Research Theme
Metabolic Disorders

Research Project Title
Characterization of Regulatory T cells in Animal Models of Experimental Autoimmune Diabetes (EAD): Development of Novel Concepts for Immunomodulation

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Project Description
Background

Insulin-dependent diabetes mellitus also called Type 1 diabetes (T1Dm) is a chronic autoimmune disease with an increased morbidity and mortality in the affected patients. The disease afflicts male and female patients in equal numbers at all ages. The disease is caused by the autoaggressive attack of the body's immune system against the insulin-producing beta cells of the pancreas. Currently the mechanisms leading to the destruction of the insulin-producing cells are not well understood. Cells of the adaptive immune system, the so-called T lymphocytes, have been pinpointed as the major drivers of the autodestruction in various animal models. However, no kind of immune intervention used in animal models has been found to be effective when applied in humans.

To overcome the drawbacks of T1Dm animal models and in order to get a more thorough understanding in the mechanisms of autoreactivity we have generated novel animal models and technologies to induce and to manipulate the insulitic process in the EAD models. The ultimate goal of the research will be to generate knowledge that will enable us to halt the autoimmune process leading to the islet cell destruction.

The experimental autoimmune diabetes model (EAD)

Transgenic mice, which express the key costimulatory molecule CD80 under the control of the rat insulin promotor, have been generated. Diabetes can be induced in these mice by a single intramuscular vaccination with a pro-insulin producing plasmid vector (Karges W et al., Diabetes, 2002: Pechhold K et al., J Autoimmun 2003). This genetic vaccination leads to the formation of cytotoxic T cells that start to infiltrate the islets (checkpoint 1: insulitic process), then build up a destructive insulitic process (checkpoint 2), and finally leads to largely elevated blood glucose levels (checkpoint 3) due to an irreversible beta cells loss. After induction of an autoimmune response in the CD80 tg mice a very aggressive destructive process driven by infiltrating CD8+ cells starts. By
blocking the PD-L1 pathway using neutralizing antibodies a less aggressive autoimmune attack can be initiated after DNA vaccination (Brosi H et al., J Immunol 2009; Rajasalu T et al., Diabetes 2010; Schuster C et al., PLoS One 2013). Thereby the CD80 tg mouse model resembles the very early onset forms of Type 1 diabetes, whereas blocking of the PD-L1 pathway resembles more the features of Type 1 diabetes with disease onset in adulthood.

Proposed work

After inducing the insulitic process with genetic vaccination we are planning to mitigate the autoreactivity by using T cells from a novel animal model. This mouse has been specifically designed to express the diabetes autoantigen proinsulin in the thymic epithelium under the control of the Foxn1 promoter (Nehls M et al., Nature 1994; Bleul CC et al., Nature 2006; Boehm T et al., Immunol Rev 2003; Boehm T et al., J Exp Med 2003) in order to foster a diabetes-specific central tolerance mechanisms. Preliminary studies have shown that these mice can generate T cells with regulatory properties. Therefore the presence of proinsulin expressing thymic epithelium can significantly slow down the development of diabetes in the RIP-CD80 tg model and even revert the disease process.

The research work will make use of these animal model systems to pinpoint both the phenotype of the autoaggressive and the regulatory T cells. The experimental work will include thymus transplantation studies as well the characterization of the early infiltrate in the islets (checkpoint 1, 2) and the characterization of the control of the diabetic process, i.e. characterization of the immune cells involved in the reversion from a malignant insulitic process to a proposed benign insulitic process (checkpoint 3 back to checkpoint 2) using analytical technologies at the single cell level.

Finally the knowledge gained will be applied to extensively immunophenotyping patients with autoimmune-diabetes in Singapore (Endl J et al., Diabetes 2006; Karges W et al., Diabetes Care 2004). We expect a more thorough understanding of the autoimmune process in humans and envision the development of immunotherapies leading to long term beta cell recovery and/or immune tolerance as already demonstrated by our group (Karges W et al., Diabetes Care 2004).

Contact Us

If you have questions regarding this project, please email the Principal Investigator.
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