by A_0; because the electron density is $(3A_0)^{-1}$, it follows that the magnitude of the charge of these elementary excitations of the system is $e/3$.

The report by Goldman and Su (*2*) describes an experiment in which an "antidot" is artificially created in the interior of an incompressible fluid of precisely this type. The antidot is created by forming a maximum in the electrostatic potential seen by the electrons. In the experiment, the antidot is surrounded by an incompressible fluid with density $(3A_0)^{-1}$. The tunneling conductance measured in the experiment has peaks when states that differ through the transfer of charge from the antidot to the outer edge of the incompressible fluid are nearly degenerate. The experiments are performed at low temperatures where only very low energy states of the electron system are relevant. According to the above discussion, we should expect the peaks to correspond to degeneracy between states in which the number of quasi-holes N_{qh}, that is, the number of zeroes of Ψ, bound inside the antidot differs by one. When the magnetic field is increased, A_0 decreases and level crossings occur in which the number of quasi-holes in the ground state increases in order to keep the area of the antidot $A_{anti} = N_{qh}A_0$ as close as possible to the value dictated by electrostatics. The separation in magnetic field between level crossings, signaled in these experiments by tunneling conductance peaks, constitutes an experimental measurement of A_{anti}. The charge associated with an individual quasi-hole can then be determined from the separation between the tunneling conductance peaks that occur as a function of the voltage between the electron system and a back gate. Provided they are sufficiently remote, the electron system and the back gate together act like a parallel-plate capacitor system, and the rate of change of the charge on the antidot with the back-gate voltage is known. The experiment shows charge transfer, flagged by tunneling conductance peaks, occurring in discrete $e/3$ units.

This experiment confirms a basic prediction arising from Laughlin's theoretical work (*1*). However, it now seems that the creation of fractional charges from whole ones is one of the simpler tricks that electrons can perform in the fractional Hall regime. When the electron density is sufficiently different from $(3A_0)^{-1}$, the fractionally charged quasi-particles become dense, and the picture described above fails. Incredibly, recent experimental (*4*) and theoretical work (*5*) appears to show that when the density is $(2A_0)^{-1}$, the electrons organize themselves into a Fermi liquid state with a phenomenology similar to that of noninteracting electrons. However, because of the kinetic energy quantization, this exotic Fermi liquid must be composed of particles with an energy due entirely to electron-electron interactions. Nevertheless, these particles appear to interact relatively weakly with each other. The method by which this artifice is achieved is not yet fully understood. The intricacy of quantum interacting electrons in the fractional Hall regime continues to surprise.

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Express Yourself or Die: Peptides, MHC Molecules, and NK Cells

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Conventional wisdom has it that the lymphocytes defend the body from infectious agents and aberrant cells by recognizing the "foreign," detecting nonself proteins in the body fluids or on surfaces of cells. However, natural killer (NK) cells can also operate by the opposite strategy: They recognize and eliminate cells because critical "self" proteins are absent from the cell surface (*1*). NK cells refrain from killing when the target cells express self class I molecules of the major histocompatibility complex (MHC). When these molecules are absent or expressed only in reduced amounts, the NK cells proceed with their attack and can thereby reject tumor, virus-infected, and transplanted cells.

But what is the exact nature of the magic password that NK cells search for when they assess a cell? Is it a protein or carbohydrate part of the polymorphic MHC class I molecule itself? Or is it the 8– to 11–amino acid peptide carried by this molecule from the cytosol of the cell to the surface, where it is displayed as a quality control sample to another lymphocyte, the T cell? At least part of the answer to these questions emerges in two new studies. Malnati *et al.*, in this issue of *Science* (*2*), show that one (but not every) peptide that binds to the empty human leukocyte antigen (HLA)–B27 class I molecules on a mutant cell can confer protection against a human NK cell clone. Notably, the peptide that protects corresponds in sequence to a peptide from class I molecules of normal cells. The phenomenon is, as immunologists would like it to be, highly specific: Protection is seen only with certain NK clones. In the murine system, Correa and Raulet (*3*) demonstrate that most if not all peptides provide binding to the class I molecule H-2D^d and can protect against a subset of NK cells.

NK cells exist as preactivated killer cells in the blood and in many organs without need for prior vaccination (*4*). They can be identified by their characteristic profile of cell surface molecules–Fc receptors for immunoglobulin, several adhesion molecules, and one or more C-type lectin-like receptors. The NK cell does not have a single rearranged *receptor magnificus*, such as that of the T cell or B cell immunoglobulin, but rather appear to operate by several different recognition strategies. Loss of class I molecules is sufficient to induce NK sensitivity (*1*, *5*), even of normal cells. Also, human NK clones kill allogeneic but not autologous cells—because of the absence of self rather than the presence of nonself molecules on the surface of the target cell (*6*).

There are two general models for how NK cells might detect missing self molecules in these situations (*1*). The "effector inhibition" model postulates that NK cells are initially triggered to kill by broadly distributed molecules on most cells, but that the lytic program will be canceled by negative signals from receptors upon their recognition of specific MHC class I alleles on the target cell. The alternative "target interference" or "masking" model (*1*, *7*) postulates that triggering receptors on NK cells recognize target structures that can be masked or otherwise interfered with by class I molecules of the target cell.

Restoration of the pathway that presents MHC class I peptides by transfection of defective mutant cells also restores their ability to resist the attack from NK cells (*8*). These experiments, however, do not directly test the role of the peptide. The elegant system used by Malnati *et al.* assesses the contribution of peptide by relying on three critical components: NK clones of different HLA specificity, a panel of genetic variants of a class I molecule called HLA-

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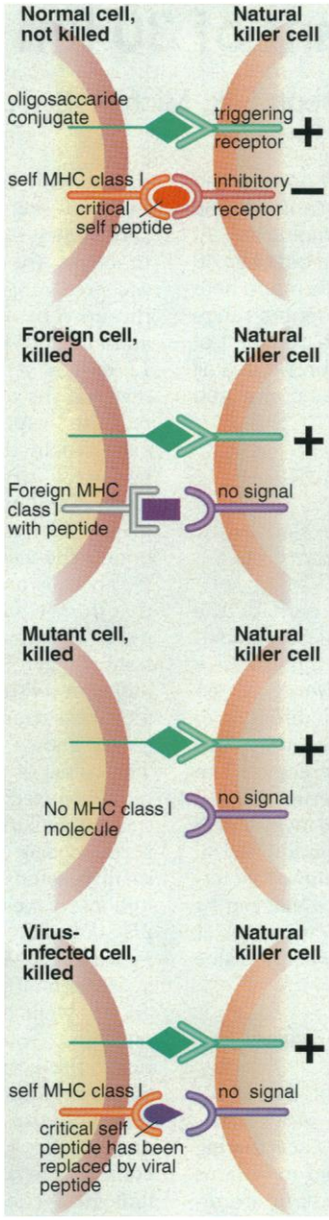
B27, and mutant cell lines deficient in the transporter associated with antigen presentation (TAP). Only some of the HLA-B27 variants will make target cells resistant to NK cells after transfection. As the variants differ only in defined parts of the special peptide binding cleft formed by the tertiary structure of the MHC molecule, these data agree with previous reports suggesting a role for the peptide (9). But until now nobody has been able to prove directly that a peptide added to a target cell actually can protect against NK cell killing. The acid test of this ability is provided in both of the new studies by the use of RMA-S lymphoma mutant cells deficient for TAP. Without this molecule, cytoplasmic peptides cannot enter efficiently into the endoplasmic reticulum, where they normally associate with class I molecules. As a consequence, class I molecules remain unstable and fall apart during transport or shortly after the arrival at the cell surface, resulting in an NK-sensitive cell phenotype (*8*, *10*). However, the class I molecules are reasonably stable and "come out in the cold"—that is, they can be transported even without the peptide at the reduced temperature of 26°C (*11*). They can then be stabilized at the cell surface by soaking the cell with high concentrations of specific peptides. This system allowed each of the research teams to load all the class I molecules (HLA-B27 and H-2D^d, respectively) on the target cell surface with one peptide species at a time, without significant interference by the cell-derived peptides that normally fill the clefts of the MHC molecules.



How natural killer cells selectively eliminate nonself cells.

Two possibile roles for peptides in NK recognition have been proposed (*1*). Peptides could be important simply because they bind and stabilize class I molecules, in which case any peptide with the structural motif (agretope) allowing binding to a class I molecule would provide protection from NK cells. Alternatively, only critical peptides that bind to the class I molecule and also provide structural motifs (epitopes) for NK receptors would protect. Malnati *et al.* clearly demonstrate that simply binding to HLA-B27 is not sufficient; only one of several binding peptides confers protection. There must be a unique feature to this peptide, that is, a "selfish" motif as perceived by the human NK clone. In contrast, Correa and Raulet find that virtually all H-2D^d binding peptides inhibit murine NK cells expressing the Ly49 receptor for this class I molecule. The discrepancy between the systems may be technical, species related, or simply reflect the characteristics of different receptors; some of these may depend mainly on the MHC molecule itself, others may rely on (or be hampered by) epitopes formed by the peptide itself. Correa and Raulet also point out that peptide specificity is not formally ruled out in their system.

It is important whether protection is peptide specific as in the system by Malnati *et al.*, because this implies that target cell surfaces can be interpreted by NK cells as "missing self" even if they do not have deleted or reduced MHC class I expression. Cells expressing normal amounts of class I molecules that are missing the critical peptides (for example, in infected cells) are equally likely to be lysed by NK cells.

The simplest interpretation of both studies is that protective peptides promote interaction of MHC class I receptors with the particular NK cells used. What is the nature of these inhibitory receptors? NK cell receptors have long been elusive, but times are changing. At last summer's international workshop on NK cells, the chair at the session on recognition remarked that "1 year ago, the problem was that we did not have any receptors. Now the problem is that we have too many!" Half a dozen NK receptors have been cloned and characterized well (*12*–*16*), and at least half a dozen others wait in the wings. Such molecules are expressed on subsets of NK cells and they inhibit killing upon interaction with a specific group of MHC ligands. The receptors can be structurally quite diverse; one subgroup belongs to the C-type lectin (carbohydrate binding) family. The C-type lectins also include triggering receptors on NK cells. One example is the NKRP-1 receptor, which was recently shown to be specific for ubiquitous oligosaccharides present on many different glycoproteins and glycolipids (*17*). This finding fits well with the effector inhibition model; the ligands of the triggering structure can also be present in normal cells, as the ultimate verdict is passed downstream by the MHC interaction.

It is thus possible that carbohydrates of the MHC glycoprotein participate in the inhibition of NK cell attack. What role is the peptide playing? It could provide an epitope recognized by NK cells, induced by stabilization or a change in the structure of the MHC molecule (including carbohydrate side chains), or acting through a direct contact with an NK cell receptor. What makes the only protective peptide in the study by Malnati *et al.* (*2*) particularly "selfish" for the NK clone? Comparisons of different peptides and systematic substitutions in their amino acid sequence will reveal the motif influencing the NK interaction. Application of critical peptides in vivo may reveal how the NK receptor repertoire adapts to self ligands, as indicated by recent studies of MHC transgenic mice (*18*, *19*). Perhaps the most exciting question arising from the observations by Malnati *et al.* concerns the evolutionary past: Was peptide transport by polymorphic MHC molecules invented for T lymphocytes to detect the "foreign" or for NK cells to detect self?

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