. Whether BAHTs exert *in vivo* biologic activity and, even if so, what fraction of total 'BLyS' biologic activity is exerted by BAHTs rather than by BLyS homotrimers remain open questions that require resolution. The answers to these questions may have profound ramifications for antagonist therapy, since a clinically efficacious BLyS antagonist may need to be directed against not just BLyS but against APRIL as well.

Are all SLE patients candidates for BLyS/BAFF antagonist therapy?

The answer to this question depends upon how one views the role of BLyS/BAFF in SLE. In principle, BLyS may assume at least two distinct functions as it pertains to SLE. The first model has BLyS functioning as a *contributor* to development of SLE. BLyS per se does not cause loss of tolerance to self-antigens. However, once such tolerance is broken, the ever-present nature of the autoantigen permits it to stimulate the host immune system repetitively, resulting in a detectable autoimmune response. In the presence of increasing amounts of BLyS, the autoimmune response is exaggerated. In the presence of additional permissive genetic and/or environmental factors, this exaggerated autoimmune response can lead to frank clinical disease.

According to this first model, reducing SLE-contributory BLyS levels to 'normal' should ameliorate disease by suppressing the BLyS-driven acceleration or exaggeration of the autoimmune response. Self-tolerance would not be 'unbroken', but the magnitude of the autoimmune response would be insufficient to drive clinical disease. Thus, SLE patients with the most elevated circulating BLyS levels should be the ones most responsive to BLyS antagonist therapy. Those patients with normal circulating BLyS levels might be relatively resistant to BLyS antagonist therapy, since 'excess' BLyS is not driving clinical autoimmunity in these patients.

A second, alternative model has BLyS functioning as a passive *facilitator* in development of SLE. In this model, development of the pathologic antiself response is inherently BLyS-independent. Regardless of whether BLyS levels are normal or elevated, the magnitude of the autoimmune response is similar. That is, the trigger of autoimmunity elicits a response so robust that it is not further amplified by elevated levels of BLyS. Accordingly, the critical genetic and/or environmental factors leading to the autoimmune response do not directly require BLyS. Indeed, the fact that many SLE patients harbor normal circulating BLyS levels strongly suggests that BLyS overexpression is not absolutely essential to development of SLE. Nevertheless, given the indispensable role for BLyS in B-cell development [9,10], a certain threshold level of BLyS is required to permit *any* antibody responses (including autoantibody responses). When BLyS levels are reduced below this critical threshold level, the ability to mount the autoimmune response fully (along with other B-cell and humoral responses) is impaired. According to this second model, the SLE patients who should be most responsive to BLyS antagonist therapy are those with normal, rather than elevated, circulating BLyS levels, since in such patients, less neutralization of BLyS would be required to reach the critical threshold level.

These two models are not necessarily mutually exclusive. Within the human SLE population, there may be individuals in whom BLyS plays more of a contributory role and others in whom BLyS plays more of a facilitative role. Indeed, from a therapeutic perspective, the models may operationally be viewed as a continuum, with some patients requiring more neutralization of BLyS than others before salutary clinical effects can be appreciated.

Conclusion

Based on very compelling *in vivo* studies in mice and initial *ex vivo* studies in humans, BLyS/BAFF very likely

contributes to and/or facilitates SLE pathogenesis. Because of the highly restricted nature of its cellular targets (i.e. B cells), specific BLyS antagonists have an excellent chance of not promoting multiple global toxicities. The clinical efficacy of BLyS antagonists remains to be demonstrated in humans. Indeed, much additional investigation is necessary, but the odds remain favorable that specific BLyS antagonists will become important and valuable therapeutic weapons in the war against SLE.

Competing interests

None declared.

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