importance in the control of virus replication *in vivo*. However, there may be many limitations to the use of adoptive transfer as a potential immunotherapeutic strategy to potentiate and maintain a strong HIV-specific CTL response *in vivo*. The production of large numbers of HIV-specific CTL for infusion requires specialized laboratory skills and facilities; multiple infusions are necessary to maintain appropriate numbers of virus-specific CTL *in vivo*; and the transient and suboptimal antiviral effect may lead to the emergence of virus mutants[14].

The third HIV paper in this issue by Vocero-Akbani *et al*.[3] reports on a novel gene therapy approach that exploits the HIV protease (which is crucial for the production of infectious virions) to kill HIV-infected cells. Many conventional therapies use small molecule drugs to target the HIV protease and block its activity. But in this new study, the investigators have taken a different approach. They have genetically engineered a fusion protein composed of caspase-3, an apoptosis-promoting protein, and the TAT transduction domain of HIV. This TAT-Casp3 protein is specifically activated by the HIV protease because endogenous caspase-3 cleavage sites have been replaced by HIV proteolytic cleavage sites. Transduction of infected and uninfected T cells with TAT-Casp3 results in selective elimination of the former. In uninfected cells that lack HIV protease, TAT-Casp3 remains inactive. The authors elegantly show that this strategy leads to massive apoptosis of HIV-infected but not uninfected Jurkat cells treated with TAT-Casp3 protein. Their study provides a new conceptual approach for developing strategies that specifically target HIV-infected cells. Obviously, many questions—for example, the efficiency of transduction of these modified apoptosis-promoting proteins in other HIV target cells, such as macrophages and dendritic cells, and how to efficiently deliver the fusion protein *in vivo*—must be answered before the potential of this new anti-HIV therapy can be established.

These three studies, although dealing with quite different issues, contain a common message. They spell out the urgent need to develop alternative therapeutic strategies—both immune-based interventions[15] to either achieve immune restoration or to better subdue virus replication, and gene therapy approaches that exploit vital components of HIV's machinery to induce viral suicide.

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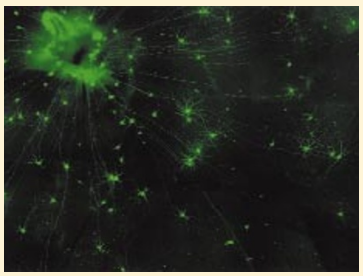
Autoimmune T cells—not always the bad guys



Autoimmune attack of central nervous system (CNS) components is associated with devastating neurodegenerative diseases such as multiple sclerosis. Although autoimmune T cells are usually viewed as detrimental, Schwartz and colleagues report on page 49 of this issue the unexpected finding that they also can be neuroprotective. They administered T cells specific for myelin basic protein (MBP) to rats in which the optic nerve had been injured and, to their surprise, found that the immune cells protected the injured neurons from further damage.

"We were somewhat worried because all of these results are against the conventional wisdom of generations of immunologists," says Schwartz. "We have all been taught that the immune system is designed to be kept out of the CNS. These results prompt us to consider the possibility that T cell-mediated immune activity against self CNS components can do good for the immune system as well."

CNS injury is accompanied by changes in the concentration of extracellular ions, free radicals, and neurotransmitters, resulting in the gradual secondary loss of adjacent undamaged neurons. The photograph shows a whole-mounted retina excised after partial injury to the optic nerve. Each retrogradely labeled cell (green) represents a neuron that escaped the primary lesion and has not yet undergone secondary degeneration. Schwartz and co-workers demonstrate that MBP-specific T cells inhibit the eventual secondary degeneration of these neurons after the primary injury. These results are particularly interesting given their previous observation that macrophage-induced inflammation can promote neuron re-growth after axonal transection (*Nature Med*. **4**, 814–821; 1998).

But how does the immune response help to preserve these neurons? The authors suggest that MBP-specific T cells cause a transient reduction in the electrophysiological activity of damaged neurons, which may prevent depletion of their energy supplies keeping them alive longer.

Although their recent investigation into 'benign autoimmunity' has caused them to diverge from their initial goal—to determine the potential of infiltrating T cells to deliver gene therapy vectors to the CNS—the Schwartz team still intends to pursue the notion of T cells as gene therapy vehicles. "At areas in which there is no lesion, T cells don't accumulate. Self-reactive T cells are the perfect gene delivery vehicle because of their specificity for CNS lesion sites," says Schwartz.

Kristine Novak