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p56^{lck}expression in type 1 diabetes

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Keywords

p56[lck], T lymphocyte, TCR-CD3 transduction pathway, type 1 diabetes

Context

Type 1 diabetes is a T cell-mediated autoimmune disease leading to the destruction of pancreatic islet ? cells. This disease is associated with numerous immunological abnormalities. A characteristic abnormality is decreased proliferation and altered cytokine production by T lymphocytes when exposed to TCR/CD3 agonists *in vitro*. This phenotype can be reversed by addition of costimulatory signals (eg combination of CD2/CD28 antibodies or exogenous cytokines), suggesting a constitutive defect in the TCR/CD3 signal transduction pathway. In T lymphocytes, TCR/CD3 engagement induces CD3?-chain phosphorylation by p56[lck] or p59[fyn] tyrosine kinases. CD3?-chain phosphorylation allows the docking and the phosphorylation of ZAP-70 tyrosine kinase, which in turn phosphorylates neighboring proteins such as linker for activation of T cells (LAT). After recruitment of various adaptor proteins, key effector enzymes such as phospholipase C ? (PLC-?) are activated. The authors studied TCR/CD3 transduction pathway in isolated T lymphocytes.

Significant findings

The CD3?-chain was hypophosphorylated in 70% of the patients tested versus none of control subjects. By contrast, phosphorylation of ZAP-70 was unaffected. The patients with CD3?-chain hypophosphorylation had reduced expression of p56[lck] in resting lymphocytes. The authors did not observe a decrease of p59[fyn], LAT, PLC-? or PI3kinase expression. In some patients, this defect was linked to low level of p56[lck]mRNA, and resulted in the failure to efficiently induce the expression of the CD69 early activation marker. The authors propose that T cell deficiency in human type 1 diabetes is due to the selective decreased expression of the p56[lck] tyrosine kinase.

Comments

The functional consequences of the $p56^{lck}$ defect are of interest because (1) during intrathymic maturation, the preferential association of $p56^{lck}$ with TCR/CD3 is required for the appropriate adjustment of threshold responses to autoantigens; and (2) differentiation toward the Th2 lineage requires high levels of recruited $p56^{lck}$ kinase, and diabetes in a non-obese diabetic mouse model is associated with a relative reduction of the Th2/Th1 cell ratio. More experiments are required to prove the role of this defect in diabetes development. However, the description of a constitutive T cell signalling abnormality in a T cell mediated autoimmune disease will permit further insights into how tolerance is broken down in diabetes and other autoimmune diseases.

Methods

T cell activation, western blot, immunoprecipitation,

References

1. Nervi S, Atlan-Gepner C, Kahn-Perles B, Lecine P, Vialettes B, Imbert J, Naquet P: Specific deficiency of $p56^{lck}$expression in T lymphocytes from type 1 diabetic patients. J Immunol . 2000, 165: 5874-5883.