ated the potential for side effects by testing the monoclonal antibody on three healthy primates. The primate studies with the new anti-DR reagent are highly reassuring that the expression of DR on a variety of non-malignant cell types, though limited, will not be clinically limiting.

Two monoclonal antibodies with specificity for some haplotypes of human DR β -chains have been used in humans and one of these, a humanized antibody called apolizumab (Remitogen) is in phase 2 clinical trials¹¹. It is not clear whether either of the antibodies tested so far can mediate signal transduction. However, the reagent reported by Nagy and colleagues certainly does and is also more broadly reactive with the range of human DR polymorphisms. The promise of the new approach is that cell death is a direct consequence of antibody binding to the target on tumor cells, and it does not require additional mechanisms that may be compromised in the cancer patient. Like chemotherapeutic agents and radiation therapy, the new antibody against HLA-DR is directly cytotoxic.

Despite promising data such as these it is dangerous to make predictions about clinical success in cancer treatment. The tumor-cell lines killed by the new antibody all have the phenotype of activated B cells and have a

growth fraction of 100%, which means all the cells were proliferating. The one cell line that failed to be killed could be rendered susceptible to killing by activation signals. By contrast, human lymphomas have a smaller growth fraction *in vivo* (8% or fewer of the tumor cells are actively proliferating). In humans, molecular characterization is defining distinct subgroups¹² that may or may not be susceptible to DR activation *in vivo*. However, there is every reason to think that antibodies capable of delivering signals through cell-surface receptors will be more effective than antibodies that either block function or recognize a structure that serves no functional role in the activation and growth of the tumor cell. The next step is to take the new weapon into the clinic. If it is as successful as expected, the path to the generation of other effective new treatments will be well illuminated by this elegant work.

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Host genetics and HIV—removing the mask

A newly discovered interplay between two human genes controlling the immune response to HIV has implications for antiretroviral drug therapy and the development of preventive vaccines.

Studies of the impact of host genetics on the susceptibility to HIV infection and rate of disease progression have revealed associations with a number of individual genes. These include those genes encoding proteins that control viral entry (CCR5, CCR2, RANTES and SDF1), immune regulation (interleukin-10, tumor necrosis factor- α and MBL) and adaptive immune recognition by T cells (human leukocyte antigen or HLA)^{1,2}. Associations have not yet been described with genes that control natural killer (NK) cells of the innate immune response.

In the August issue of *Nature Genetics*, Martin *et al.* describe a complex interplay between genes that control NK cell activity and HLA genes

NELSON L. MICHAEL

that control immune recognition³. They find that the influence of the former genes masks that of the latter. This masking, or 'epistasis', represents the first such interplay between host genes to be associated with HIV disease progression. Identification of such an association advances the field to the next level in defining host genetic influences on HIV pathogenesis. This research also implicates a key interaction between the innate and adaptive arms of the cellular immune response in controlling HIV replication.

Viral pathogens are targeted by diverse immune-effector mechanisms.

Cytotoxic T-lymphocytes (CTLs) represent the adaptive immune response. They control the expansion of antigen-specific cellular clones, which recognize viral antigens displayed on infected target cells by HLA class I gene products. Previous exposure to antigen provides for a more rapid immune response upon re-exposure. NK cells are part of the innate immune response, as previous antigen exposure does not modulate NK pathogen recognition. NK cells express cell-surface killer immunoglobulin-like receptors (KIRs) that recognize HLA class I molecules on infected target cells. KIRs can both stimulate and inhibit NK activity⁴. Thus, a mechanistically cogent but complex interplay occurs between HLA and KIR genes in the host im-

Fig. 1 A proposed mechanism of interaction between *HLA-B*48:01* and *KIR3DS1* genotypes. **a**, HIV-infected T cells expressing non-*HLA-B*48:01* molecules (*HLA-B*80X*) on the cell surface attract fewer NK cells expressing either *KIR3DL1* or *KIR3DS1*, as either is a ligand for the HLA protein. DAP12 is not activated and minimal NK-mediated cytotoxicity occurs. **b**, HIV-infected T cells expressing *HLA-B*48:01* molecules are preferentially engaged by *KIR3DS1*-expressing NK cells which are activated through transmembrane DAP12. The result is killing of the HIV-infected T cell.

immune response to HIV.

Studies of associations between host genes and HIV have focused on genetic suspects involved in the HIV life-cycle and host immune response. The challenge of these studies is to assess the typically small impact of individual genetic polymorphisms. This requires the analysis of large cohorts of individuals both infected with HIV and those at risk of acquiring it. Subjects must be followed for infection and disease outcomes, respectively, for many years.

Initial host gene identification efforts were largely limited to associations of HIV pathogenesis with *HLA* class I and II genes located on chromosome 9 (ref. 1). The discovery of chemokine receptors as HIV-1 entry coreceptors⁵ generated numerous reports that associated genetic polymorphisms in single chemokine and chemokine receptor genes with HIV pathogenesis. The two most powerful

and compelling associations that have emerged from all of these studies have zeroed in on the *HLA-B* gene and the HIV coreceptor *CCR5* (chemokine receptor 5). An inactivating 32-basepair deletion in *CCR5* (*CCR5Δ32*) reduces disease progression and susceptibility to infection^{2,6}. *HLA-B*35-Px* alleles are associated with accelerated disease progression due to a single amino-acid difference in HLA-binding domains for HIV antigens⁷.

In the current study Carrington and colleagues built on their previous findings that different HLA class I B alleles can influence the rate of HIV disease progression^{7,8}. They asked what modulating influence *KIR* genotypes would have on *HLA* genotypes, as *KIRs* bind HLA molecules and influence NK-cell activity. They used standard screening techniques to assign *HLA-B*48* and *KIR3* genotypes to over 1,000 subjects enrolled in 5 HIV cohorts. Next, they associated genotype with disease pro-

gression after normalizing for the influence of previously associated genotypes such as *CCR5Δ32*.

Martin *et al.* drew four conclusions. First, they noted that *HLA-B*48* exerted a weak protective effect on AIDS progression when *KIR* genes were not accounted for. This effect was strictly limited to class B genotypes with isoleucine at position 80 (*HLA-B*48:01*). Second, the *KIR3DS1* allele was moderately associated with an increased rate of AIDS progression when *HLA-B*48:01* was not accounted for. Third, individuals with both *KIR3DS1* and *HLA-B*48:01* genotypes show a marked delay in disease progression. This delay was striking as these genotypes, when analyzed independently, had divergent associations with disease progression: inclusion of both *KIR3DS1* and *HLA-B*48:01* in a covariate model eliminated the association of *HLA-B*48:01* with delayed disease, but enhanced the association of *KIR3DS1* with rapid disease progression. Thus, the *HLA-B*48:01* association was masked by *KIR3DS1*, making the former epistatic to the latter. Fourth, the combined effect of *KIR3DS1* and *HLA-B*48:01* occurred in both Caucasian and African-American individuals representing diverse risk exposures and cohorts. The most striking effect of these combined genotypes on disease progression outcomes was on CD4⁺ T-cell levels in early-stage HIV disease.

These results are novel as they represent the first association of an epistatic interaction between two human genes that modulate the progression of HIV disease. The results are important as they reinforce the critical interface between the adaptive and innate immune response to HIV. However, the precise mechanism that explains the physiological effect of the *HLA-KIR* epistatic interaction remains speculative (Fig. 1). The *KIR3DL1* allele encodes cell-surface NK receptors with long cytoplasmic tails that inhibit NK activity⁹. In contrast, the *KIR3DS1* allele encodes a NK receptor with the hallmarks of an NK-cell activator, which possibly acts via the transmembrane adaptor DAP12 (ref. 10). A plausible explanation for the current findings is that *HLA-B*48:01* molecules are ligands for the activating *KIR3DS1* NK receptor. Thus, HIV-positive individuals with both the *HLA-B*48:01* and *KIR3DS1* genotypes

would express an HLA-B molecule on their infected target cells that could bind to a KIR receptor capable of increasing NK cell-mediated killing of these cells.

What are the clinical implications of this type of research? A comprehensive map linking host genes—both individually and in concert—to HIV pathogenesis would help predict susceptibility for HIV infection and would provide prognostic information for disease progression. A firmer understanding of the host–pathogen interaction could also guide the optimum use of therapeutics. Drug toxicity and resistance increasingly complicate the management of HIV-infected patients, resulting in a larger fraction of patients with deferred treatment. More rational stratification of treatment intensity could be based on a refined knowledge of which individuals are genetically more susceptible to early immune deterioration and disease. Conversely, it might be possible to optimize treatment interruptions and viral-reservoir depletion for patients with greater natural resistance to disease progression. Increased knowledge of host susceptibility to HIV infection could refine the approach to preventive

vaccine development by adjusting vaccine effectiveness for innate predisposition for infection. Lastly, better definition of pre-exposure risk for HIV infection might be helpful in the approach to post-exposure treatment of such individuals.

These optimistic implications of a more refined understanding of host genetics and HIV pathogenesis will be challenged by the difficulty in sorting out small influences of any given gene, and the enormous complications of determining sophisticated interactions between genes. Moreover, we must address the ethical considerations of performing large-scale genetic research that predicts disease outcome and therapeutic response with increasing accuracy. The genetic privacy of HIV-infected patients must be respected to avoid employment or insurance discrimination. Nevertheless, the mask has been removed on the first complex interaction between two host genes and HIV pathogenesis—with the promise of more to come.

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Erythropoietin strikes a new cord

There are currently no effective means to treat acute spinal cord injury, except for glucocorticoids, which produce moderate benefits at best. A new study suggests erythropoietin, now recognized as a potent neuroprotective cytokine, as a potential treatment for spinal cord injury.

Spinal cord injury (SCI) is one of the most frustrating maladies faced in neurology and medicine. The vast majority of SCI patients are young, and most survivors of significant injury face the prospects of limited recovery and permanent disability. The incidence of new SCI cases is high, exceeding 12,000 new cases per year of paraplegia or quadriplegia in the United States¹. Yet with improved management, the mortality rate of SCI has steadily fallen. As a result, the prevalence of patients disabled by SCI now approximates 200,000 in the US alone. The need for effective acute intervention, both to limit the numbers of permanently impaired patients—and to give real hope to the newly injured—has never been greater.

Current treatment of SCI is limited to high-dose glucocorticoid therapy, which is useful only when adminis-

tered within hours of injury. The mechanisms by which the steroids exert their moderately beneficial effects remain unclear, though they are generally attributed to the anti-inflammatory effects of the glucocorticoids. Yet despite the fundamental inadequacy of high-dose glucocorticoid treatment, it has remained the only available therapy for SCI.

In a recent issue of the *Proceedings of the National Academy of Science USA*, Gorio *et al.* report that the acute administration of erythropoietin (EPO) can attenuate the effects of acute SCI, and accelerate recovery after injury². In two different experimental models of SCI in rats, one chosen to mimic brief crush injury, and the other a model of trau-

matic contusion, EPO treatment markedly improved neurological recovery.

In the crush-injury model, in which the thoracic spinal cords of anesthetized rats were briefly compressed with a clip, untreated animals were initially paraplegic, and still barely able to move their hind limbs 4 weeks after injury. The authors quantified spinal cord injury using a standardized 21-point scoring system, called the BBB scale (on which 0 is plegic and 21 normal)³. The untreated rats had mean BBB scores of 1 immediately after SCI, and of 10 when assessed 4 weeks later. In contrast, their treated counterparts, who received a single injection of EPO (1,000 U/kg) an hour after injury, improved to a BBB score of 18 at 4 weeks. Notably, a single injection of EPO at 1 hour was as effective as daily injections given for the first several days; accordingly, most of