Systemic lupus erythematosus and its ABCs (APRIL/BLyS complexes)

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Abstract

BLyS and APRIL are closely related members of the TNF ligand superfamily. These cytokines individually may contribute importantly to the development and maintenance of systemic lupus erythematosus (SLE). Dillon and colleagues demonstrate that in contrast to most members of the TNF ligand superfamily, which form only homotrimers, BLyS and APRIL can complex as heterotrimers. These complexes have in vitro biological activity, and circulating levels of BLyS/APRIL heterotrimers are frequently elevated in SLE, but not rheumatoid arthritis, patients. Although the mechanism and regulation of heterotrimer formation, the interconversion (if any) between homotrimers and heterotrimers, and, indeed, the normal physiologic role for such heterotrimers remain unknown, their preferential overexpression in SLE, but not in rheumatoid arthritis, raises the possibility that such heterotrimers may be playing a contributory role in SLE.

BLyS (also commonly known as BAFF) and the closely related APRIL are members of the TNF ligand superfamily. These molecules have enjoyed considerable attention from a diverse audience, ranging from basic investigators studying B-cell biology to clinical rheumatologists eagerly anticipating (and praying for) new (better) medications for their patients with systemic lupus erythematosus (SLE).

In general, individual members of the TNF ligand superfamily are highly parochial. That is, they routinely exist in homotrimeric form and, thereby, exclude other TNF ligand superfamily members from their complex domains. In sharp contrast, the recent report by Dillon and colleagues reminds us that BLyS and APRIL can, and do, couple with each other as heterotrimeric [1]. By extending the previous findings of Roschke and colleagues [2], Dillon and colleagues have convincingly documented the in vitro biologic activity of their recombinant BLyS/APRIL heterotrimers (whose stoichiometry is predominantly two parts APRIL plus one part BLyS) and the ability of soluble fusion proteins expressing either of two BLyS receptors (TACI and BCMA, which each also bind APRIL), but not the third BLyS receptor (BAFFR, which does not bind APRIL), to neutralize the in vitro biologic activity of these recombinant heterotrimers.

The clinical interest in the BLyS axis (which includes BLyS, APRIL, and the three BLyS receptors) initially stemmed from experiments in mice. These experiments, on the one hand, demonstrated causality between BLyS overexpression and development of SLE and, on the other hand, documented the amelioration of clinical disease in SLE mice following either treatment with a BLyS antagonist or the genetic elimination of BLyS [3-6]. The relevance of these observations in mice to the human condition was buttressed by the findings of BLyS overexpression in human SLE and the correlation of disease activity with circulating BLyS levels in these patients [7,8].

The appeal of BLyS as a therapeutic target has prompted substantial time and effort (and money) in the development of BLyS antagonists. The two BLyS antagonists that are the furthest advanced in clinical development are belimumab, an anti-BLyS monoclonal antibody, and atacicept, a fusion protein between TACI and the Fc portion of IgG. Results from phase II and phase III trials have demonstrated modest, but statistically significant, efficacy for belimumab in SLE [9,10], and late-stage clinical trials with atacicept in SLE are either currently underway or will soon begin.

It must be stressed that although belimumab and atacicept each binds to and neutralizes BLyS, their respective biologic activities importantly differ. Belimumab has no APRIL-neutralizing capacity, whereas atacicept is fully capable of neutralizing APRIL. Although APRIL-overexpressing mice, in marked contradistinction to BLyS-overexpressing mice, develop only subtle immunological abnormalities with no serological or clinical
autoimmune features [11], APRIL does contribute to plasma cell survival [12]. Accordingly, APRIL may enhance the longevity of autoantibody-producing plasma cells in a SLE host, and its neutralization may therefore result in decreased production of autoantibodies. Due to the fact that atacicept (TACI-Ig), but not the BLyS-specific BAFFR-Ig, neutralized the in vitro biologic activity of the recombinant BLyS/APRIL heterotrimers of Dillon and colleagues [1], atacicept probably neutralizes BLyS/APRIL heterotrimers (and APRIL homotrimers) in vivo, whereas belimumab may have little-to-no neutralizing effect on BLyS/APRIL heterotrimers (and no effect against APRIL homotrimers).

Whether this probable differential neutralization of BLyS/APRIL heterotrimers has any therapeutic ramifications remains entirely speculative. In principle, the biologic activity of BLyS/APRIL heterotrimers in vivo may be greater than, less than, or equal to that of BLyS or APRIL homotrimers. Accordingly, the net effect of therapeutics neutralization of APRIL concomitant with neutralization of BLyS might be beneficial, harmful, or neutral in the context of the ongoing autoimmunity of SLE. Of note, the recombinant heterotrimers of Dillon and colleagues were considerably less potent in promoting in vitro human B-cell proliferation than were the corresponding BLyS or APRIL homotrimers, raising the possibility (but certainly not proving) that the in vivo biologic activity of BLyS/APRIL heterotrimers may be relatively insignificant in comparison with those of BLyS or APRIL homotrimers.

Dillon and colleagues have also documented elevated circulating levels of native BLyS/APRIL heterotrimers in patients with SLE (but not with rheumatoid arthritis), although the precise stoichiometry of these heterotrimers in vivo remains unknown. The relative impotence of the recombinant BLyS/APRIL heterotrimers coupled to the uncertainty surrounding the in vivo stoichiometry of BLyS/APRIL heterotrimers highlight our current state of ignorance regarding these heterotrimers. We remain in the dark with regard to the mechanism and the regulation of heterotrimer formation in vivo, the interconversion (if any) between homotrimers and heterotrimers, and the dysregulation (if any) of such heterotrimers in disease states, such as SLE. Nonetheless, the preferential overexpression of heterotrimers in SLE, but not in rheumatoid arthritis, raises the possibility that such heterotrimers may be playing a contributory role in SLE. Development of reagents that can specifically neutralize the BLyS (or APRIL) homotrimers but not the heterotrimers (or vice versa) will help resolve the BLyS/APRIL heterotrimeric enigma.

Competing interests
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