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*Studies of immunological risk factors
in type 1 diabetes*

Jenny Walldén

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Fakultetsopponent är Vivianne Malmström, KI, Stockholm

Division of Pediatrics and Diabetes Research Centre
Department of Clinical and Experimental Medicine
Faculty of Health Sciences, Linköping University
SE-581 85 Linköping, Sweden



Linköping University
FACULTY OF HEALTH SCIENCES

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ABSTRACT

Background: Type 1 diabetes (T1D) is a chronic, autoimmune disease caused by a T cell mediated destruction of β -cells in pancreas. The development of T1D is determined by a combination of genetic susceptibility genes and environmental factors involved in the pathogenesis of T1D.

This thesis aimed to investigate diverse environmental and immunological risk factors associated with the development of T1D. This was accomplished by comparing autoantibody development, T cell responses and the function of $CD4^+CD25^+$ regulatory T cells between healthy children, children at risk of T1D and T1D patients.

Results: Induction of autoantibodies in as young children as one year old, was associated with previously identified environmental risk factors of T1D, such as maternal gastroenteritis during pregnancy and early introduction of cow's milk. We did not see any general increase in the activity of peripheral blood T_H subtypes in children with HLA class II risk haplotypes associated with T1D, nor were HLA class II risk haplotypes associated with any aberrant cytokine production in response to antigenic stimulation of peripheral blood mononuclear cells. However children with a HLA class II protective haplotype showed an increased production of IFN- γ in response to enteroviral stimulation.

CTLA-4 polymorphisms connected with a risk of autoimmune disease were associated with enhanced production of IFN- γ .

Healthy children with β -cell autoantibodies had a lower expression level of GATA-3 compared to health children with HLA risk genotype or children without risk. Instead, children with manifest T1D showed lower expression levels of T-bet, IL-12R β_1 and IL-4R α .

Both T1D and healthy children showed the same expression of the regulatory markers Foxp3, CTLA-4 and ICOS in peripheral blood mononuclear cells, and the amount of $CD4^+CD25^+$ T cells did neither reveal any differences. The regulatory T cells seemed also to be functional in children with T1D, since increased proliferation after depletion of $CD4^+CD25^{high}$ cells from PBMC was demonstrated in T1D as well as in healthy children.

However, T1D children did have more intracellular CTLA-4 per $CD4^+CD25^{high}$ T cell, increased levels of serum C-reactive protein and higher spontaneous expression of IFN- γ in CD25depleted PBMC, all which are signs of activation of the immune system. This suggests a normal or enhanced functional activity of regulatory T cells in T1D at diagnosis.

Conclusions: Our findings emphasize that environmental risk factors do have a role in the development of β -cell autoimmunity. Our results do not support a systemic activation of the immune system in pre-diabetes or T1D, but instead a possible up-regulation of regulatory mechanisms seems to occur after diagnosis of T1D, which probably tries to dampen the autoimmune reaction taking place.
