than we observe in galaxies.

Finally, there are observations that connect ROSAT with the beginnings of x-ray astronomy. The historical rocket flight in 1962 aimed at the detection of x-rays from the moon but discovered the brightest x-ray source (Sco X-1) in the sky and the diffuse x-ray background (*1*). Twenty-eight years later a ROSAT snapshot produced the first x-ray image of the moon (Fig. 2). It shows scattered solar x-rays from the sunlit side and the occultation of the diffuse sky background by the dark side of the moon (*13*). To reveal the nature of this diffuse background—the "holy grail" of x-ray astronomy—the longest ROSAT observation (42 hours) has been made in the constellation Ursa Major (*14*) (Fig. 3). At the source flux level reached (2×10^{-15} erg cm^{-2} s^{-1}, which is a factor of 20 fainter than that of the deepest Einstein survey), 435 sources per square degree show up. At least 75% of the total "background" is resolved into discrete sources. Optical identification shows that most of the brighter sources (>10^{-14} erg cm^{-2} s^{-1}) are quasars with a wide distribution in redshifts. Identification of the faintest ROSAT sources has to await the next generation of optical telescopes, which shall become available soon.

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Natural Selection at Work on the Surface of Virus-Infected Cells

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In the last 7 years, considerable progress has been made in understanding how foreign antigens are presented to cytotoxic T lymphocytes (CTLs), a process that enables the CTL to "look inside" other cells and detect abnormalities within, such as a virus infection, and ultimately to destroy the infected cell.

The key element in this recognition of foreign proteins (antigens) by CTLs is the class 1 glycoprotein encoded by the major histocompatibility gene complex (MHC-1). These MHC-1 molecules bind peptide fragments of internal cellular proteins that have been degraded in the cytoplasm (*1*) (see figure). Cytoplasmic proteases, such as those of the proteasome complex, degrade cytoplasmic proteins to peptide fragments. Many of these pieces may be further degraded, but some are taken into the endoplasmic reticulum by a transport mechanism that involves a dimeric protein of the adenosine triphosphate (ATP)–binding cassette family (*2*, *3*). (Other members of this family are the cystic fibrosis gene product and the multidrug resistance protein, also involved in transport across cell membranes.) The two chains of the transporter are encoded in the MHC (*2*, *3*), as are 2 of the 28 or so subunits of the proteasome (*4*).

The peptides generated and transported into the endoplasmic reticulum are derived from many intracellular proteins. Peptides from viral proteins are mixed into this pool. Some genetic polymorphism in the transporters may influence the type of peptides that reach the lumen of the endoplasmic reticulum (*5*); some viruses may also influence the general composition of this peptide pool by inhibiting host cell protein synthesis. Inside the endoplasmic reticulum, newly synthesized class 1 glycoprotein molecules need peptides to stabilize their folded structure (*6*).

The MHC-1 molecules comprise two chains, the α (heavy) chain of 45 kilodaltons and a light chain, β_2-microglobulin. The former is the product of the MHC and is uniquely polymorphic. The MHC-1 α chains are encoded by genes at three loci—in humans *HLA-A*, *-B*, and *-C*. There are at least 40 alleles at *A*, 80 at *B*, and about 10 at C (*7*). (As more ethnic groups are studied, more alleles are being found, often differing in only a few amino acids from previously sequenced molecules.) HLA-A and HLA-B are expressed at much higher levels than HLA-C and are found on the surface of most nucleated cells. The structures of four MHC-1 molecules, HLA-A2, HLA-A68, HLA-B27, and H-2K^b have been determined (*8*); all are closely related, and on the surface of the molecule that is farthest from the cell membrane is a groove that contains a peptide, 8 to 11 amino acids in length (*9*). Identical MHC-1 molecules on a cell bind many different peptides: the 10^5 HLA-A2 molecules on lymphocytes bind about 10^3 different peptides (*10*). When the mature MHC-1 peptide complex reaches the cell surface, the bound peptides are displayed for many hours; some empty molecules can reach the cell surface but tend to be unstable and fall apart (*11*).

Most of the polymorphism in MHC-1 molecules is found in amino acids with side chains that contribute to the peptide-binding groove (*12*). Thus, the groove of different allelic products differs in its fine structure and binds different peptides. However, the ends of the groove are remarkably conserved, and invariant tyrosines and threonines form hydrogen bonds with the amino-end carboxyl termini of the peptides, so that all peptides bind with the same orientation (*13*). When the bound peptides are eluted from the purified MHC-1 molecules and sequenced, they show similarities at the residues that are involved in binding to the groove (*14*). For instance, in peptides that bind to HLA-B27 there is invariably an arginine at its second residue, often followed by an aromatic residue at position three and an arginine or lysine at the carboxyl terminus (*15*). This is explained by the way the peptides bind to the HLA-B27 molecule; the side chain of the arginine-2 fits into a pocket with features unique to HLA-B27, and the other anchoring side chains also fit into pockets within the groove. Other MHC-1 molecules require different characteristics in their bound peptides. Therefore, different allelic products of the MHC-1 loci present different families of peptides at the cell surface. Among these will be abnormal or foreign peptides if the cell is damaged (for example, by abnormal expression of oncogenes) or infected with a virus, bacterium, or protozoal parasite.

CTLs are crucial for the immune response to viral infections (*16*). They cannot neutralize free virus, but by eliminating virus-infected cells they are often largely responsible for the recovery of the organism from the viral infection (*17*). CTLs are designed to monitor the MHC-1 molecules of cells within the body; if the antigen receptors (also called T cell receptors) on the T cells are bound by antigen, the T cells are activated and they kill the target cells. As CTLs develop in the thymus, those with T cell receptors that react with self peptide–MHC-1 complexes are eliminated (negative selection) or

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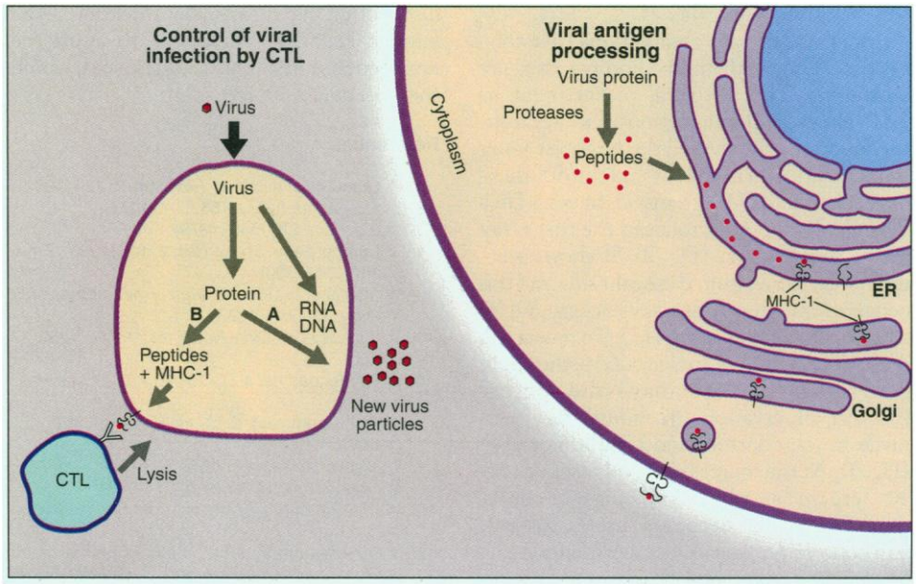
otherwise rendered inactive. By a different process, T cells with receptors that will recognize foreign peptides bound to self-MHC molecules are amplified (positive selection). A fine balance is struck between MHC-1 molecules that bind too many peptides, which would eliminate an excessive number of T cells, and MHC-1 molecules that bind too stringently and would be of little value in combating infections.

The polymorphism of the MHC-1 molecules means that most individuals will be heterozygous and will thereby have a better chance of presenting peptides from an infecting organism, particularly a virus where the choice on offer may be small—peptides derived from less than ten proteins in many instances. Similarly, a species with a diverse array of MHC-1 molecules may be able to survive epidemic infections that can have very high mortalities. The selective forces on the MHC in the face of epidemic infections can be very strong and are believed to be largely responsible for maintaining MHC polymorphism, as well as contributing to geographic variations in HLA allelic frequencies. Selective pressure can also act on the pathogen, and it can do so more rapidly than it can on the host genome. Although direct evidence for these selective forces in human infections is hard to obtain, there are three promising examples that have recently come to light.

HLA-B53 has been associated with resistance to severe (fatal if untreated) malaria in young children in The Gambia (*18*). HLA-B53 occurs in 25% of the population of The Gambia; this is in contrast to Europe where it occurs in just 1% of the people. This difference implicates selection at the HLA locus in West Africa, probably by malaria. The most likely mechanism for this selection is attack on the early liver stage of the malarial parasite by CTLs, a process that occurs in animal models. Recently, Hill and co-workers showed that Gambians with HLA-B53 have responded to malaria infection by generating CTL responses to a conserved region of the liver stage antigen-1 (*19*). In this example, selection has increased the frequency of the protective HLA type.

The fatal infections by the human immunodeficiency virus–type 1 (HIV-1) could be starting to exert selective pressure on the HLA system, particularly in the developing world. In the West, certain HLA types are associated with poor outcome after HIV-1 infection. In recently infected patients, there is a strong CTL response, which probably contributes to the temporary control of the infection. However, HIV accumulates mutations and replicates continuously. Mutations in epitopes of the HIV protein gag, which are presented by HLA-B8, have been found that are not recognized by CTL present in the same patients (*20*). These are potential escape mutants; the rate of virus escape from CTLs ought to vary according to the HLA type, because different regions of the virus may be more prone to variability (where viral competence is not affected). The HLA-A1, -B8,-DR3 haplotype has been associated with more rapid progression of HIV infection to AIDS, although it is not known whether this is due to the presence of HLA-B8.



Fighting viral infections. (**Left**) When a virus infects a cell, it directs the cellular machinery to synthesize new viruses (pathway A). In self-destructive defense, the cell degrades viral proteins, and via the antigen-processing pathway the resulting peptides are presented on the cell surface bound to MHC-1 molecules (pathway B), where they trigger lysis of the infected cell by cytotoxic T lymphocytes. (**Right**) A detailed diagram of the antigen-processing pathway. ER, endoplasmic reticulum.

The third example involves infection with Epstein-Barr virus, which is the causative agent of infectious mononucleosis and is responsible for nasopharyngeal carcinoma and Burkitts lymphoma in tropical areas. HLA-A11 normally provokes a particularly strong CTL response to a peptide from the Epstein-Barr virus. HLA-A11 occurs in about 12% of Northern Europeans but is much more common (25 to 50%) in Papua New Guinea. De Campos–Lima and co-workers (*21*) report that the normally dominant peptide epitope presented by HLA-A11 has a sequence change in Epstein-Barr viruses isolated from Papua New Guinea at a residue critical for binding to the HLA-A11 molecule. Therefore, individuals from Papua New Guinea infected with the Epstein-Barr virus do not generate a CTL response to this epitope presented by HLA-A11, in contrast to people in other parts of the world. The authors suggest that the high frequency of HLA-A11 in Papua New Guinea has selected this virus escape mutant.

These examples illustrate the dynamic interplay between the MHC and pathogens. It is probable that MHC type has similar subtle influences on susceptibility to many other infectious diseases. The extraordinary polymorphism of the MHC in most species is probably the legacy of those battles. They are still in progress.

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