IMMUNE REGULATION

Overactive cytokines

Interleukin-27 (IL-27) signalling through its receptor (WSX1) has been shown previously to promote T helper 1 (T_H1)-cell differentiation of naive $CD4^+$ T cells. Surprisingly, two reports published in *Immunity* now indicate that WSX1 is also required for the suppression of cytokine responses.

T_H1-type cytokines are crucial for resistance to intracellular pathogens. To determine the contribution of the IL-27–Wsx1 pathway to immunity, two groups have independently analysed Wsx1-deficient mice infected with intracellular pathogens, *Trypanosoma cruzi* and *Toxoplasma gondii*, respectively.

Hamano *et al.* observed that Wsx1-deficient mice were more susceptible to infection with *T. cruzi* than wild-type animals, showing increased mortality, prolonged parasitaemia and severe liver damage. Unexpectedly, although the percentage of splenocytes producing interferon-γ (IFN-γ) was no different in infected Wsx1-deficient and wild-type mice, the T_H2-type cytokines IL-4 and IL-13 were highly overexpressed. By contrast, when liver mononuclear cells isolated from infected Wsx1-deficient mice were exposed to *T. cruzi* antigens *in vitro*, they produced markedly more IFN-γ, IL-6 and tumour-necrosis factor (TNF) than wild-type cells. IFN-γ was largely produced by $CD4^+$ T cells and natural killer cells, whereas IL-6 and TNF were produced by both macrophages and T cells.

By treating Wsx1-deficient mice with either IL-4- or IFN-γ-specific antibodies, skewing to the T_H2 phenotype was shown to be responsible for the sustained parasitaemia, but not liver damage or increased mortality, both of which were dependent on IFN-γ. These results indicate that although regulation of the parasite burden and control of the immune response to prevent liver damage are independent processes, they both require Wsx1-mediated suppression of cytokine production.

In an independent study, Villarino *et al.* showed that Wsx1-deficient mice were more susceptible than wild-type animals to infection with *T. gondii*. Susceptibility was not a result of inefficient parasite clearance, but was due to $CD4^+$ T-cell-mediated immune pathology. Although splenocytes isolated from infected Wsx1-deficient and wild-type animals produced similar levels of IFN-γ after *in vitro* stimulation at early time points post infection, at later times, Wsx1-deficient splenocytes produced markedly increased levels of the cytokine. This was a result of an increase in both the number of IFN-γ-producing $CD4^+$ T cells and the amount of cytokine they produced.

Interestingly, in *in vitro* culture systems, Wsx1 was required for optimal production of IFN-γ by naive $CD4^+$ T cells stimulated under non-polarizing conditions, but under T_H1-cell-polarizing conditions, naive $CD4^+$ T cells from Wsx1-deficient mice produced greater amounts of

AUTOIMMUNITY

Splenocytes caught moonlighting

A long-term cure for autoimmune type 1 diabetes requires both the prevention of further immune attack of the pancreatic islets and replacement of the destroyed islets. New research published in *Science* indicates that both of these tasks can be carried out by donor splenocytes.

Denise Faustman and colleagues first reported this in 2001 in the *Journal of Clinical Investigation*. They used donor splenocytes matched for MHC class I to restore peripheral T-cell tolerance to pancreatic islets in non-obese diabetic (NOD) mice, and were then planning to carry out islet transplants to restore islet function. However, they found that many of the mice did not require islet transplants and began to produce insulin after splenocyte infusion. Now, these authors have revisited these findings to determine the source of the new pancreatic islets.

The authors compared the ability of live versus irradiated, male donor splenocytes to restore normoglycaemia in severely diabetic female mice. A temporary implant of syngeneic islets under the kidney capsule was used to maintain normoglycaemia during the treatment. When the islet implant was removed after 40 days, none of the animals that received irradiated splenocytes remained normoglycaemic, compared with two-thirds of the mice that received live splenocytes. By contrast, when the islet graft was maintained for 120 days, almost all of the mice that received irradiated splenocytes also remained normoglycaemic. Therefore, both live and irradiated splenocytes can result in islet replacement, but irradiated splenocytes require longer.

Using fluorescence *in situ* hybridization (FISH) analysis to detect the Y chromosome of the male donor splenocytes, Faustman and colleagues showed that a significant proportion of the new islets in mice treated with live cells were of donor origin. Fusion between host and donor cells is not thought to have occurred as the regenerated islet cells were of normal size, and did not contain enlarged nuclei or multiple nucleoli. Also, there were few, if any, islet cells with an XXY or XXXY genotype. Therefore, live splenocytes can not only re-educate peripheral T cells, but also reconstitute functional islets, and further studies attributed this property to a subset of $CD45^-$ non-lymphoid cells.

However, in NOD mice treated with irradiated splenocytes, none of the regenerating islet cells contained a Y chromosome, indicating that these cells are of host origin. Adult NOD mice must also contain endogenous precursor cells that can contribute to islet regeneration over a longer time scale, once the autoimmunity has been corrected by donor splenocytes.

This demonstration of adult precursor cells in both host and donor could have important implications for future treatments for type 1 diabetes, while avoiding the ethical and technical difficulties associated with the use of embryonic stem cells or islet transplants.

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References and links

ORIGINAL RESEARCH PAPER Kodama, S. *et al.* Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science* **302**, 1223–1227 (2003)

FURTHER READING Ryu, S. *et al.* Reversal of established autoimmune diabetes by restoration of endogenous β-cell function. *J. Clin. Invest.* **108**, 63–72 (2001)