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Role of anti-CD4-binding site antibodies in modulating gp120-specific CD4 T cell and antibody responses

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Background

MHC II presentation of antigenic peptides to CD4 T cell is critical for the initiation of the primary immune response as well as for the maintenance of the secondary immune response. Previously we have shown that gp120-specific human CD4+ T cell responses are inhibited in the presence of antibodies to the CD4-binding site of gp120 (CD4bs) [1,2]. But the role of these antibodies in modulating the immune responses to gp120 in vivo is not yet determined.

Materials and methods

The current study used the murine system to address the effects of anti-CD4bs antibodies on the presentation of gp120 antigen to MHC class II-restricted CD4 T cell and B cells. First, gp120 uptake and processing were assessed using mouse spleen cells as APCs in the presence of CD4bs or irrelevant mAbs. A sandwich ELISA was used to detect the remaining intact gp120 associated with the APCs over time. Gp120 presentation was then assessed with or without CD4bs mAbs using a gp120-specific mouse CD4 T cell clone in a T-cell proliferation assay. Structural changes induced by the CD4bs mAb binding that result in increased exposure of specific Ab epitopes were also assessed by ELISA. Finally, the in vivo effects of anti CD4bs mAbs were evaluated in Balb/c mice that had been immunized with gp120 complexed with CD4bs or control mAbs. Both lymphoproliferation and Ab responses were examined.

Results

Upon binding to gp120, CD4bs mAbs inhibited gp120 antigen processing in mouse APCs, such that gp120 complexed with anti-CD4bs antibody was mostly intact after 8 days in culture. In contrast, gp120 mixed with an irrelevant antibody was totally digested by the cells. Consistent with these results, the CD4bs Abs significantly suppressed the presentation of gp120 to mouse CD4 T cells. Furthermore, the binding of CD4bs mAb also induced structural alterations that increased the exposure of Ab epitopes in C1 and V3 but not in C5 and C2. When mice were immunized with gp120 in the presence of CD4bs mAbs, weaker lymphoproliferation (SI = 8) in response to gp120 was detected as compared to mice immunized with gp120 mixed with other mAbs (SI = 14). However, the mice immunized with the gp120/CD4bs complex had a higher titer of antibodies specific for gp120 and particularly Abs directed to V3.

Conclusion

Anti-CD4bs mAbs suppress gp120 antigen presentation to CD4 T cells both in vitro and in vivo due to their capacity to block gp120 processing. However, the binding of these Abs to gp120 increased the antigenic exposure of specific regions of gp120, resulting in induction of higher titers of Abs to gp120. Further studies are needed to evaluate the mechanisms by which the CD4bs Abs differentially modulate CD4 T cell response and antibody response to gp120.

References

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