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A Monoclonal Antibody to the CDR-3 Region of CD4 Inhibits Soluble CD4 Binding to Virions of Human Immunodeficiency Virus Type 1

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The CDR-3 region of CD4 has been proposed to be involved in the fusion reaction between human immunodeficiency virus type 1 (HIV-1) and CD4$^+$ cells, either at a stage involving virus binding or subsequent to virus binding. Part of the evidence for this has been the observation that monoclonal antibodies (MAbs) to CDR-3 block HIV infection potently without strongly inhibiting the binding of monomeric gp120 to CD4. Here I show that, in a system using oligomeric, virion-bound gp120, a MAb to CDR-3 resembles those to CDR-2 in that it inhibits soluble CD4 binding to virions. Consequently, ternary complexes of MAb-soluble CD4-gp120 cannot be detected with CDR-2 MAbs and are detectable only at a very low level with a CDR-3 MAb, but they clearly form when a control MAb to CD4 domain 4 is used. Although not in direct conflict with previously published data on the role of CDR-3 MAbs in the inhibition of HIV-1 infection, these experiments do not support the hypothesis that the CDR-3 region is specifically involved in virus entry at a postbinding stage.

Human immunodeficiency virus (HIV)-cell fusion is initiated by an interaction between the viral glycoprotein gp120 and the cell surface differentiation antigen CD4 (for reviews, see references 9, 13, 23, 33, and 37). The high-affinity binding site for gp120 on CD4 has been defined by mutagenesis, antibody-blocking, and crystallographic techniques as comprising the CDR-2-like loop and supporting β-strands of domain 1 (D1) (1, 2, 10, 31, 32, 34, 41). More specifically, amino acids Phe-43, Lys-46, and Arg-59 are candidates for contacting gp120 directly to form intramolecular bonds that are both polar and hydrophobic (10, 29, 37). There has also been considerable speculation concerning the role of a separate segment of CD4-D1, the CDR-3-like region (amino acids 81 to 102), as a second binding site for gp120 during HIV-mediated, CD4-dependent fusion (3, 13). The platform on which this hypothesis is built has four legs. Firstly, benzoylated, acetylated peptides corresponding to CDR-3 have anti-HIV type 1 (HIV-1) activity and prevent HIV-1-mediated syncytium formation (17, 19, 20, 27, 28, 35). Moreover, these derivatized peptides have variously been shown to inhibit gp120 binding to CD4 (17, 20), to mimic soluble CD4 (sCD4) by inducing gp120 dissociation from gp41 (4), and to bind to the V3 region of gp120 (3, 40). Secondly, several mutations in CDR-3 reduce the gp120-binding ability of CD4 (2). Thirdly, a polymorphism at amino acid 87 (Glu or Gly) between human and chimpanzee CD4 has been reported to reduce the ability of chimpanzee CD4 to induce cell-cell fusion (8). Finally, monoclonal antibodies (MAbs) directed against the CDR-3 region potently antagonize HIV-1 infection while only partially inhibiting the gp120-CD4 interaction (39). However, in other very recent studies, each of the first three lines of experimental evidence has been shown to be flawed (5, 10, 30, 34, 36). Here I present data which may clarify the role of CDR-3 MAbs in infection inhibition.

MAbs specific for the CDR-3 region of CD4 have been shown not to strongly inhibit the binding of soluble, recombinant gp120 to cell surface CD4 (39). Furthermore, ternary complexes between CDR-3 MAbs, sCD4, and recombinant gp120 can be demonstrated in enzyme-linked immunosorbent assay (ELISA)-based or radioimmunoprecipitation assays, whereas no such complexes are possible with MAbs to the CDR-2 region of CD4 (39). However, the experiments mentioned above used monomeric gp120, and it seemed possible that a different pattern of results might be obtained in a more physiologically relevant situation with oligomeric gp120, as found on the surfaces of virions. I therefore evaluated the ability of a panel of CD4 MAbs to interfere with the binding of sCD4 (39) to virions of the HIV-1 RF isolate, using a gel filtration-ELISA system described elsewhere (24–26). The CD4 MAbs used were Leu3a, which recognizes CD4-D1 at a site overlapping the CDR-2 region (32); L77, also binding in CDR-2 but at a site distinct from Leu3a (39); L71, which binds to CDR-3 (39); and L120, which binds to an epitope in D4 (16). Leu3a, L71, and L77 all inhibit HIV infection; L120 does not (16, 26, 39). L71 was selected to represent the panel of CDR-3 MAbs used in a previous study, as it was the most potent inhibitor among these antibodies (39).

A consequence of sCD4 binding to virions from T-cell-line-adapted HIV-1 isolates such as RF is the induction of gp120 dissociation from gp41 (4, 15, 18, 24, 25), although this is not likely to be part of the physiological fusion reaction (26, 38). The effects of CD4 MAbs on this process were evaluated (Fig. 1). At 37°C, sCD4 (220 nM) reduced the amount of gp120 on the virions by about fourfold. This effect was inhibited by Leu3a, L71, and L77 but not by the D4 MAb L120 (Fig. 1a). Approximately three- to fivefold-greater concentrations of L71 and L77 than Leu3a were required to give equivalent degrees of inhibition. For L77, this reduction in potency is consistent with its approximately threefold-lower affinity for CD4 compared with that of Leu3a (39). At 4°C, at which sCD4 does not induce rapid gp120 dissociation from RF virions (24, 26), none of the MAbs, with or without sCD4, had any significant effect on virion gp120 levels (Fig. 1b).

To assess how the CD4 MAbs might be acting, we measured the formation of sCD4-virion complexes (Fig. 2).

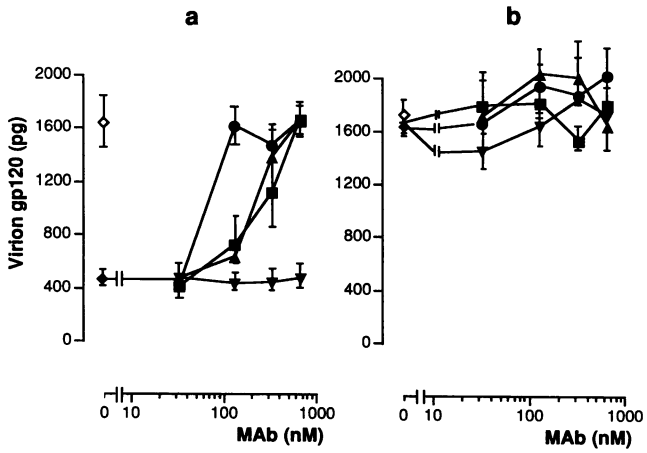

FIG. 1. Effect of CD4 MAbs on sCD4-induced gp120 dissociation from RF. RF virions were incubated for 1 h at 37°C (a) or 2 h at 4°C (b) with 220 nM sCD4 and the indicated concentrations of Leu3a (●), L71 (■), L77 (▲), and L120 (▼) or with no MAb (◆) or without either sCD4 or MAb (◇) in a total volume of 100 μl. Virions and their bound sCD4 or sCD4-MAb complexes were separated from free gp120, sCD4, and MAb by gel filtration on Sephacryl S-1000. The virion fraction was collected and disrupted with 1% Nonidet P-40 detergent. Virion gp120 levels were determined by ELISA and are presented as means ± standard deviations (error bars) of triplicate ELISA determinations. sCD4 and MAbs had no effect on the amount of virion-associated p24 (data not shown).

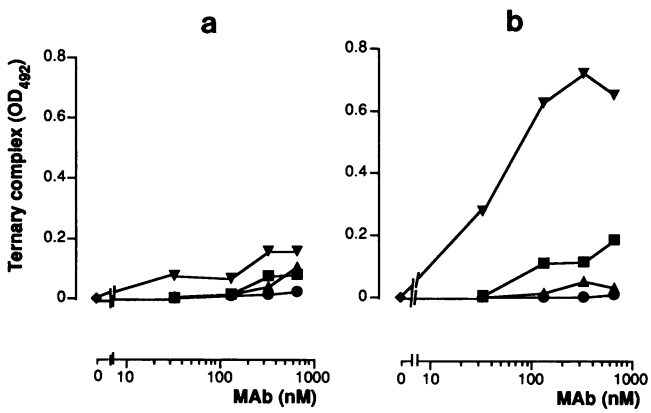

FIG. 3. Formation of ternary complexes among CD4 MAbs, sCD4, and RF. RF virions were incubated for 1 h at 37°C (a) or 2 h at 4°C (b) with 220 nM sCD4 and the indicated concentrations of Leu3a (●), L71 (■), L77 (▲), and L120 (▼) or with no MAb (◆). Virions and their bound MAb-sCD4 complexes were collected by gel filtration, and MAb bound to virions via sCD4 was quantitated by ELISA. Data are means of duplicate ELISA determinations. In the absence of sCD4 and MAb, the mean assay background value was 0.074, which has been subtracted from all values. OD_{492}, optical density at 492 nm.

At 37°C, the level of stable complex formation was low because, once formed, gp120-sCD4 complexes dissociate from the virions. The low level of net sCD4 binding was, however, reduced by Leu3a but not by L71, L77, or L120 (Fig. 2a). It was notable, however, that despite the substantial increase in gp120 retention on the virions in the presence of L71 and L77 (Fig. 1a), there was no corresponding increase in the amount of sCD4-virion complexes (cf. Fig. 2a). This suggested that, like Leu3a, L77 and the CDR-3 MAb L71 were acting by antagonizing the binding of sCD4. This was confirmed for L71 when sCD4 binding to virions was measured at 4°C, a temperature at which there is no gp120 shedding (Fig. 1b and 2b). At this temperature, L71 clearly inhibited sCD4 binding to RF, although at three- to fourfold-higher concentrations than those required for Leu3a. L77 had only a weak effect on sCD4 binding at the highest concentration tested, and L120 was not inhibitory (Fig. 2b).

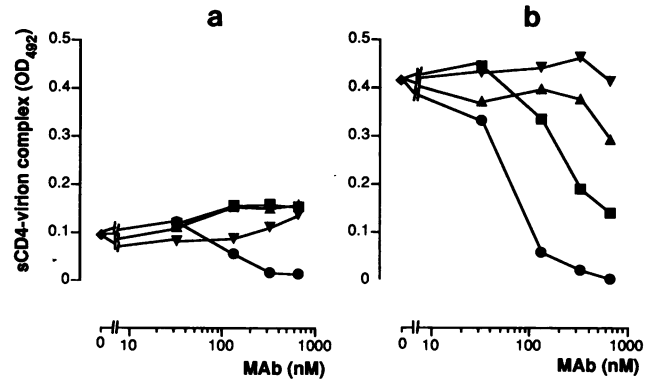

FIG. 2. Effect of CD4 MAbs on the binding of sCD4 to RF. RF virions were incubated for 1 h at 37°C (a) or 2 h at 4°C (b) with 220 nM sCD4 and the indicated concentrations of Leu3a (●), L71 (■), L77 (▲), and L120 (▼) or with no MAb (◆). Virion gp120-sCD4 complexes were collected by gel filtration and quantitated by ELISA using rabbit anti-sCD4 antiserum to detect bound sCD4. Data are means of duplicate ELISA determinations. In the absence of sCD4, the assay background value was 0.060, which has been subtracted from all values. OD_{492}, optical density at 492 nm.

If the CDR-3 MAbs were allowing sCD4 to bind to the virions but subsequently blocking sCD4-induced gp120 dissociation (as observed with the CD4-D2 MAb 5A8 [26]), then ternary complexes of MAb-sCD4-virions should be detectable. These were not found (Fig. 3). At 37°C, a small amount of ternary-complex formation among L120, sCD4, and the residual unshed virion gp120 was observed. Only trace amounts of ternary complexes were formed with L71 and L77 at the highest concentrations tested (Fig. 3a). As expected, Leu3a did not form a ternary complex, as it competes with gp120 in binding to sCD4 (cf. Fig. 2). At 4°C, there was clear formation of ternary complexes of L120-sCD4-virion gp120, and the level of complexing was substantially greater than that seen at 37°C (Fig. 3b), because of the increased gp120 retention on the virions after sCD4 binding at the lower temperature (cf. Fig. 1b). A low level of ternary complexes was detectable with L71, but no such complexes were observed with L77 or Leu3a (Fig. 3b). This result is consistent with the data described by Truneh et al. (39).

Although complete inhibition of sCD4 binding to virions by L71 at 4°C could not be demonstrated, this MAb was a more potent inhibitor than the CDR-2 MAb, L77 (Fig. 2b). Furthermore, the increased retention of gp120 on virions at 37°C in the presence of L71 (or L77) (Fig. 1a) was not mirrored by an increase in the amount of virion-sCD4 complexes (Fig. 2a). This suggests that most of the extra gp120 retained on the virion was present as free gp120, which is why it remained bound, and that sCD4 had therefore been prevented from binding. Consistent with this, although some ternary MAb-sCD4-virion complexes could be detected with L71 (but not with Leu3a or L77) at 4°C,

they were present at a very low level, much lower than that observed with the control D4 MAb, L120 (Fig. 3b).

I infer from the data that the CDR-3 MAb L71 is a weak inhibitor of sCD4 binding to virions and that this is the principal mechanism by which it, like the more potent CDR-2 MAb Leu3a, blocks sCD4-induced gp120 dissociation from virions. By extrapolation, I suggest that inhibition of gp120-CD4 binding is the principal way in which CDR-3 MAbs block HIV infectivity and syncytium formation. The data should not, however, be taken to imply that there is a direct interaction between CDR-3 and gp120 that is blocked by CDR-3 MAbs; it is more probable that the presence of CDR-3 MAbs on CD4 hinders binding of the CDR-2 region to gp120 by a steric effect that is most noticeable in the crowded environment of a virion's surface. Antibodies are large compared with CD4. It is notable that a monovalent Fab fragment of MAb L71 was found to allow some binding of sCD4 to oligomeric, cell surface gp120-gp41 complexes, yet it prevented sCD4-induced syncytium formation (14). In contrast, the bivalent L71 MAb completely blocked sCD4 binding (14), as found in the present study (Fig. 2).

It is still, however, both curious and unexplained that L71 is almost as potent an inhibitor of HIV-1 infection as Leu3a (39), given its relative ineffectiveness as a gp120-CD4 antagonist (39) (Fig. 2b). Furthermore, a recent report suggests that a different CDR-3 MAb, 13B8-2, behaves much as L71 in some respects but not in others: it blocks monomeric gp120 binding to CD4 and prevents HIV-induced, CD4-dependent syncytium formation, yet 13B8-2 is reported to inhibit neither the binding of HIV virions to CD4-expressing cells nor their ability to infect the cells (11). However, it is possible that the failure of 13B8-2 to inhibit infectivity by cell-free virus is more apparent than real: Corbeau et al. washed excess MAb and unbound virions from the cells after the initial incubation period (11), thereby potentially allowing MAb dissociation from the cells to take place and virus entry to occur. Whether a CD4 MAb is present to inhibit secondary infection cycles is also an important factor in infectivity assays (26).

There may be as-yet-unappreciated subtleties in the actions of CDR-3 MAbs. One possibility is that the presence of a CDR-3 MAb prevents the packing of sufficient CD4 molecules onto the spatially constrained surface of a glycoprotein spike and blocks the formation of a fusion complex and, subsequently, syncytium formation. There are quantitative differences in the rates of fusion complex formation and full-blown syncytium formation (12), but it seems unlikely that there will be a qualitative difference between the mechanisms of virus-cell and cell-cell fusion (23). The mode of action of CDR-3 MAbs might therefore include noncompetitive, as well as competitive, inhibition of the gp120-CD4 binding reaction. While L71 is clearly distinguishable from the D2 MAb 5A8 in its mechanism of action (26), there may also be some similarities in the ways in which they inhibit HIV-1 infection. For example, gp120 shedding is probably more sensitive to weak antagonists than sCD4 binding is (26), as shedding requires multiple occupancy of gp120 molecules on a glycoprotein spike (24). The data in Fig. 1 would not be inconsistent with L71 preventing the packing of sufficient sCD4 molecules onto a gp120 oligomer, but they do not prove the concept.

Other studies have shown that there is no compelling evidence that CDR-3 amino acids are important for contacting gp120 (10, 34), that CDR-3-based peptides are not specific inhibitors of the gp120-CD4 interaction (22, 30) and also inhibit human T-cell leukemia virus-1 infectivity (30), and that the polymorphism between chimpanzee and human CD4 is unimportant for virus-cell fusion (5, 36). Here I present evidence that MAbs to the CDR-3 region act, at least in part, as inhibitors of the gp120-CD4 interaction by virtue of their bulk. Others have made similar observations (11, 14). Taken together, these data do not support the theory that the CDR-3 region of CD4 acts as a second binding site for gp120 in HIV-cell fusion (13). Although an interaction between CDR-3-derived peptides and the V3 loop of gp120 can undoubtedly occur under experimental conditions (3, 22, 40), probably by virtue of their strong, opposing charges, it is highly unlikely that this reaction is anything other than an in vitro phenomenon. There is no evidence that it occurs between the V3 loop and the CDR-3 region of CD4 in situ. CDR-3-based peptides induce the dissociation of gp120 from gp41 (4, 22), but then so does dextran sulfate (6, 22), which also binds to the gp120 V3 loop because of its polyanionic nature (7, 22). CDR-3 may have a role in normal CD4-mediated T-cell activation (21), and it is not inconceivable that interference with this could influence syncytium formation. The true mechanism of HIV-mediated, CD4-dependent syncytium formation remains to be definitively established. However, all four legs that support the platform for the direct involvement of CDR-3 as a domain interactive with gp120 have now been chopped away, and the model will presumably fall.

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