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A future vaccine for diabetes?

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Researchers have developed a plasmid DNA (pDNA) vaccine for type 1 diabetes that has successfully prevented the onset of diabetes in a mouse model for over one year[1]. Roland Tisch and colleagues at the University of North Carolina (Chapel Hill, NC, USA) suggest these findings could have important implications, both for the prevention of type 1 diabetes in susceptible individuals, and for improving the chances of successful islet transplantation.

People who suffer from type 1 diabetes still depend on daily injections of insulin to maintain adequate blood glucose levels. They often suffer from severe complications including heart and kidney failure, blindness and arteriosclerosis. Therapies that reliably restore endogenous insulin production or prevent type 1 diabetes have been a goal of medical research for many years, but success has been limited.

Type 1 diabetes is an autoimmune disease characterized by the destruction of the insulin-producing β cells in the islets of Langerhans. The disease involves the progressive infiltration of lymphocytes and monocytes into the islets. The primary mediators of β cell destruction are $CD4^+$ and $CD8^+$ T lymphocytes[2]. $CD4^+$ cells can be subdivided into two classes, Th1 and Th2, depending on the cytokines they secrete and their role in the immune response. Th1 cells, which secrete interferon-γ (IFN-γ) and interleukin-2 (IL-2), are normally involved in cell-mediated immune events; Th2 cells, which secrete IL-4, are typically associated with antibody response. In healthy individuals, there is cross-regulation of these cell types through secretion of cytokines. In type 1 diabetes, this functional balance is skewed towards the production of Th1 cells, which can recognize certain β cell autoantigens, including glutamic acid decarboxylase 65 (GAD65), and destroy the cells.

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Figure 1. Non-obese diabetic (NOD) mice are protected from diabetes following immunization with plasma DNAs encoding GAD65–IgGFc. **(a)** Female NOD mice at 4 weeks of age received three intramuscular injections of JwHEL + JwIL-4, JwGAD65 and JwGAD65 + JwIL-4 over 21 days or were left untreated. **(b)** Female NOD mice at 12 weeks of age received four intramuscular injections of JwHEL + IL-4, JwGAD65 and JwGAD65 + IL-4 over 28 days or were left untreated. Treatment groups were monitored for the development of diabetes once a week. Reproduced, with permission, from Ref. 1.

Induction of Th2 differentiation

Many groups have attempted to modulate the diabetogenic autoimmune response by inducing the differentiation of Th2 cells. Tisch and colleagues have previously induced Th2 cell differentiation in a mouse model by inoculation with GAD65 peptides. However, this approach requires multiple injections of large quantities of peptide, and is therefore unlikely to be feasible in a clinical setting.

Tisch and colleagues then decided to test the effect of DNA 'vaccines' constructed from the Jw4303 vector on non-obese diabetic (NOD) mice[2], at 4 and 12 weeks of age (Fig. 1)[1]. This vector contains a transcriptional unit of a cytomegalovirus promoter/enhancer element and polyadenylation and transcriptional termination sequences derived from the bovine growth hormone gene. Normally, 80% of female NOD mice spontaneously develop type 1 diabetes in their first 30 weeks of life. Separate groups of mice were injected with GAD65–IgGFc fusion proteins, with GAD65-IgG and IL-4, or with hen egg lysozyme–IgGFc and IL-4. Of the four-week-old mice injected with GAD65-IgG and IL-4, 29% developed diabetes before 52 weeks of age, compared with 75% of untreated mice. There was no significant change in the percentage of mice developing diabetes in either the mice injected with lysozyme and IL-4 constructs or those injected with GAD65–IgG alone. Importantly, similar results were obtained in mice injected at 12 weeks, when β cell autoimmunity is already established.

'All we did was inject the mice with solutions of pDNA in saline solution. Initially, we were sceptical that such a simple protocol could work,' says Tisch. 'It did not matter whether we used two separate pDNAs or one single plasmid

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incorporating both genes.' However, none of the vaccines could suppress the development of diabetes in mice homozygous for an inactive IL-4 gene. This indicated that both endogenous and pDNA-encoded IL-4 are necessary for protection to be established.

Anne Cooke (Pathology/Immunology Division, Cambridge University, Cambridge, UK) is not convinced of the novelty of these results. 'This is an interesting development, bringing together two approaches,' she says. 'However, Tisch is not the first to prevent diabetogenesis using pDNA vaccination. Terry Delovitch and coworkers (Autoimmunity/Diabetes Group, The John P. Robarts Research Institute, London, Ontario, Canada) have recently shown that diabetes onset in NOD mice can be prevented with IL-4 pDNA alone, using an adenovirus vector[3]. As Tisch found IL-4 administered with hen egg lysozyme to be ineffective, this paper raises more questions than it answers.'

Conclusions

Tisch observed that the level of islet infiltration observed in the islets of protected mice at 52 weeks was no greater than that in untreated 12-week-old NOD mice. 'It is possible that pDNA vaccines will be able to prevent disease onset in individuals at high risk of developing type 1 diabetes,' he says. Continued efforts to determine the genes that promote diabetes susceptibility will permit accurate identification of those individuals at greatest risk.

Vaccination is not the only new treatment for preventing diabetogenesis that is under investigation. Immunosuppressive drugs have already been shown to delay diabetes onset. However, cyclosporin and similar drugs have limiting long-term side effects, including increased susceptibility to infectious diseases and cancer. Now, Isotechnika (Edmonton, Canada) has developed a drug that is more potent and less toxic than cyclosporin in the NOD mouse model. They hope that this compound, known as ISA(TX)247, will enter Phase II clinical trials later in 2001.

Islet transplantation in type 1 diabetes has recently been shown to be a feasible approach, enabling diabetic patients to become independent of insulin injections[4]. Nevertheless, these individuals need to receive immunosuppressive drugs continuously to protect the islet transplants. Tisch believes that pDNA vaccination might reduce the need for these drugs: 'Vaccination with GAD65 and IL-4 pDNAs should modulate the immune response and prevent the rejection of the transplanted β cells.' His group is now testing the efficacy of this vaccine in protecting islet transplants in the mouse model. They hope that clinical trials of a pDNA vaccine will start within three or four years.

References

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