non-typical open-closed transitions. The authors estimate that the single-channel conductance is low, but that channel density in the peribacteroid membrane is high ($300\text{--}2,400\ \mu\text{m}^{-2}$). Most importantly, they show that total ammonium currents carried by the NH_4^+ -permeable channels can easily accommodate physiological rates of ammonium uptake into the plant. The identification of the NH_4^+ uptake channel in the peribacteroid membrane will allow further characterization of its proposed physiological function and regulation mechanisms (for example, block by calcium²), and for comparisons with other cation transporters to be made.

The biophysical and cell biological characterization, as well as the cloning, of

initial cDNAs encoding key members of the NPK macronutrient transporters are now allowing accurate analyses of numerous physiological questions. For example, interactions of transporters with toxic compounds in soils, such as herbicide uptake by the low-affinity *CHL1* nitrate transporter³, or the interactions of toxic cations with cation-uptake transporters, are now open to investigation. We are no doubt in for surprises as we find out more about plant macronutrient uptake and the associated environmental stresses. □

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HIV

An elusive soluble suppressor

Anthony S. Fauci

THE study by Baier *et al.* on page 563 of this issue¹ describes the identification of a soluble factor (lymphokine) secreted by CD8^+ -bearing T lymphocytes that inhibits the replication of the human immunodeficiency virus (HIV). The potential implications of this study are substantial.

A variety of classical antibody and cell-based immune responses have been described that contribute to anti-HIV immunity, including neutralizing antibodies, antibody-dependent cellular cytotoxicity, natural killer cells, and HIV-specific cytotoxic T cells (reviewed in ref. 2). Several years ago, a phenomenon of non-cytolytic suppression of HIV replication was described³: the suppression was shown to be due to a soluble factor or factors derived from CD8^+ T lymphocytes of HIV-infected individuals, and these findings were subsequently corroborated by several laboratories (reviewed in ref. 4). Similar phenomena and factors have been described in the simian immunodeficiency virus (SIV) model of HIV infection in the monkey⁵ (also reviewed in ref. 4).

Despite continued attempts to isolate the factor(s), however, their precise identification has remained elusive. It is likely that the difficulties can be explained at least in part by the facts that there may be a family of suppressor factors, and that attempts to purify and assay just one of them have resulted in marked decreases and inconsistencies in suppressor activity compared to that of the crude supernatants. This may very well be the case with the human factor cloned by Baier and colleagues, which gives lower levels of suppression than those seen in studies on crude supernatants³⁻⁵.

Baier *et al.* identified a factor that had been previously described⁶ in a different context from HIV. The factor has been

designated lymphocyte chemoattractant factor (LCF) or IL-16, and it suppresses HIV replication in CD8^+ T-lymphocyte-depleted human peripheral blood mononuclear cells¹. The current authors had previously identified an "immunodeficiency-virus-suppressing lymphokine" (ISL) that was secreted by CD8^+ T cells of African green monkeys (AGM) and which potentially suppressed the replication of SIV in monkey cells as well as the replication of HIV in human CD4^+ T lymphocytes⁵. Baier *et al.* note that the sequences encoding human IL-16 and AGM IL-16 are very alike, in that the IL-16 genes of humans differ from those of African green monkeys in only 16 of their 390 coding nucleotides, resulting in only seven non-clustered amino-acid changes.

It is not surprising, despite the intensive and hitherto unsuccessful search for the identity of the soluble suppressor factor(s) of HIV replication, that at least one of the factors is a lymphokine with other well-known functions apart from suppression of HIV replication. In this regard, it is highly likely that other discrete factors with different non-HIV related functions will be described that also suppress the replication of HIV. This might lead to understandable confusion as to the true identity of the suppressor factor; in fact, it is likely that a combination of factors will be required for optimal suppression.

It is out of the question that soluble factor(s) have emerged in the host species specifically to suppress HIV replication. Rather, it is conceivable that the virus has evolved to use existing factors of its host to its own advantage. Because the suppression of virus replication by the newly cloned factor is non-cytolytic (that is, it does not involve host destruction of infected host cells), a consequence might

be the establishment of latency, with the resulting implication of prolonged viral infection without killing the host.

Although CD8^+ T-lymphocyte-derived LCF (IL-16) is a natural CD4 ligand⁷, the ways in which it inhibits HIV replication are unknown. It is likely that those mechanisms will be quickly elucidated as investigators come to grips with the cloned factor. It will be important to determine the effect of the factor on replication of primary isolates of HIV, as well as on *in vitro* endogenous replication of virus in cells from HIV-infected individuals.

Work on the CD8^+ T-lymphocyte-suppressor phenomenon has been seriously impeded by the unavailability of purified factors, necessitating the use of crude or only partially purified supernatants. In essence, the new study¹ opens up fresh avenues of research into pathogenesis, treatment and vaccine development. Of particular importance is the possibility of a novel form of 'immune-based' therapy. Transplantation of tissue and reinfusion of *ex vivo* expanded autologous immune-competent cells into HIV-infected individuals have met with the difficulties common to any such approach, including tissue rejection, graft-versus-host reactions and unforeseen toxicities (reviewed in ref. 8). The availability of a soluble factor with demonstrable ability to suppress HIV replication will certainly expand the options for experimental therapy. It is particularly relevant that there is considerable homology between human IL-16 and AGM IL-16, adding importance to the SIV monkey model of HIV infection.

Of course, there is no guarantee that such therapy would be effective, and more than a decade of experience with HIV has taught us to be conservative in our projections of success until properly designed and controlled clinical trials have been performed. However, at the very least, the availability of this and other HIV-suppressive factors alone or in combination will tell us a great deal about HIV pathogenesis, and in this respect will provide the framework for the development of strategies for therapy and vaccine development. □

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1. Baier, M., Werner, A., Bannert, N., Metzner, K. & Kurth, R. *Nature* **378**, 563 (1995).
2. Pantaleo, G., Graziosi, C. & Fauci, A. S. *New Engl. J. Med.* **328**, 327-335 (1993).
3. Walker, C. M. *et al. Science* **234**, 1563-1566 (1986).
4. Mackewicz, C. & Levy, J. A. *AIDS Res. Hum. Retrovir.* **8**, 1039-1050 (1992).
5. Ennen, J. *et al. Proc. natn. Acad. Sci. U.S.A.* **91**, 7207-7211 (1994).
6. Cruikshank, W. W. *et al. Proc. natn. Acad. Sci. U.S.A.* **91**, 5109-5113 (1994).
7. LaBerge, S. *et al. J. Immun.* **155**, 2902-2910 (1995).
8. Fauci, A. S. *Science* **262**, 1011-1018 (1993).