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Central tolerance requires a Bim

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Keywords

Bim, knockout mice, negative selection

Context

"Negative selection" or deletion of potentially autoreactive immature thymocytes occurs by apoptosis of cells bearing an antigen receptor with high affinity for self major histocompatibility complex (MHC). The molecular requirements for thymocyte apoptosis induced during negative selection are beginning to be defined. Functional defects in the signaling cascade downstream of the T-cell antigen receptor (e.g. mutations in CD3?, the adaptors Grb2 and Gads, the kinases Itk and Rlk) have already been associated with impaired deletion. In contrast, and perhaps surprisingly, proteins known to play a role in apoptosis induced by "death receptor" ligation (e.g. CD95, FADD, Caspase-8) have limited roles in thymocyte deletion. The present paper is, therefore, among the first to show that mutation of a protein within the machinery of death influences thymocyte apoptosis.

Significant findings

Bim is a proapoptotic member, containing only the BH3 domain, of the Bcl-2 family of intracellular membrane proteins. Aging Bim knockout mice exhibit autoantibody production and immune complex glomerulonephritis (see Additional information [1]). Here, evidence is presented that autoimmunity in Bim-deficient animals is associated with defective negative thymic selection. The authors employ *in vivo* and *in vitro* anti-T-cell receptor (TCR) treatment, exposure to endogenous and exogenous superantigen, and several TCR-transgenic models to examine thymocyte deletion. Results are consistent throughout; Bim deficient thymocytes are refractory to apoptosis induced by TCR engagement. The authors show evidence that TCR engagement normally results in enhanced Bim protein levels and increased association between Bim and Bcl-XL. The Bim-Bcl-XL complex may impair antiapoptotic function of Bcl-XL. The authors conclude that Bim is required for TCR-mediated apoptosis and deletion of autoreactive thymocytes.

Comments

Recent work in other autoimmune animal models has suggested that perturbations in thymocyte selection may alter the threshold for autoimmune phenomena. Bim-deficient animals show parallels with nonobese diabetic (NOD) mice (see Additional information [2]) and "motheaten" mice (lacking the signaling protein SHP-1) (see Additional information [3]); each exhibits defects in thymic selection. A causal link between autoimmune phenomena and skewed thymic development in these mice remains to be demonstrated, such that it is unclear if defects in peripheral tolerance contribute to autoimmunity. One experimental approach would be to "rescue" thymic selection in Bim-deficient mice through reconstitution with a thymocyte-restricted transgenic form of Bim. In such a system, Bim protein would be engineered to be present during T-cell development, yet absent in mature peripheral T cells. Those autoimmune features dependent upon thymic development should, therefore, be eliminated.

Methods

Knockout mice

Additional information

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