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Activation of the PTEN substrate PI3K contributes to tumour generation and autoimmunity

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Keywords

Apoptosis, autoantibodies, autoantigen, MCTD, Raynaud's phenomenon, SLE, U1 snRNP

Context

PI3K is composed of a regulatory (p85) and a catalytic (p110) subunit and catalyses the formation of phosphatidylinositols P2 and P3, thus regulating cell survival, division and migration. In addition to having specific functions in B cells, PI3K has been implicated in tumour formation. Interestingly, the tumour suppressor PTEN, mutated in many human tumours, downregulates PI3K pathways. Selective impairment of 3-phosphoinositide recognition has been described for only one human PTEN mutation and it remains unclear whether other substrates of PTEN are essential mediators of this tumour suppressor. To elucidate the involvement of PI3K in T cell function and in tumour formation.

Significant findings

Transgenic mice showed a pronounced increase in $CD4^+$ cells leading to an accumulation in the spleen and lymph nodes after 12-15 months. The number of T cells expressing the shared memory/activated $CD44^{high}$ $CD62L^{low}$ $CD45RB^{low}$ phenotype was elevated as compared to the wild-type animals. The expression of CD25, CD54, CD69, CD11b, and VLA-4 activation markers was not significantly increased in the $CD4^+$ cells of the p65PI3K Tg mice between week 6 and month 10, suggesting that the $CD4^+$ T cells were enriched in memory cells. In some 12-15 month old p65PI3K Tg mice, the expanding $CD4^+$ cell population acquired a partially activated phenotype with increased expression of CD69 and CD54, but not CD25, CD11b, or VLA-4. The expansion of the $CD4^+$ lymphocyte pool in the p65PI3K Tg mice was accompanied by an increased survival of $CD4^+$ memory cells. Adult p65PI3K Tg mice developed a lymphoproliferative disorder with large lymphoid infiltrates in non-lymphoid organs. Flow cytometry of lung cell suspensions revealed a dominance (60%) of $CD4^+$T cells. The majority of animals with advanced lymphoproliferative disease developed severe autoimmune glomerulonephritis that was accompanied by a polyclonal hypergammaglobulinemia with an increase in IgG1 and IgG2. Levels of anti-ds DNA autoantibodies were also elevated in the sera of p65PI3K Tg mice. No tissue destruction by T cells was observed. To examine whether PTEN

counteracts the action of PI3K in cellular transformation, the ability of PTEN to inhibit p65PI3K-induced 3T3 cell transformation was examined. A focus formation assay, was used to assess the transformation of 3T3 cells. Ectopic expression of PTEN (two- to four-fold higher expression as compared to the endogenous enzyme) inhibited focus formation by p65PI3K alone or in combination with v-Raf, but did not affect foci induced by v-Raf alone or by v-Src.

Comments

Interest is growing in the relevance of the PI3K-Akt-NF-?B pathway to rheumatic disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Downregulation PTEN, a key regulator of PI3K-mediated signalling, occurs in the RA synovium. In their paper, Borlado *et al*demonstrate that transgenic mice expressing an active form (p65PI3K) of the phosphoinositide 3-kinase in T cells develop an infiltrating lymphoproliferative disorder as well as autoimmune renal disease with increased numbers of memory T cells. In addition, overexpression of p65PI3K affects fibroblasts by inducing focus formation in 3T3 cells. Interestingly, p65PI3K induced fibroblast transformation is inhibited selectively by the overexpression of PTEN. Although the relevance of these findings for specific rheumatic diseases needs to be established, the data provide new insights into cellular signalling and suggest that PTEN/PI3K pathways may constitute interesting targets for rheumatic diseases.

Methods

Mice transgenic for the thymic lymphoma p65PI3K mutant of p85a (p65PI3K Tg) were generated by inserting a restriction fragment of p65PI3K into the p56 Lck promoter (pLck) human growth hormone (hGH) vector and subsequently injecting a purified fragment containing the pLck-p65PI3K-hGH transgene into the pronuclei of fertilised oocytes of (C57BL/6 x CBA) F_1 mice. Transgene-positive lines of the offspring were backcrossed onto the C57BL/6 background. Mice were examined for the appearance of tumours and other clinical abnormalities twice weekly. They were sacrificed at different times and organs were investigated by standard histology and immunohistochemistry. Cell suspensions from the thymus, spleen, and lymph nodes were analysed for surface markers and for apoptosis by flow cytometry. Human PTEN cDNA was amplified from poly(A)-mRNA of MCF-7 cells and subcloned in pRK5. Focus formation of 3T3 fibroblasts was investigated in $p65PI3K^+$ cells with and without overexpression of PTEN.

References

1. Borlado LR, Redondo C, Alvarez B, Jimenez C, Criado LM, Flores J, Marcos MAR, Martinez AC, Balomenos D, Carrera AC: Increased phosphoinositide 3-kinase activity induces a lymphoproliferative disorder and contributes to tumour generation *in vivo*. FASEB J. 2000, 14: 895-903.