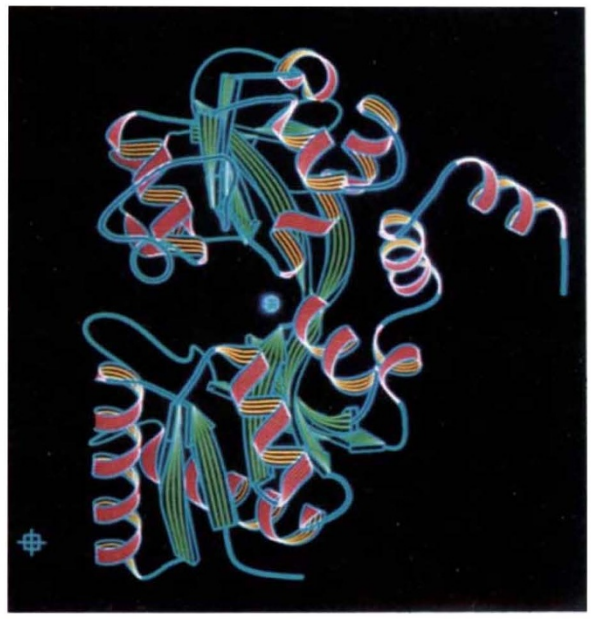
The jaws of lactoferrin



TRAPS come in all shapes and sizes, but most work on the 'lure and snare' principle. The iron-binding protein lactoferrin, one of whose two jaw-like 'iron traps' is depicted in the colour figure, is no exception. On page 784 of this issue, Edward Baker and colleagues of the Massey University in New Zealand show that in the absence of any bound metal one of lactoferrin's two traps lies wide open, with its molecular jaws poised to close firmly around an incoming iron cation.

Lactoferrin, like all members of the transferrin family of proteins, plays an essential part in regulating levels of vagrant, free iron inside animals. Earlier studies of the molecular structure of lactoferrin bound to iron showed that it consists of two similar, adjoining protein lobes each of which encloses a single trapped iron cation. But whether these lobes are permanently closed or whether their closure is triggered by iron binding was left unanswered.

By determining the crystal structure of apolactoferrin, Baker and colleagues now show that in the absence of trapped iron the hinged protein domains of one of the two lobes swing open, whereas the second lobe remains firmly closed. Their findings imply that there is only a small energy difference between the open and closed states, and that minor perturbations of lactoferrin's structure such as those resulting from crystal packing forces or the binding of iron are sufficient to trigger the mechanical closure of the protein's molecular jaws. Lactoferrin, it seems, can justifiably be likened to a Venus fly trap.

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a formerly influential concept, a clarification of the collective wisdom and a lightening of the literature.

Although many cellular and molecular phenomena have been associated with β2-m and β2-m-associated class I molecules, there are only two substantiated functions and they are both to do with immunity. One is the presentation of antigens by classical class I MHC molecules (H-2K, D and L in mice), to T lymphocytes bearing αβ antigen receptors and the CD8 coreceptor; the other is the transepithelial transport in neonates of IgG from mothers' milk by the β2-m-associated Fc receptor. In the β2-m negative mouse both functions have disappeared. IgG does not bind to the epithelial brush border membranes of neonatal intestines. The peripheral lymphoid organs have less than 1 per cent of the normal number of $CD8^+$ αβ-receptor-bearing T cells, and cytotoxic functions that are normally provided by these cells cannot be detected. How does one reconcile such damage to the immune system with the paradoxical vigour of the mice?

Specific immunity is found only in organisms having many specialized tissues and cell types. In the past, when some level of organismal complexity was attained it clearly became advantageous to evolve cells and molecules that were increasingly committed to protection and defence. An analogous progression can be seen in the evolution of military defence as human societies have become increasingly complex and individuals more specialized and interdependent (see box, on previous page).

Two key features distinguish components of the specific immune system from those of cells and tissues that have more constructive roles. First, they are used sporadically, only when something goes wrong. Second, the opponents of the immune system — bacteria, viruses, parasites — are unpredictable and rapidly changing, so that past experience does not necessarily prepare the immune system for the future. Thus the selective forces acting upon specific immune functions are constantly varying and this leads to products that are often poorly adapted to a particular set of circumstances. Hence the continuing loss of human life from infectious diseases, the incapacitation resulting from the all too common cold and our frightening vulnerability to HIV.

The fitness in the face of immunodeficiency of Zijlstra *et al.*'s mice confirms the view that the immune system has an essentially defensive role — that it is only needed when things go wrong. Naturally, the authors have been careful to protect their first homozygotes from attack by microorganisms; the animals are kept in a pathogen-free environment, and are not required to forage. But as numbers of mice accumulate, Jaenisch and colleagues will be able to change their tactics and challenge the immune system of their β2-m negative mice. Cytotoxic $CD8^+$ cells kill virally infected cells and are involved in limiting virus spread and thereby ending infections. In contrast it is soluble antibody that often prevents initiation of an infection. One might therefore expect that β2-m negative mice will show poor recovery from viral infections, but on specific immunization their B cells and $CD4^+$ helper T cells will provide normal protection from viral infection[11].

Using transgene technology, immunologists have been able to introduce exogenous genes into mice and see how they perturb the immune system; with targeted gene disruption they can now take out the endogenous genes. Combination of these two techniques will prove geometrically powerful and lead to an even more detailed understanding of the workings of the immune system. For example the function(s) of β2-m can now be finely dissected by making the β2-m negative mice transgenic for β2-m genes containing engineered mutations.

Studies with transgenic mice have demonstrated positive thymic selection of αβ-receptor-bearing T cells by class I and class II MHC molecules[12]. The β2-m negative mice provide a particularly clear illustration of this previously controversial mechanism: without class I MHC molecules there is no selection and consequent migration into the peripheral lymphoid tissues of $CD8^+$ T cells with αβ receptors. In contrast there is no effect on the numbers of peripheral γδ-receptor-bearing T cells, including those expressing CD8. T cells with γδ receptors are much less frequent than their companions with

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