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Characterization of Antibodies That Inhibit HIV gp120 Antigen Processing and Presentation

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Background

The capacity of Ab to alter antigen uptake and processing resulting in enhanced or suppressed antigen presentation has been demonstrated with a number of antigens, including tetanus toxoid, β-galactoside, apo-cytochrome c, and HIV-1 envelope glycoproteins [1–6]. In the case of HIV-1, the inhibitory activity is correlated with the serum Ab titers to the CD4-binding site (CD4bs) of gp120 [7]. In fact, by screening a panel of human anti-gp120 mAb, we ascertained that this inhibitory activity is mediated by Ab to the CD4bs; Ab to V2, V3, C2, or C5 did not exhibit such effect [1]. In previous studies only high affinity anti-CD4bs mAb were examined; these mAb completely block MHC class II presentation of gp120 antigens [1, 2]. However, it is not known if all anti-CD4bs Ab equally mediate such a strong inhibition. Since gp120/mAb complex formation was shown to be critical for anti-CD4bs mAb to block gp120 processing and presentation [1, 2], we postulated that the Ab affinity could be a key determinant for their suppressive activity.

Material and methods

In the present study we selected a panel of six anti-CD4bs mAb with different relative affinities for gp120, and examined their ability to suppress gp120 presentation to CD4 T cells. In addition, we tested CD4i mAb binding to the chemokine-receptor-binding site that, similar to anti-CD4bs mAb, were previously reported to render gp120 more resistant to degradative enzymes [7]. For comparison, a mAb specific for a conformation-dependent epitope outside the receptor binding sites and a relatively high affinity anti-V3 mAb were also tested. The ability of each of these mAb to suppress class II antigen presentation to gp120-specific CD4 T cells was correlated with the mAb affinity for gp120. The uptake of gp120 by APC was also evaluated in the presence of these mAb. Furthermore, we measured the stability of the mAb-gp120 interaction at acidic pH representing the endolysosomal environment in APC and quantified the effect of the mAb on the rate of gp120 proteolytic processing by lysosomal enzymes in vitro.

Results

Anti-CD4bs antibodies that completely obstruct gp120 presentation exhibit three common properties: relatively high affinity for gp120, acid stable interaction with gp120, and the capacity to slow the kinetics of gp120 proteolytic processing. None of these antibodies prevents gp120 internalization into APC.

Conclusion

The present studies demonstrate that poorly neutralizing anti-CD4bs Ab produced by chronically HIV-1 infected patients prevent the stimulation of gp120-specific CD4 T cell responses. These Ab form relatively stable high-affinity immune complexes, which are resistant to proteolytic processing by lysosomal enzymes. The presence of such Ab in sera of HIV-1-infected patients may contribute to the dearth of helper CD4 T responses to the virus envelope antigens and consequently weaken the anti-viral immu-

nity necessary to control the chronic HIV infection and disease.