

Harnessing of Tregs for treatment of recent-onset diabetes

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Regulatory T cells are of high therapeutic interest to treat or prevent autoimmunity, because they can act locally as bystander suppressors of heterologous immune responses when they are induced with autoantigens. This occurs *in vivo* in most cases in a cytokine dependent manner (i.e. IL-10, IL-4 and/or TGF- β) and can result in long lasting tolerance. In type 1 diabetes models, it is possible to induce autoreactive adaptive Tregs therapeutically with islet antigens such as insulin and GAD, but such immunizations are only effective early during the pre-diabetic phase and can lead to deleterious acceleration of the autoimmune response when administered later. In order to facilitate translation to the clinic by increasing Treg efficacy, we administered non-Fc binding CD3-specific monoclonal antibody in combination with various islet antigens or antigen-derived peptides using various routes of delivery in two mouse models of type 1 diabetes. Intranasal delivery of a pro-insulin-derived peptide had the strongest synergy with the CD3-specific monoclonal antibody and was shown to reverse recent-onset diabetes long-term in the NOD and RIP-LCMV mouse models. This was associated with increased numbers of peptide-specific Tregs, which were shown to produce regulatory cytokines *in vitro* and exerted bystander suppression *in vivo* on heterologous autoreactive CD8 T-cell responses in the pancreas and pancreatic lymph node. Thus, the combination of a systemic immune modulator and the induction of autoantigen-specific Tregs has the dual advantage of reversing recent-onset type 1 diabetes and of reducing the risk of side-effects, because the antigen-induced Tregs did not suppress systemic immune responses. This approach should therefore be a useful clinical strategy.

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