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New receptor critical for BAFF-mediated B cell survival

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Keywords

BAFF-R, BAFF/BLyS, TACI

Context

The TNF family member BAFF (also known as BLyS, TALL-1, THANK and zTHF4) is overexpressed in autoimmune diseases such as SLE and RA. Inhibition of BAFF function through recombinant receptor TACI-Ig has dramatic effects on the onset and progression of CIA in a mouse model of the disease (see Additional information [1]). Two receptors for BAFF, TACI and BCMA, have previously been described, both of which are also receptors for another TNF family member, APRIL. This paper describes the cloning of a unique BAFF receptor that does not bind APRIL and may mediate effects of BAFF on B-cell survival.

Significant findings

Initial studies of the BJAB B-cell line suggested the existence of a third BAFF receptor, since it bound high levels of BAFF although no or/low levels of TACI and BCMA were found. A novel BAFF receptor, BAFF-R, which was found to be specific for BAFF, was cloned from a BJAB library. The authors also generated a recombinant BAFF-R-Fc fusion protein, which inhibited BAFF binding to BJAB cells and inhibited BAFF-mediated co-stimulation of B-cell proliferation. BAFF-deficient mice have profound B-cell defects reminiscent of the A/WySnJ mouse strain, the authors examined BAFF-R expression in A/WySnJ mice. BAFF-R expressed in the A/WySnJ mice lacks exon 3, which encodes the intracellular signalling domain of BAFF-R; this defect presumably eradicates its function. Neither the TACI nor BCMA knockout mice have B-cell deficiencies similar to BAFF knockout mice, implicating BAFF-R as the major effector for BAFF-mediated B-cell survival. Additionally, APRIL and BAFF signalling through TACI and BCMA could not compensate for loss of BAFF-R, demonstrating its critical role in B-cell survival and homeostasis. BAFF-R and its deficiency in A/WySnJ have been reported by another group (see Additional information [2]), although they name the new receptor BLyS receptor 3.

Comments

BAFF-R is a suitable, specific receptor for BAFF, which may mediate the effects of TACI-Ig in mouse models of SLE and RA (see Additional information [1]). Given the inhibition of mouse CIA seen with TACI-Ig treatment, BAFF-R-Fc should also have clinical applications. In fact, it is presumed that TACI-Ig inhibition is through inhibition of BAFF and not APRIL, but BAFF-R-Fc could prove this. The current model of BAFF-BAFF-R function is that its primary function is in B-cell homeostasis, providing a signal to block cell death of mature B cells. In the A/WySnJ mice, the result is a severe block in B-cell development. In normal mice, blocking BAFF function through TACI-Ig results in a dramatic decrease in mature B cells (see Additional information [2]). In autoimmune disease, the functional consequence of blocking BAFF may be the elimination of autoreactive B-cell clones. Uncovering how BAFF-R functions and designing strategies to inhibit BAFF-R function could have direct clinical applications to autoimmune diseases.

Methods

Expression cloning, northern analysis, receptor-ligand associations

Additional information

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