ly, in the presence of a molar excess of soluble CD14.

One explanation for this is that the CD14 could be damaged or inactivated upon release from cells. In any event, the absence of an effect of soluble CD14 at the relatively high concentrations present in plasma suggests that the released CD14 does not play an important role in blunting responses to LPS. The converse, however, may be true. Because cell-bound CD14 is important to a cell's response to LPS, depletion of CD14 from the cell surface through cleavage and release may effectively prevent a cell from responding to LPS. We have observed that stimulation of monocytes with LPS led to loss of surface CD14 (Table 1), which suggests a role for CD14 in the well-documented desensitization of leukocytes to the effects of LPS (*5*).

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REFERENCES AND NOTES

1. C. R. Maliszewski, E. D. Ball, R. F. Graziano, M. W. Fanger, *J. Immunol.* **135**, 1929 (1985); C. R. Maliszewski, J. Currier, J. Fisher, R. J. Smith, M. W. Fanger, *Mol. Immunol.* **24**, 17 (1987).
2. V. Bazil *et al.*, *Eur. J. Immunol.* **16**, 1583 (1986); V. Bazil *et al.*, *Mol. Immunol.* **26**, 657 (1989).
3. S. D. Wright, R. A. Ramos, P. S. Tobias, R. J. Ulevitch, J. C. Mathison, *Science* **249**, 1431 (1990).
4. In a recent study of septic patients, S. J. H. Van Deventer *et al.* [*Lancet* **i**, 605 (1988)] found maximum serum levels of 0.1 ng of LPS per milliliter ($<2 \times 10^{-11}$ M), while other patients with 20-fold less LPS were gravely ill. This is consistent with the finding of H. R. Michie *et al.* [*N. Engl. J. Med.* **318**, 1481 (1988)] that injection of LPS to $\sim 0.5 \times 10^{-11}$ M in healthy human volunteers initiates TNF release and fever.
5. J. C. Mathison, *J. Clin. Invest.* **85**, 1108 (1990).

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Receptor-Mediated Activation of Immunodeficiency Viruses in Viral Fusion

The mechanisms underlying human immunodeficiency virus (HIV) infection, thus far elusive, have important implications in the development of vaccines and therapeutics. The report by Moore *et al.* (*1*) provides convincing evidence that soluble receptor proteins block HIV infection by removing the gp120 protein from the viral envelope. They suggest that gp120 stripping may initiate viral fusion. We have found that simian immunodeficiency virus (SIVagm) infection was enhanced in the presence of soluble receptor protein (sCD4) and have proposed that sCD4 enhancement could be caused by the modulation of the viral envelope, resulting in the exposure of fusogenic domains that are involved in viral fusion (receptor-mediated activation) (*2*). Activation of the viral membrane through receptor binding has been reported for other fusogenic viruses (*3*) and may be a common mechanism in viral fusion.

In this light, we could not reconcile the blocking effects of sCD4 on HIV with our model. Moore *et al.* have provided an answer to these conflicting observations. In contrast to the activation of SIVagm by sCD4 that leads to viral enhancement, inactivation of the viral membrane by sCD4 in the case of HIV-1 would result in the premature loss of fusogenic sites. Although Moore *et al.* suggest that gp120 stripping may be a normal process in the initiation and exposure of fusogenic domains in viral entry, we believe that inactivation by sCD4 is an abnormal process and does not reflect events occurring at the cell surface.

To account for the enhanced infection of SIVagm by sCD4, we proposed (*2*) that association of CD4 with the oligomeric complex of gp120 molecules would expose fusogenic domains. This would be followed closely by viral fusion, presumably through a second receptor interaction with the exposed sites on the transmembrane protein. The intact oligomeric structure of gp120, in association with the transmembrane proteins, is probably essential in providing an environment for the correct orientation and exposure of fusogenic sites. Dissociation or stripping of gp120 from the viral membrane as it penetrates would be considered the last stage in viral fusion. If this model is correct, then the premature stripping effects observed in HIV would destroy the exposed fusogenic domains, which would inactivate HIV.

In the case of SIVagm, we hypothesize that a stronger association of gp120 with its transmembrane counterpart would allow for the activation by sCD4, which would result in enhanced viral infection through multiple sites on the virus. Stripping of gp120 by sCD4 in HIV would therefore not support viral infection because the integrity of the viral membrane would be lost. The final stage in viral entry would be artificially induced before the virus associates with the cell membrane.

In light of these findings, one should view therapies that involve receptor molecules with caution. It is possible that HIV strains may exist with more stable membranes. Therapeutic administration of sCD4 might activate more stable fusogenic domains on the virus, resulting in an enhanced rate of infection rather than viral inactivation.

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REFERENCES

1. J. P. Moore, J. A. McKeating, R. A. Weiss, Q. J. Sattentau, *Science* **250**, 1139 (1990).
2. J. S. Allan, J. Strauss, D. W. Buck, *ibid.* **247**, 1084 (1990).
3. D. C. Flynn, W. J. Meyer, J. M. Mackenzie, Jr., R. E. Johnston, *J. Virol.* **64**, 3643 (1990).

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Response: Allan presents a model for sCD4-mediated enhancement of immunodeficiency virus-cell fusion (*1*). Enhancement was first observed for SIVagm infection of CD4-positive cells (*2*) and has since been demonstrated for HIV-2 (*3*). We have observed sCD4 enhancement of HIV-1 infection under certain conditions, but it is variable and incompletely characterized at present (*4*). A consequence of sCD4 binding to virions of HIV isolates adapted to tissue culture is the dissociation of gp120 from gp41 on the virion surface (*5–8*). We (*7*) and Allan *et al.* (*2*) hypothesized that sCD4 binding to SIVagm virions induces the viral envelope to expose cryptic fusogenic domains and that this enhances the efficiency of virus-cell fusion.

Conformational changes in the structure of gp120 or gp41 occur after CD4 binding. Thus sCD4 binding to gp120 increases the exposure of the V3 domain of gp120 to proteinases in vitro (*9*, *10*), and sCD4 binding to HIV-1 envelope-expressing cells induces conformational changes in gp120 that lead to increased exposure of gp41 epitopes (*6*, *10*). Changes in conformation can occur without complete dissociation of gp120 from gp41 (*10*). Therefore gp120 shedding may take place at a late stage of the fusion reaction (*1*) or may not occur at all at the cell surface. We suggest that an ordered sequence of conformational changes in gp120, gp41, and possibly CD4 (*11*) occurs during the fusion reaction. Perhaps this sequence involves cellular proteins in addition to CD4 (*9*, *12*).

Precisely how CD4 activates the fusion

potential of the gp120/gp41 complex is obscure, but CD4 may alter the conformation of neighboring molecules of an oligomer that are either occupied or unoccupied by CD4 (*13*). The number of component glycoproteins in a complex on the virion is controversial, but one view is that the structure is a dimer of dimers (*14*). Another view is that the structure is trimeric (*15*). Our data on sCD4 binding to virions and gp120 shedding are best explained if one assumes that sCD4 occupancy of multiple components of an oligomer is necessary for dissociation of the entire complex (*8, 13*).

Crucial to the sCD4 enhancement model (*1*) is the question of whether sCD4 induces gp120 loss from HIV-2 or SIV virions. There are indications that gp120 is retained more efficiently on HIV-2 than on HIV-1 virions (*16*), but the stability of the HIV-2/SIV outer envelope glycoprotein after sCD4 binding is not known. If HIV-2 or SIV gp120 remains on the virion as an sCD4 complex, then conformational changes induced in the envelope glycoproteins may prime the system for fusion (*1, 2, 7, 10*). This may require that the fusion peptide on gp41 not be exposed prematurely and inactivated. Indeed, it may require that gp120 and gp41 remain associated. However, sCD4 enhancement of HIV-2 infection is more complex than was suggested by initial observations of enhancement with SIVagm (*1, 2*). For example, enhancement has not been found to occur with sCD4-immunoglobulin chimaeras (*3, 4*), and we have found that enhancement of HIV-2 infection depended on the cell type and also occurred with CD4-negative cells (*4*). One plausible explanation for this is that when sCD4 binds to the HIV-2 or SIV virion, it exposes a binding site on gp120 or gp41 for an unidentified cellular protein that is necessary for virus-cell fusion. For example, a region of HIV-1 gp41 that is exposed after CD4 binding (*10*) corresponds to a putative binding site for a cell surface protein (*17*).

There are limitations to the present models. The use of sCD4 in solution to mimic virion binding to CD4 on the cell surface is not wholly satisfactory. Events within the virion-cell complex linked through gp120, CD4, and conceivably other proteins may differ in detail from events that happen when sCD4 binds to a virion (*7*).

We have no biochemical data for SIVagm and insufficient data at present for HIV-2, the viruses for which sCD4 enhancement is most consistently observed. Therefore we are limited in our analysis to extrapolations from HIV-1 isolates adapted to tissue culture, viruses with properties that are somewhat different from those of HIV-2, SIV, and perhaps primary HIV-1 isolates. The elucidation of the mechanism of HIV-2 and SIV enhancement of infection may reveal that receptor activated virus-cell fusion is a common feature of retroviral fusion mechanisms.

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REFERENCES

1. J. S. Allan, *Science* **252**, 1322 (1991).
2. _____, J. Strauss, D. W. Buck, *ibid.* **247**, 1084 (1990).
3. I. Sekigawa, S. M. Chamow, J. E. Groopman, R. A. Byrn, *J. Virol.* **64**, 5194 (1990); A. Werner, G. Winowsky, R. Wurth, *ibid.*, p. 6252.
4. P. R. Clapham, J. A. McKeating, A. McKnight, R. A. Weiss, unpublished observations.
5. R. Kirsh *et al.*, *AIDS Res. Human Retroviruses* **6**, 1215 (1990).
6. T. Hart *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 2189 (1991).
7. J. P. Moore, J. A. McKeating, R. A. Weiss, Q. J. Sattentau, *Science* **250**, 1139 (1990).
8. J. P. Moore, J. A. McKeating, W. A. Norton, Q. J. Sattentau, *J. Virol.* **65**, 1133 (1991).
9. G. Clements *et al.*, *AIDS Res. Human Retroviruses* **7**, 3 (1991).
10. Q. J. Sattentau and J. P. Moore, *J. Exp. Med.*, in press.
11. D. Healey *et al.*, *J. Exp. Med.* **172**, 1233 (1990).
12. P. A. Ashorn, E. A. Berger, B. Moss, *J. Virol.* **64**, 2149 (1990); P. R. Clapham, D. Blanc, R. A. Weiss, *Virology* **181**, 703 (1991).
13. J. A. McKeating and J. P. Moore, unpublished observations.
14. R. W. Doms, P. L. Earl, S. Chakrabarti, B. Moss, *J. Virol.* **64**, 3537 (1990).
15. C. D. Weiss, J. A. Levy, J. M. White, *ibid.*, p. 5674.
16. D. J. Looney *et al.*, *J. Acq. Immun. Def. Synd.* **3**, 649 (1990).
17. N. M. Qureshi, D. H. Coy, R. F. Garry, L. A. Henderson, *AIDS Res. Human Retroviruses* **4**, 553 (1990).

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