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Treatment with anti-α4β7 integrin antibody reduces virus-mediated gastrointestinal pathology by targeting distinct mucosal tissues

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Background: Our laboratory has recently demonstrated that in vivo administration of a monoclonal anti-α4β7 antibody (α4β7-mAb) during acute SIV infection following

1) intravenous,

2) intra-rectal or

3) repeated low-dose intra-vaginal SIV challenge lead to markedly lower gastro-intestinal tissue viral loads compared to rhesus macaques (RM) treated with a control mAb.

The purpose of the present study was to compare the tissues that served as primary targets of viral infection in the α4β7-mAb versus control mAb-treated RM, in order to identify mechanisms by which α4β7-mAb antibody reduces virus-mediated gastrointestinal pathology.

Methods: Groups of 12-16 RM were administered a rhesus α4β7-mAb monoclonal antibody or an isotype-matched control rhesus IgG mAb (50 mg/kg) intravenously (i.v.) starting on day -1 and then every 3 weeks after infection. Each monkey was then repeatedly challenged with a low-dose SIVmac251 intra-vaginally or a single high-dose intrarectally.

Results: i.v. administration of α4β7-mAb blocked the detection of α4β7 on CD4+ T cells in the blood, cervicovaginal tissue, and GALT throughout the period of mAb administration. Viral DNA was reduced in GALT biopsies of the α4β7-mAb treated RMs compared to those treated with control mAb treated (median 3.5 vs. 12.8 copies/ng DNA respectively, p=0.006). Furthermore, in-depth analysis performed on a subset of animals (n=4/group) indicated that proviral DNA was 5 to 25 fold more abundant in jejunum, ileum, or colon of control-treated RMs compared to those treated with a4b7-mAb. In contrast, no difference in proviral loads in the spleen and lymph nodes from various sites was noted in the 2 groups. Immuno-PET/CT assisted analysis revealed that for animals with comparable plasma viral loads, the α4β7-mAb treated monkeys showed a lower signal in the large intestine. In addition, only the control treated monkeys showed a clear PET/CT signal in lymph nodes surrounding the genital tract suggesting that treatment with α4β7-mAb prevents viral replication in this tissue, leading to different patterns of tissue localization of the virus between the two groups.

Conclusions: The α4β7-mAb either protects or delays intravaginal SIV transmission, reduces gastrointestinal pathology following infection, and results in both quantitative and qualitative differences in the level of viremia and tissue localization of virus.

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