page 795 of this issue[1], and Borrego *et al.*, in a forthcoming issue of the *Journal of Experimental Medicine*[2], reveal a highly specific function in immune recognition for signal sequences of class I molecules of the major histocompatibility complex (MHC — a family of molecules well known to immunologists).

This finding opens a completely new perspective on the evolution and functional potential of signal sequences, which were previously thought to be rather inert.

Self–nonself discrimination is a central property of the immune system, and is of obvious importance in preventing destruction of the body's own tissues by killer lymphocytes such as cytotoxic T cells and natural killer (NK) cells. NK cells, which are easily activated upon binding to a target cell, are prevented from killing healthy cells of the host by inhibitory receptors. These inhibitory receptors are specific for MHC class I molecules, which are encoded by a family of genes that vary widely between individuals. Whereas MHC class I proteins turn off NK cells, they activate cytotoxic T cells, a more educated class of lymphocytes that achieve self tolerance by several different mechanisms. T cells recognize peptide fragments that are bound to self MHC class I proteins. Such peptides are derived from foreign proteins or from self proteins that failed to induce T-cell tolerance. Virus-infected cells and tumour cells that evade T-cell responses by interfering with MHC class I expression become targets for NK-mediated lysis.

The new findings[1,2] provide a surprising link between NK cell tolerance to self and protein translocation mediated by signal sequences, and they explain the following, puzzling feature of NK inhibitory receptors. One type of inhibitory receptor used by human NK cells is a heterodimer of the polypeptides CD94 and NKG2 (ref. 3). Both are members of the calcium-dependent lectin superfamily. The CD94/NKG2 receptor seemed to react with products of different alleles of the HLA-A, -B and -C class I loci, as well as the invariant, nonclassical class I molecule HLA-G. This reactivity was perplexing because several related allelic forms of HLA-A and -B were not recognized.

The CD94/NKG2 receptor now turns out to be specific for HLA-E, a nonclassical class I molecule. Expression of HLA-E at the cell surface depends on the binding of peptides derived from signal sequences[4] of precisely those HLA class I molecules whose expression correlates with recognition by CD94/NKG2 (Fig. 1). The signal sequence of HLA-E itself, as well as those from several HLA-A and -B gene products, produces peptides that do not bind to HLA-E. Although specific for HLA-E, the CD94/NKG2 receptor is evidently designed to gauge the overall level of HLA class I expression on cells, which is one indicator of their health status.

The evidence for this mode of recognition through HLA-E is compelling. Braud *et al.*[1] show, first, that a soluble tetrameric form of HLA-E binds to CD94/NKG2 receptors on transfected cells. Second, they find that grafting an HLA-E-binding signal sequence onto an HLA-B molecule that lacks such a sequence permits surface expression of HLA-E and inhibition of NK cells expressing CD94/NKG2. Finally, Borrego and colleagues' results[2] indicate that recruitment of HLA-E at the surface of a transfected mouse cell by the addition of synthetic peptide ligands provides protection from lysis by NK cells expressing CD94/NKG2.

An analogy can be made in the mouse, where the nonclassical class I protein Qa-1 predominantly binds peptides from class-I-derived signal sequences[5] that are very similar to those bound to HLA-E. The MHC class I proteins having suitable signal sequences predict that a receptor for Qa-1 analogous to CD94/NKG2 would have an apparent specificity for products of H-2D alleles. The approach described by Braud *et al.* may prove rewarding in the search for ligands of Qa-1 and other nonclassical class I proteins.

As well as CD94/NKG2, human NK cells also express a very different type of inhibitory receptor, named the killer cell immunoglobulin-like receptor (KIR). Single NK cells often co-express inhibitory CD94/NKG2 and KIR, suggesting that there is redundancy among inhibitory receptors[3]. But it now seems that the two receptor systems operate in distinct ways (Fig. 1). Different members of the KIR family mediate specific recognition of distinct groups of HLA-B and -C gene products. Therefore, NK cells that rely on KIR for inhibition can detect the loss of a specific MHC class I gene product, as occurs in some tumours. Many of the peptides among the vast array of those bound to HLA-B and -C proteins confer protection from lysis by NK cells that express KIR. The great variability in HLA class I genes between people suggests the need for a diverse repertoire of receptors that inhibit NK cells. Indeed, the predominant use of CD94/NKG2 for inhibition of NK cells in one person, but of KIR in another, was observed in two individuals having different sets of HLA class I ligands for these receptors[6].

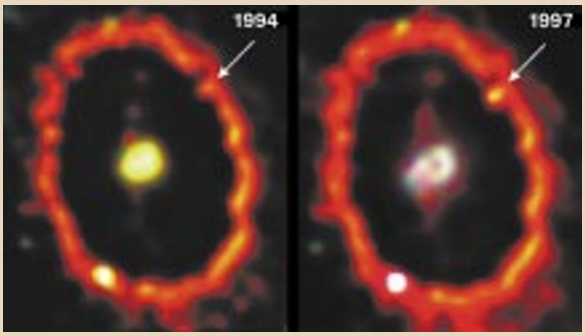
Several issues are raised by this unexpected involvement of signal sequences in NK cell tolerance to self. Every immune defence mechanism presents a challenge to pathogens. Certain viruses use specific strategies to interfere with MHC class I function or expression. An effective evasion tactic against both T and NK cells would be to selectively block peptide presentation by classical class I molecules, and to allow HLA-E to carry signal sequences to the surface. The selectivity of HLA-E for HLA class-I-derived signal sequences is not controlled by other properties of HLA class I molecules, because Braud *et al.* found that a class I signal sequence tagged onto an unrelated protein

Supernova 1987A

Shockwave hits the ring

About 170,000 years ago, a star exploded in the Large Magellanic Cloud, a satellite galaxy of the Milky Way. When light and neutrinos from this explosion reached the Earth in 1987, SN1987A became the brightest supernova seen since 1604 — and the best studied ever.

Eleven years later, a second light show is beginning. The blast wave from the original explosion has finally reached a dense and mysterious ring of gas surrounding the star. Its first contact can be seen in these Hubble Telescope images, which show a small patch of the ring suddenly brightening.



What produced this ring? It may have been thrown off by a merger between the main star and a binary companion, some 20,000 years before the explosion.

That idea is appealing because it could also explain why the progenitor star was a blue supergiant, instead of the red supergiant that usually precedes this type of supernova. But the ring could instead be the waist of a more extended shell of gas, emitted as a dense stellar wind in a passing stage of the precursor star's evolution.

Within a year or two we may know better. As the shockwave passes through at 18,000 km s^{-1}, it will heat the gas. The ring will then shine brightly, allowing highly detailed spectroscopy and imaging, and illuminating gas elsewhere in the system.

It is a familiar story — often, the best way to learn about an object is to watch what happens when something hits it.

Stephen Battersby