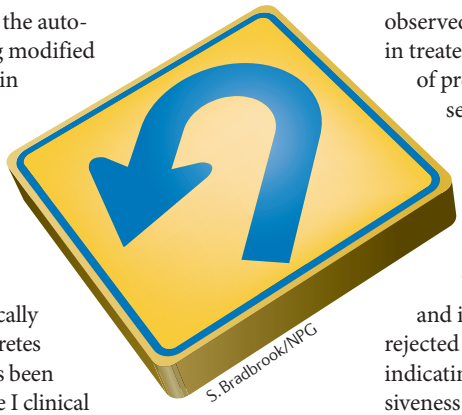
TOLERANCE

Reversing diabetes in mice

Several therapeutic approaches have been investigated for the treatment of type 1 diabetes. However, these interventions have had minimal success or are associated with nonspecific immune modulation, as in the case of high-dose CD3-specific antibodies. Takiishi *et al.* now show that the induction of tolerance to the autoantigen pro-insulin using modified *Lactococcus lactis* results in the stable reversion of diabetes in non-obese diabetic (NOD) mice.



S. Bradbrook/NPG

L. lactis is a common, non-colonizing, non-invasive bacterium that is used extensively in the food industry. Genetically modified *L. lactis* that secretes interleukin-10 (IL-10) has been used previously in a Phase I clinical trial for the treatment of Crohn's disease. In the current study, the authors modified *L. lactis* to secrete the human autoantigen pro-insulin and human IL-10. NOD mice that had recently developed diabetes were given the modified bacteria orally 5 days per week for 6 weeks in conjunction with an initial short treatment course (5 days) of systemic low-dose CD3-specific antibodies.

The modified *L. lactis* plus antibody treatment restored normal glycaemia after disease onset in 59% of treated NOD mice, with no adverse effects. Normal glycaemia remained stable in these mice for at least 14 weeks after treatment commenced and no disease recurrence was observed. In addition, insulin levels in treated mice were similar to those of pre-diabetes NOD mice, and severe insulitis resolved in most of the treated mice.

Splenic T cells from the 'cured' NOD mice proliferated normally in response to PMA (phorbol 12-myristate 13-acetate) and ionomycin, and these mice rejected allogeneic skin transplants, indicating that general T cell responsiveness remained intact following the modified *L. lactis* plus antibody treatment.

Cured NOD mice were shown to have increased frequencies of $CD4^+CD25^+FOXP3^+$ regulatory T (T_{Reg}) cells in the pancreatic lymph nodes, with increased expression of the co-inhibitory molecule CTLA4, compared with mice treated with CD3-specific antibodies alone. *In vitro,* these T_{Reg} cells suppressed the proliferation of polyclonally stimulated $CD4^+CD25^-$ effector T cells, indicating that the T_{Reg} cells are functional. Indeed, in a T cell-transfer model of diabetes, the co-transfer of T_{Reg} cells from cured mice significantly delayed the onset of disease. Furthermore, accumulation and *in situ* proliferation of T_{Reg} cells was observed around the pancreatic islets of cured NOD mice.

Finally, T_{Reg} cells from cured mice suppressed the activation of pro-insulin-specific effector T cells but not ovalbumin-specific effector T cells, as evidenced by reduced CD44 expression and interferon-γ production by the effector T cells. This indicates that the modified *L. lactis* plus antibody treatment induced T_{Reg} cells that suppressed immune responses in an autoantigen-specific manner.

So, modified *L. lactis* plus CD3-specific antibodies may be a possible treatment strategy for the induction of antigen-specific tolerance in type 1 diabetes.

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ORIGINAL RESEARCH PAPER Takiishi, T. *et al.* Reversal of autoimmune diabetes by restoration of antigen-specific tolerance using genetically modified *Lactococcus lactis* in mice. *J. Clin. Invest.* 9 Apr 2012 (doi:10.1172/JCI60530)

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