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BLyS in B-Cell Maturation and Autoimmune Disease

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Abstracts

BAFF/ BLyS (B lymphocyte stimulator) is a newly identified TNF family cytokine. It has been implicated in the development of autoimmunity, and functions as a potent costimulator with anti-IgM in B cell proliferation in vitro. Overproduction of BAFF in transgenic mice caused accumulation of immature and mature B-cells, increased serum immunoglobulin levels, and elicited systemic lupus erythematosus (SLE)-like autoimmune symptoms. Furthermore, Patients with various autoimmune symptoms, SLE, rheumatoid arthritis, or Sjogren's syndrome have elevated levels of BAFF in their sera. we demonstrate that BLyS prominently enhances the humoral responses to both T cell–independent and T cell–dependent antigens, primarily by attenuation of apoptosis as evidenced by the prolonged survival of antigen-activated B cells in vivo and in vitro. BLyS acts on primary splenic B cells autonomously, and directly cooperates with CD40 ligand (CD40L) in B cell activation in vitro by protecting replicating B cells from apoptosis. Moreover, although BLyS alone cannot activate the cell cycle, it is sufficient to prolong the survival of naive resting B cells in vitro. Attenuation of apoptosis by BLyS correlates with changes in the ratios between Bcl-2 family proteins in favor of cell survival, predominantly by reducing the proapoptotic Bak and increasing its prosurvival partners, Bcl-2 and Bcl-xL. Together, these results provide direct evidence for BLyS enhancement of both T cell–independent and T cell–dependent humoral immune responses, and imply a role for BLyS in the conservation of the B cell repertoire. The ability of BLyS to increase B cell survival indiscriminately, at either a resting or activated state, and to cooperate with CD40L, further suggests that attenuation of apoptosis underlies BLyS enhancement of polyclonal autoimmunity as well as the physiologic humoral immune response.

BAFF has an affinity for three different receptors, BAFF-R, TACI, and BCMA. BAFF-R appears to be the major BAFF receptor for B-cell development *in vivo*. Mice with impaired BAFF-R have a phenotype that closely resembles that of BAFF-deficient mice. We also have determined the crystal structure of BAFF-R extracellular domain bound to BAFF at a resolution of 3.3 Å. The cysteine-rich domain (CRD) of the BAFF-R extracellular domain adopts a β-hairpin structure and binds to the virus-like BAFF cage in a 1:1 molar ratio. The conserved DxL motif of BAFF-R is located on the tip of the β-turn, and plays an indispensable role in the binding of BAFF. The crystal structure shows that a unique dimeric contact occurs between the BAFF-R monomers in the virus-like cage complex. Both of the CRDs of TACI contain the DxL motifs and simultaneously interact with the BAFF dimer in the virus-like cage.

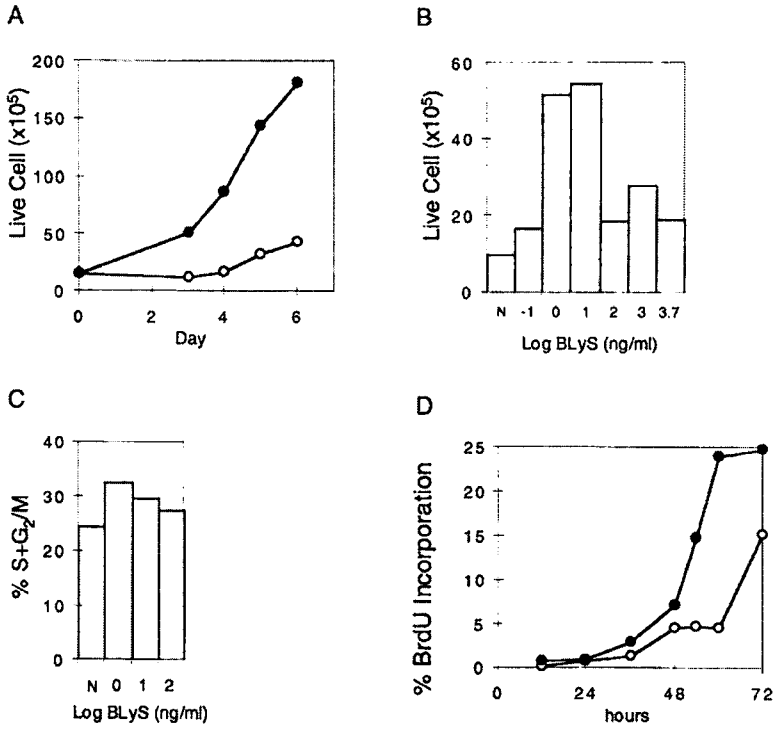

Fig. 1 BLyS enhances the activation of B cells by CD40L in vitro. (A) Resting mouse splenic B cells were cocultured with CD40L cells, in the presence (•) or absence (○) of BLyS (50 ng/ml). The accumulation of live cells was determined on the days indicated, by trypan blue staining and counting in triplicate. This experiment has been performed three times. (B) The accumulation of viable cell number on day 3 of coculture with CD40L cells in the presence of indicated concentrations of BLyS or without BLyS (N). (C) FACS® analysis of DNA content on day 3 of coculture with CD40L cells in the presence of indicated concentrations of BLyS or without BLyS (N), and expressed as the percentage of cells in the S and G2/M phases of the cell cycle. (D) Analysis of BrdU incorporation in a 2-h period, at 12-h intervals of coculturing with CD40L cells in the presence (•) or absence (○) of BLyS (5 ng/ml).

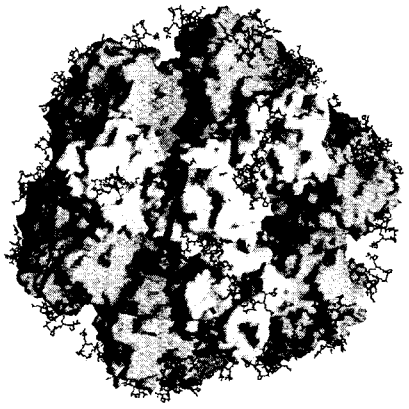

Fig. 2 Structure of the BAFF-R extracellular domains bound to the virus-like BAFF cage.

References

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