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IEX-1 transgenic mice develop a lupus-like disease

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Keywords

apoptosis, mouse models, SLE, TNF

Context

The lifespan of effector T lymphocytes is crucial for the termination of immune responses and for the prevention of autoimmunity. Immediate early gene X-1 (IEX-1), also called IER3, p22/PRG1, *Dif-2* or mouse homology *gly96*, was found in a variety of cells, including hepatocytes, keratinocytes, monocytes and lymphocytes. IEX-1 expression is directly induced by the transcription factor nuclear factor (NF)-?B/Rel, which is important in signal transduction through the T cell receptor as well as signals delivered by tumour necrosis factor (TNF) and IL-1. Several groups reporting on IEX-1 found different effects on apoptosis and proliferation, which led the authors of this article to generate transgenic mice with lymphocyte-specific overexpression of IEX-1.

Significant findings

Human peripheral blood T cells upregulated IEX-1 after T-cell receptor crosslinking, which coincided with protection against Fas (CD95) induced apoptosis. IEX-1 transgenic lymphocytes were resistant to Fas-induced cell death and apoptosis following T cell receptor crosslinking. IEX-1 transgenic animals had prolonged delayed type hypersensitivity (DTH) reactions and more pronounced reactions upon rechallenge with the same antigen. After *in vivo* superantigen stimulation, the activated lymphocytes persisted (instead of undergoing apoptosis). As compared to wild-type mice, spleens and lymph nodes of IEX-1 transgenics contained more T lymphocytes, and $CD4^{+}CD44^{hi}$ lymphocytes in particular. However, the numbers of B lymphocytes were unaffected. While young animals were normal, splenomegaly and lymphadenopathy developed in an increasing percentage of mice with age, beginning at eight weeks. At nine months of age more than half of the transgenic animals demonstrated considerably increased IgG2a levels and a lupus-like disease with anti-dsDNA antibodies, proteinuria

and immune complex glomerulonephritis. Thirty percent of the mice also developed arthritis and erythema with alopecia of the skin.

Comments

Like other mouse models with defects in apoptosis regulation, transgenic mice with constitutive lymphocytic IEX-1 overexpression develop a lupus-like disease. However, IEX-1 transgenic mice may be a particularly interesting model of SLE: the disease phenotype is variable and the increasing incidence with age suggests that environmental factors, including infectious agents, play a role. Moreover, the authors point out that IEX-1 has mapped within the MHC locus, where most probably several lupus susceptibility genes are situated. Finally, IEX-1 is a TNF-induced immediate early gene, and TNF is increased in human SLE. A critical question is whether IEX-1 overexpression acts in a similar fashion as mutant Fas and Fas ligand (the defects in the *lpr* and *gld* murine models of SLE, respectively). That is, is IEX-1 playing a critical role in breaking tolerance, or is it acting as an "accelerant", as is the case for *lpr* and *gld*?

Methods

Transgenic mice, fluorocytometry, Fas and T-cell receptor crosslinking, peripheral T-cell depletion, DTH response, ELISA (Immunoglobulin, anti-dsDNA), histology and immunofluorescence of kidney sections.

Additional information

References

1. Zhang Y, Schlossman SF, Edwards RA, OU C-N, Gu J, Wu MX: Impaired apoptosis, extended duration of immune responses, and a lupus-like autoimmune disease in IEX-1 transgenic mice. Proc Natl Acad Sci USA. 2002, 99: 878-883.