P47 – Gut inflammation and modifications in microbiota composition trigger intestinal activation of islet-reactive T cells and autoimmune diabetes

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Background and Objective: The gut commensal microbiota play an important role in modulating the pathogenesis of extra-intestinal autoimmune diseases. In support to this idea there is the observation that autoimmune diseases such as Type 1 Diabetes (T1D) are often precede by dysbiosis and signs of enteropathy (e.g., low-grade chronic inflammation, loss of gut barrier integrity, etc.) both in patients and animal models. However, it remains to be determined if there is a causal relationship between enteropathy and T1D how damage of gut barrier integrity promotes ß-cell autoimmunity.

Methodology: We induced chronic DSS colitis in *BDC2.5XNOD* mice that carry a transgenic TCR specific for an selfantigen of insulin-producing ß cells and have a large diabetogenic T cell repertoire (90% of circulating T cells) but do not normally develop T1D. In this chronic colitis model we studied how modifications of gut barrier integrity (IEB and mucus layer structure and composition) induced by DSS lead to activation of the islet-reactive T cells and to T1D. We analyzed the activation state and cytokine-secretion phenotype of the diabetogenic T cell clone within the gut mucosa, pancreatic lymph nodes and intra-islet lymphocytes of BDC2.5XNOD mice with or without colitis and measured diabetes incidence (by weekly measurements of glycemia) and microbiota composition (by 16S rRNA analysis). To assess how the gut microbiota activates the diabetogenic T cells, we performed *in vitro* experiments in which islet-reactive BDC2.5 T cells were stimulated with total bacterial isolated from intestine of DSS-colitis or healthy mice.

Results: Our data demonstrate that loss of gut barrier integrity and modifications of the mucus structure and composition associated with chronic colitis are directly capable to activate islet-reactive T cells within the gut mucosa and trigger T1D. The intestinal activation of islet-reactive T cells requires the presence of gut microbiota and is abolished when mice are depleted of endogenous commensal microbiota by antibiotic treatment. Furthermore, our data show that the murine commensal microbiota contains molecules that mimic self-antigens and directly trigger TCR-mediated activation of islet-reactive T cells.

Conclusions / Implications for practice: Our data show that loss of the intestinal barrier continuity is directly responsible for activation of isletspecific T cells by commensal gut microbiota and provide a strong rationale to design innovative therapeutic interventions aimed at restoring gut barrier integrity to prevent islet-autoimmunity in genetically at risk individuals.

References

- Badami et al. *Defective differentiation of regulatory FoxP3+ T cells by small-intestinal dendritic cells in patients with type 1 diabetes*. Diabetes (2011) 60:2120-2124
- Bosi et al. *Increased intestinal permeability precedes clinical onset of type 1 diabetes*. Diabetologia (2006) 49:2824-2827.
- Knip et al. *The role of the intestinal microbiota in type 1 diabetes mellitus*. Nature Reviews Endocrinology (2016)12:154-167.
- Lee et al. *Gut barrier disruption by an enteric bacterial pathogen accelerates insulitis in NOD mice*. Diabetologia (2010) 53:741-748.
- Sorini et al. *Shaping the (auto)immune response in the gut: the role of intestinal immune regulation in the prevention of type 1 diabetes.* American Journal of Clinical and Experimental Immunology (2013) 2:156-171.
- Tai et al. *Microbial antigen mimics activate diabetogenic CD8 T cells in NOD mice*. The Journal of Experimental Medicine (2016) 213:2129-2146.
- Vaarala et al. *Is the origin of type 1 diabetes in the gut?* Immuno Cell Bio (2012) 90:271.276