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Autoimmunity in *PTEN*+/- mice

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Matthew Pickering

Keywords

Apoptosis, autoimmunity, Fas

Context

The *PTEN* gene encodes a phosphatase that is homozygously mutated in a high percentage of human tumours. A major substrate of PTEN is phosphatidylinositol triphosphate (PIP-3), a lipid second messenger produced by phosphatidylinositol-3 kinase (PI-3K). In the absence of PTEN activity, PIP-3 concentrations are increased, resulting in enhanced phosphorylation and activation of the survival-promoting factor Akt/PKB (protein kinase B). Inactivating mutations in the *PTEN* tumour suppressor gene occur in three related human autosomal dominant disorders characterised by tumour susceptibility. Homozygous deficiency of PTEN in mice results in embryonic death. This paper studies the consequences of haploinsufficiency of PTEN by analysing the phenotype of PTEN heterozygous mice. To characterise the phenotype of mice heterozygous for the tumour suppressor gene *PTEN*.

Significant findings

Approximately 100% of *PTEN* +/- females developed severe lymphadenopathy between the ages of 4 and 5 months and died before the age of 1 year. Male mice were less severely affected, with 83% developing lymphadenopathy at 8 months and surviving to at least 15 months. Inflammatory infiltrates were present in most organs, particularly the lungs, and affected mice developed nephritis with immune complex deposition. Increased serum immunoglobulin (Ig) concentrations and elevated ANA and anti-ssDNA titres were present in tumour-free *PTEN* +/- mice. T cell activation markers (CD44, CD54 and CD69) were upregulated and the number of B lymphocytes positive for CD44, B7-2 and CD5 was increased. In addition, the level of expression of Fas on the surface of T and B cells from the *PTEN* +/- mice was increased by a factor of two and three respectively. Activation-induced cell death was reduced in the *PTEN* +/- splenocytes by approximately 50% and apoptosis mediated by anti-CD95 antibodies in both activated T- and B-*PTEN* +/- lymphocytes was impaired. In *PTEN* +/- splenocytes, Akt (a survival promoting factor) was hyperphosphorylated and the caspase-dependent degradation of Akt and Parp following anti-Fas treatment was defective. The PI-3K inhibitor, Wortmannin, reversed this latter finding and restored the sensitivity of *PTEN* +/- splenocytes to anti-Fas mediated apoptosis.

Comments

This is an interesting paper demonstrating a critical physiological role for PTEN in the Fas-mediated removal of self-reactive cells. Heterozygous deficiency resulted in a lethal murine autoimmune phenotype. The importance of normal PTEN function in humans is highlighted by rare autosomal dominant syndromes in which heterozygous inactivation of PTEN occurs. These conditions are all strongly associated with an increased incidence of malignancy. It will be of interest to determine if mutations in this allele can be demonstrated in human autoimmune disorders.

Methods

PTEN +/- mice were developed using standard gene targeting techniques. Histological analysis at various ages was performed. Anti-nuclear antibody (ANA) titres were measured using indirect immunofluorescence and anti-single stranded DNA antibodies by ELISA. Expression of T- and B-lymphocyte activation markers was measured by flow cytometry. Activation-induced cell death was generated with anti-CD3e with or without Fas:Fc chimeric protein and assessed by trypan blue exclusion and *in situ* terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) assay. Apoptosis was induced with CD3e and CD95(Fas) agonistic antibodies after activation of cultured splenocytes, or CD3 positive cells, with lipopolysaccharide (LPS) or cross-linked anti-CD3e. Apoptosis was measured at 24 h and 48 h by *in situ* TUNEL assay. Apoptosis was also assessed in cells preincubated for 30 min with Wortmannin prior to anti-CD95 treatment. Protein extracts from stimulated cells with or without Wortmannin were analysed by protein immunoblotting.

Additional information

The three human autosomal dominant disorders associated with heterozygous deficiency of PTEN are Cowden disease (a multiple hamartomatous syndrome with a high risk malignancy, eg breast carcinoma), Lhermitte-Duclos syndrome (dysplastic cerebellar gangliocytomas) and Bannayan-Zonana syndrome (a hamartomatous disorder with macrocephaly, multiple lipomas, and haemangiomas).

References

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