IMMUNOLOGY

Tolerance by exhaustion

Harald von Boehmer

VIRUSES use various strategies to escape protective immune responses and persist in their host. On page 758 of this issue[1], Moskophidis *et al.* show that such persistence can be achieved by brute force: large numbers of viruses produce antigenic loads that force the immune system to give in after a brief and intense struggle, ending with the exhaustion and deletion of cytotoxic T-lymphocytes.

Viruses try to remain in their hosts without killing them too quickly. Viruses such as the lymphocytic choriomeningitis virus (LCMV) — which is the one Moskophidis *et al.* looked at and which is noncytopathic (that is, does not disrupt or kill cells) — nevertheless induce protective immunity which interferes with the goal: the virus can be eliminated and the associated immunopathology, such as destruction of nervous tissue, may even cause the death of the host. This phenomenon can be observed in animal model systems, and is very infrequently seen in humans exposed to high virus doses. The virus may escape for some time, for instance by infecting cells in the skin that lack cofactors (such as the B7 molecule) required for T-cell stimulation, or through mutation of its immunogenic epitopes. But eventually the immune system may still catch up with it.

It would clearly be most advantageous for the virus if it could induce specific immunological tolerance; the virus would not suffer and the host could still combat other threatening microorganisms. This goal is achieved by LCMV when it infects mice with an immature immune system during the neonatal period. The viral antigens will delete immature T cells with complementary receptors[2], much as self-antigens delete immature self-specific T cells. As a result the mice become virus carriers for the rest of their life. Mature T cells are not so easily deleted, but Moskophidis *et al.* show that this can also be achieved.

The authors used high doses of virus, a somewhat artificial approach, but they suggest that a 'proper' virus isolate in a host with the 'proper' major histocompatibility complex (MHC) and non-MHC background will cause specific tolerance even when inoculated in low doses. What is 'proper' in this context remains to be seen. The data presented in the paper show that the 'complete' induction of cytotoxic T cells results initially in a vigorous response followed by their exhaustion and deletion. This can be nicely documented because, as well as normal mice, the authors employed mice with a transgenic, virus-specific T-cell receptor which allowed them to determine the fate of virus-specific cells.

The induction of specific immunological tolerance in a mature immune system does not only represent an ideal case for viruses, but is also the goal of transplantation surgeons hoping to achieve acceptance of mismatched grafts without having to suppress the entire immune system. It is hardly surprising, therefore, that the results obtained with viruses do not find immunologists totally unprepared. High zone tolerance is an established phenomenon[3], and relatively high doses of cell-surface antigens[4], including transplantation antigens[5], can induce exhaustion and deletion (and thereby specific tolerance) in a mature immune system of normal mice or mice with transgenic T-cell receptors.

Further experiments should aim at elucidating the molecular mechanisms of exhaustion and deletion of mature T cells. This will help our understanding of whether (or how) viruses establish specific immunological tolerance in adult organisms in real life. It is possible, for instance, that the disappearance of specific cytotoxic T cells during the late stages of AIDS may also be due to exhaustion and deletion. An understanding of this type of tolerance should likewise help immunologists to improve their protocols for inducing tolerance to transplantation antigens. □

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COMETS

Great balls of mire

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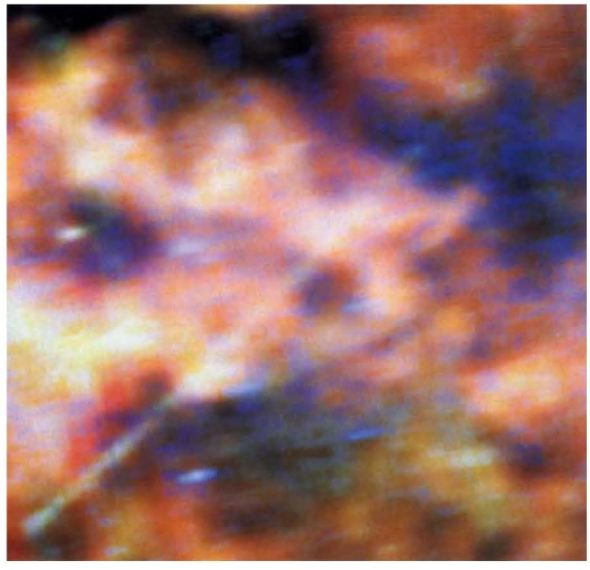
THE Giotto mission continues to add to its accomplishments since its encounter with comet Halley in 1986. In 1992 the spacecraft flew within 200 km of the nucleus of comet Grigg–Skjellerup and sampled its dust environment. On page 732 of this issue[1], McDonnell and colleagues report that the mass distribution of the dust is dominated by the largest particles, indicating a greater mass loss rate and dust-to-gas mass ratio than comets were previously thought to have. These results continue to undermine the ice-dominated 'dirty-snowball' model of comets in favour of the 'frozen-mudball' model, dominated by non-volatile, refractory materials.



A comet and its dust trail, shown against a background of interstellar dust clouds in this image constructed from scans made by the Infrared Astronomical Satellite.

Dust-to-gas mass ratios corresponding to the dirty-snowball model range between 0.1 and 1. If we were to compress comet nucleus material so that refractories had a density of 3 g cm^{-3} and volatiles had a density of 1 g cm^{-3}, this would give us a nucleus in which 3–33 per cent of the volume consisted of refractory material. Support for this picture comes largely from ground-based observations of dust and at visual wavelengths, sensitive to particles within a factor of ten or so of 1 μm in size. It seems, however, that such observations underestimate the mass fluence of dust from comets, most of which is in the form of larger particles which are difficult to detect at these wavelengths. So much was concluded when Giotto flew by comet Halley[2], and was strikingly illustrated by