ANTIBODY RESPONSES

Getting the balance right

Antibodies are generated by B cells in a process that involves V(D)J recombination followed by somatic hypermutation and selection of high-affinity antibodies. But if there is an alternative, biologically plausible mechanism for speedier production of higher-affinity antibodies, then why is this mechanism not used by the immune system? This question has been addressed in a recent study by Jun Sun and colleagues.

The authors used a modelling system that captures important features of the immune response to vaccination and disease, as well as features of protein molecular evolution. Using this system, they replicated the typical immune-system dynamics of combinatorial joining of subdomains (that is, V(D)J recombination) followed by rounds of point mutation (PM). They also modelled an alternative system that included V(D)J recombination and PM, as well as gene-segment swapping (referred to as GSS+PM). They found that GSS+PM yields antibodies of higher affinity than PM alone and has faster dynamics.

The authors then compared the specificity of the antibodies generated by each strategy. They found that antibodies generated by GSS+PM recognized more antigens and with higher affinity than those generated by PM alone. That is, the antibodies generated by GSS+PM have greater crossreactivity than those generated by PM alone. Antibodies generated by GSS+PM could therefore crossreact with self-molecules, and crossreactivity has been proposed as one mechanism by which autoimmune responses might arise. In fact, the authors found that a typical antibody generated by GSS+PM would be 1,000 times more promiscuous than a typical antibody generated by PM alone (which usually recognizes only its intended target).

These results could explain why the immune system does not use GSS+PM, even though such antibodies would be generated faster and would have higher affinity than those generated by PM alone — the immune system must balance responses to non-self, invading pathogens while avoiding antiself, autoimmune responses.

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References and links

ORIGINAL RESEARCH PAPER Sun, J., Earl, D. J. & Deem, M. W. Glassy dynamics in the adaptive immune response prevents autoimmune disease. *Phys. Rev. Lett.* **95**, 148104 (2005)

TRANSPLANTATION

NKT cells and neutrophils collaborate in graft rejection

Although there has been much excitement surrounding the transplantation of insulin-producing islets for the treatment of patients with diabetes, many patients fail to achieve insulin independence with a single transplant, owing to rapid rejection of the donor islets. To explore the mechanism of islet rejection, Yasunami *et al.* studied a mouse model of islet transplantation, and they report that natural killer T (NKT) cells might be behind such early graft loss.

NKT cells have a key role in immediate immune responses and, mainly through their ability to produce large amounts of interferon-γ (IFN-γ), function as a bridge between innate and adaptive immune responses. Because IFN-γ has been shown to be an important factor in the destruction of islet β cells, the authors proposed that NKT cells might be involved in early islet-graft failure.

Diabetes, as measured by hyperglycaemia, was induced in C57BL/6 mice by intravenous injection of streptozotocin. A transplant of 400 islets harvested from 2 syngeneic mice and injected into the liver of the diabetic mice was required to restore normal blood-glucose levels; mice that received 200 islets remained hyperglycaemic and had few intact islets. But if the diabetic mice lacked NKT cells, a transplant of only 100 islets was sufficient to restore normal blood-glucose levels, indicating that NKT cells might be responsible for the loss of the transplanted islets.

Next, tetramers of CD1d complexed with α-galactosylceramide (α-GalCer) were used to analyse NKT-cell numbers in mice that showed islet-graft destruction. Although NKT-cell numbers seemed to decrease immediately after transplantation (consistent with activation-induced downregulation of their antigen receptors), NKT-cell numbers increased markedly 24 hours after transplantation. As a consequence of NKT-cell activation, neutrophils infiltrated the transplanted islets and were induced to produce high levels of IFN-γ, indicating that they might mediate destruction of the islets.

On the basis of the observation that a single dose of α-GalCer induces NKT-cell activation but repeated stimulation with α-GalCer inhibits IFN-γ production by NKT cells, the authors tested whether graft loss could be prevented by repeated injection of α-GalCer. Diabetic mice that received 400 islets and were treated with a single injection of α-GalCer remained hyperglycaemic and had increased IFN-γ production by neutrophils and NKT cells. By contrast, when diabetic mice were pretreated three times with α-GalCer, a transplant of only 200 islets was sufficient to restore normal blood-glucose levels and reduce IFN-γ production.

So, *in vivo* modulation of NKT-cell activation to prevent this collaboration between NKT cells and neutrophils might be a novel approach for improving the efficiency of islet transplantation.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Yasunami, Y. *et al.* Vα14 NK T cell-triggered IFN-γ production by Gr-1$^+$CD11b$^+$ cells mediates early graft loss of syngeneic transplanted islets. *J. Exp. Med.* **202**, 913–918 (2005)