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TALL-1 and autoimmunity

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Keywords

Autoimmunity, B cell proliferation, TNF ligand family

Context

The TNF- and ApoL-related leukocyte-expressed ligand (TALL-1), known also as BAFF (B cell activating factor), THANK and BLYS (B lymphocyte stimulator), is a type II membrane protein of the TNF ligand superfamily which is involved in the modulation of B cell proliferation. *In vitro* recombinant TALL-1 induces B cell proliferation in a dose-dependent manner. *In vivo* administration intraperitoneally of recombinant TALL-1 into BALB/c mice causes disordered splenic architecture, B cell expansion and increased levels of IgM and IgA, but not IgG. To investigate the biological function of TALL-1 *in vivo*.

Significant findings

Necropsy of 8-week-old transgenic mice showed enlarged spleens (45% increase), lymph nodes and Peyer's patches. Immunohistologic staining with T- and B-cell- specific markers and flow cytometry analysis demonstrated that the B cell numbers were significantly increased, while the T cells numbers were reduced. All the other organs, including the thymus, were comparable between the transgenic mice and the littermate controls. No differences in B cell developmental stages were found. In addition to having B cell hyperplasia the TALL-1 trasgenic mice also had severe hypergammaglobulinemia. This was accompanied by the presence of elevated level of autoantibodies (ANA, anti-dsDNA and antihistone antibodies). Kidney lesions, compatible with immune complex deposits in the glomeruli, were detected in 8-month-old mice. Renal function was also impaired. *In vitro* transgenic expression of TALL-1 was shown to prolong B cell survival. In addition TALL-1 was demonstrated to be a weak stimulant and a powerful co-stimulant of B cell growth *in vitro*.

Comments

This interesting paper suggests a physiological role for TALL-1 (TNF- [tumour necrosis factor] and ApoL-related leukocyte-expressed ligand) in the regulation of B cell proliferation and activation. Transgenic TALL-1 mice developed an autoimmune phenotype, supporting the hypothesis that abnormalities in the regulation and thresholds of B and T cell activation may drive an autoimmune response. To understand the biological significance of these findings, however, it would have been useful to know the amount of transgenic TALL-1 present in circulation. It will be also of interest to determine if overexpression of this gene can be demonstrated in human autoimmune disorders.

Methods

TALL-1 transgenic mice were developed using standard techniques. Transgene expression was identified by RT-PCR of splenic total RNA. Histological analysis at various ages was performed. Expression of T and B lymphocyte activation markers from spleen, thymus and mesenteric lymph nodes was analysed by flow cytometry. Serum immunoglobulin levels, antinuclear antibody (ANA), anti-dsDNA and antihistone antibodies were quantitated by ELISA. B cell survival was investigated using B cells purified by negative selection from spleens of mice that were 2 to 4 months old. FACS analysis was used to confirm the purity of the B population. B cells were cultured in medium and the percentage of dead cells, identified by propidium iodide staining, was calculated daily. B cell proliferation was measured by the uptake of tritiated thymidine after stimulation with anti-mouse IgM and/or TALL-1 for 4 days.

References

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