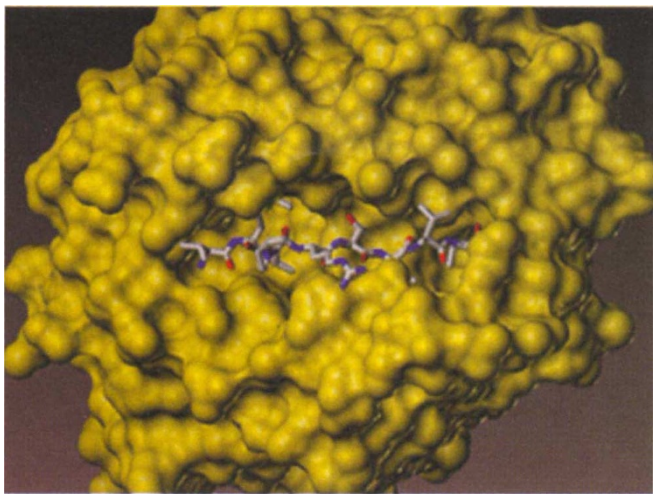
# To kill or not to kill



Cytotoxic cells — the assassins of the immune system — must be sure that they should kill a potential target cell. Hence, there are probably many checkpoints for lysis by natural killer cells and T cells. Recent research has suggested that a natural killer cell's decision to lyse a potential target cell involves sensing whether or not the cell is functioning properly in immunological terms — that is, whether or not the major histocompatibility complex (MHC) class I molecules are being expressed and are presenting antigenic peptides properly. At least part of this readout seems to occur through a little-discussed set of MHC molecules, the class Ib group, not through the commonly known MHC class Ia molecules that present most of the antigenic peptides.

Although they are very similar in overall structure, class Ia and class Ib differ in their ligand-binding capabilities: the class Ia molecules are promiscuous (necessary for binding diverse viral and bacterial peptides) whereas the class Ib molecules, such as human HLA-E, bind a limited number of ligands very tightly. Remarkably, the most common HLA-E ligand is a highly conserved hydrophobic nine-residue peptide from the cleaved signal sequence of class Ia molecules, and this specific HLA-E–class Ia peptide complex can bind receptors on natural killer cells that inhibit cytotoxicity. If this complex is absent from the cell surface, as occurs in some infected cells because of viral down-regulation of class I molecules, then natural killer cells are more likely to kill the cell. Since the HLA-E–class Ia leader peptide complex incorporates a portion of the class Ia molecule, it is presumably a good reporter of both class Ia and class Ib expression, and of MHC loading and transport to the cell surface.

Now, thanks to recent structural work on the human HLA-E-class Ia peptide complex (O' Callaghan, C. A. *et al. Mol. Cell* 1, 531–541), we can envision part of what the natural killer cell recognizes on the cell surface as it makes its cytotoxic decision. Also, we can see how the MHC scaffold can be altered to bind peptides specifically, and not promiscuously — in particular, why the class Ia leader peptide is a high affinity ligand for the HLA-E molecule. Unlike the class Ia–peptide complexes in which the peptides are anchored mainly at their ends by only a few contacts, in the HLA-E–peptide complex, the peptide binds in a groove along the HLA-E molecule and is contacted along its entire length by hydrogen bonds and hydrophobic contacts in specific pockets. These contacts fix the positioning of the peptide in the groove and limit the kinds of residues that can bind tightly. TLS



# History in the making

In the days when anatomy was the main focus of science, Galen proposed that nervous tissue (thought to be a syncytium) conducts fluids from the brain and spinal cord to peripheral tissues. In the modern era, the merging of diverse disciplines — from histology to medicine to electrophysiology to molecular biology — has been required to understand the function of this complicated network. The concept that neurons are individual units that participate in signaling began in the 19th century, and was developed from the work of many scientists, including Camillo Golgi (who developed a staining technique that allowed whole nerve cells to be visualized along with their dendrites and axons), Santiago Ramón y Cajal (who developed the concept of individual neurons connecting at synapses), Luigi Galvani (who showed that muscle cells produce electricity), and Emil DuBois-Reymond (who described action potentials).

Today's commonly accepted view of neurophysiology came much later, in 1952, when Hodgkin and Huxley[1] proposed that nerve cells signal by regulating the flow of ions across their membranes. However, the definitive experiments proving the existence of single ion channels were conducted only in 1976, when Erwin Neher and Bert Sakmann developed the technique of patch clamping[2], allowing single channel recordings, and identification of different channel properties, to be made. For this achievement, they won the Nobel prize in 1991. As one of the early examples of the power of this now widespread technique, Neher, Patlak and Sakmann determined the rates of activation and desensitization of the acetylcholine receptor channel in 1980[3]. Soon after, in 1984 and 1987, the cloning of genes coding for a sodium channel from the electric eel[4] and a potassium channel from Drosophila[5,6] allowed molecular research at the protein level to advance substantially. Now, only 10 years later, we are able to see — with the presentation of the first structure of an ion-selective channel (see ref. 7 and News and Views pages 342–344) — the mechanism by which a potassium channel selectively regulates the flow of ions. Given the long and exciting history of research into excitable tissues, this structure has been met with considerable enthusiasm. The next molecular challenges lie in understanding how all of the known channels are gated by the multitude of intracellular signaling mechanisms. TLS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