is another Little Ice Age, in a millennium or so. But human-induced greenhouse warming might intervene and amplify the cycles.

Oppo and colleagues found that climate oscillations were largest when ice sheets were growing and when they were disintegrating. Variations were subdued in the depths of an ice age, although not as much as during an interglacial. That pattern, also seen in earlier work, suggests to Richard Alley of Pennsylvania State University in University Park that climate shifts might be strongest not just when it's cold but when the climate system is being pushed from one state to another. If so, a push toward warmth during an already-warm interglacial might boost climate shifts to devastating proportions. Then again, because past climate swings have been smaller in warm periods, continued global warming might dampen them even further.

How to choose between the two possibilities? For better or worse, the answer will come as human beings continue to pour greenhouse gases into the atmosphere, says Alley: "The experiment to answer that question is the one we're doing now."

–Richard A. Kerr

IMMUNOLOGY

Viral Saboteurs Caught in the Act

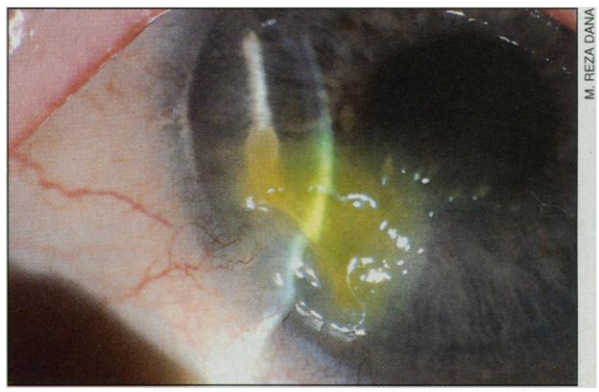
Disguising yourself as your enemy is an age-old ruse of human saboteurs. Viruses, those saboteurs of the cell, have adopted it as well, fashioning components that are the spitting image of normal host proteins. This "molecular mimicry" can help a virus evade detection by the host immune system long enough to create an infection. Occasionally, though, the immune system catches on, and immunologists think that the resulting immune attack may damage host cells as well as the virus. Although this is an attractive explanation for such devastating autoimmune diseases as insulin-dependent diabetes and multiple sclerosis, until now, no one has been able to show conclusively that this type of molecular mimicry really can cause disease.

On page 1344, however, immunologist Harvey Cantor and his colleagues at Harvard Medical School in Boston show that molecular mimicry is at work in herpes stromal keratitis (HSK), a common autoimmune disease of the eye triggered by herpes simplex virus 1 (HSV-1). The group found that HSK, which can cause blindness by clouding the cornea, is much more likely to develop in mice if the infecting virus carries a particular protein segment that closely resembles part of a protein found on the animals' corneal cells than if that viral segment is removed. The result is the "final piece of evidence that during an infection, a virus can bring about autoimmune disease [by molecular mimicry]," says viral immunologist Michael Oldstone of The Scripps Research Institute in La Jolla, California, who first proposed the hypothesis in 1982.

Discovery of the target of the immune attack also has clinical implications for people with ocular herpes, which can lead to HSK and is the principal infectious cause of blindness in developed countries, affecting an estimated 400,000 people in the United States alone. M. Reza Dana, an ophthalmologist and ocular immunologist at Harvard Medical School, notes that if the immune system is indeed attacking the corneal protein identified by the Cantor group, then the discovery could "in principle allow us to disrupt or arrest this component" of the attack, perhaps by inactivating the specific set of immune cells responsible for it.

Cantor and his team got their first clue to the importance of molecular mimicry in HSK about 3 years ago, while trying to determine why some mice infected with HSV-1 don't develop the disease. Previous genetic studies had suggested that mice are protected if they have a particular variant of a gene coding for antibodies of the immunoglobulin G2a (IgG2a) class. At the time, no one knew exactly how the IgG2a variant might offer protection. What Cantor's team found is that it contains a sequence that renders T cells that would otherwise damage the corneal tissue incapable of mounting their immune attack.

That finding suggested that the same short protein sequence is present on cornea cells as well, and that it might be the target of the autoimmune attack in HSK, an idea that the members of the Cantor group confirmed when they found that the sequence is indeed located on the cornea cells of resistant animals. Apparently, its fortuitous presence on the IgG2a variant trained those animals' T cells, which can encounter antibodies in the blood, to recognize that protein as "self." As a result, they respond neither to it nor to the corneal protein sequence that it resembles. Animals not having the IgG2a variant are susceptible, because T cells do not ordinarily contact corneal cells and so do not develop such tolerance.



M. REZA DANA

Invidious infiltrator. Herpesvirus may produce eye damage such as this by triggering an immune attack on corneal cells.

The link to viral mimicry came when Cantor's group found the same sequence in a herpesvirus protein called UL6. That suggested a mechanism by which the virus might cause HSK: by triggering immune cells that recognize both UL6 and the same protein sequence on corneal cells. Still, Cantor says, "we had to show how viral infection could use this mechanism to actually induce disease."

So, in their current work, Cantor and his team members infected mice with either normal HSV-1 or a virus that they had genetically altered so that it lacked the UL6 protein. The result was striking: T cells from mice given virus containing native UL6 protein caused disease, while T cells of animals given the altered virus did not. Furthermore, more than 75% of mice infected with virus bearing the normal protein developed severe corneal autoimmune disease, whereas fewer than 20% of those infected with mutant virus did, and their symptoms were barely detectable.

Although researchers say the work demonstrates that molecular mimicry can play a role in triggering autoimmune disease, it is unlikely to be the whole story. "These results are clear, as far as they go," says Abner Notkins, a viral immunologist at the National Institute of Dental Research in Bethesda, Maryland. "But in many autoimmune diseases, T lymphocytes and antibodies target many proteins, not just the initial one mimicked by a virus. The model does not account for these other targets."

Cantor agrees, but says molecular mimicry must be at least one piece of the puzzle. "Now," he says, "the task is to find out just how frequently this mechanism accounts for the link between infection and autoimmunity." If it is common and the viral triggers can be identified, he adds, the work might aid efforts to develop therapies aimed at preventing autoimmune damage. For instance, if researchers can determine which sequences trigger human T cells, it may be possible to induce the patient to develop tolerance to the viral protein before it sends the immune system down the road to self-destruction.

–Steven Dickman

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