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OR.105. Activation of Intestinal Macrophages is Associated with Increased Control of HIV-1 Replication and Enhanced Microbial Translocation in African AIDS Patients

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The intestinal mucosa is an important target for HIV-1 replication and a site of severe CD4+ T depletion. Both phenomena appear to be driven by chronic immune activation. Despite the central role of intestinal macrophages in orchestrating inflammatory responses, these cells have received relatively little attention in the setting of HIV-1. Here, we examined the relationships between macrophage activation, viral load and bacterial translocation (plasma LPS) in cohort of treatment-naïve African AIDS patients with no evidence of enteric co-infections. Compared to the duodenum, HIV-1 infection in the colon was associated with a less severe depletion of CD4+ T cells, higher tissue viral loads, a greater increase in macrophages expressing innate response (CD14, CD16) and co-stimulatory (CD80, CD86) receptors, and a slower rate of CD4+ T cell restoration following the initiation of ART. Also in the colon, but not the duodenum, a negative correlation was detected between the frequency of CD14+ macrophages and tissue viral loads. In contrast, a strong positive association was observed between CD14+ macrophages and plasma LPS suggesting that pro-inflammatory macrophages may be contribute to increased microbial translocation. We therefore hypothesize that, in mediating an immune response to HIV-1 in the colon, pro-inflammatory macrophages may drive microbial translocation.

OR.106. The Epithelial Adherens Junction Protein E-cadherin Inhibits HIV-1-specific CD8+ T Cell Responses by Binding to KLRG1

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Background: Extensive damage to gut associated lymphoid tissue (GALT) and disruption of intestinal mucosal integrity likely play a crucial role in HIV pathogenesis. Here we explore the potential link between an epithelial antigen released upon mucosal damage and HIV-specific CTL dysfunction. Methods: The distribution of E-cadherin in intestinal tissue was determined by immunohistochemistry. Plasma levels of soluble E-cadherin were determined using ELISA. Cytokine secretion and proliferative capacity by HIV-specific CD8+ T cells in the presence or absence of recombinant soluble E-cadherin was assessed by intracellular cytokine staining and CFSE. Results: HIV-1 infected individuals had abnormal distribution of E-cadherin in the intestinal mucosa relative to uninfected individuals. These subjects also had significantly increased soluble E-cadherin levels in the plasma relative to HIV-negative subjects ($p<0.05$). HIV-1-specific CD8+ T cells in subjects with chronic-progressive HIV-1 infection showed elevated levels of KLRG1 expression ($p<0.05$). In the presence of soluble E-cadherin, a natural ligand for KLRG1, KLRG1hi HIV-1-specific CD8+ T cells showed reduced amounts of cytokine production and proliferation upon antigenic stimulation. Conclusions: Our data suggest that breaches within the gastrointestinal epithelium may lead to increased amounts of systemic soluble E-cadherin, which specifically inhibits KLRG1hi expressing HIV-1-specific effector-memory cells.

OR.107. Virosome-Gp41 Vaccination Triggers Mucosal Defense Mechanisms that Highly Protects Female Macaques from Repeated Intravaginal Low-dose Challenges with SHIV-162P3

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AIDS is mainly a sexually transmitted infection. Blocking sexual transmission of HIV requires developing a prophylactic vaccine that promote mucosal IgA in genital and intestinal compartments for preventing initial HIV transmission events. We have developed a mucosal vaccine candidate based on two complementary conserved gp41 antigens (a trimeric recombinant gp41 and the petide P1 covering the gp41 MPER) that focus the immune response on relevant neutralizing IgA and IgG epitopes. Antigens are grafted on virosome, a market-approved vaccine carrier with intrinsic adjuvant properties. Female Macaca mulata were immunized 4 times with both rgp41- or P1 peptide-virosomes, using the i.m. or the combined i.m./i.n. routes. Five weeks post-vaccination, animals were challenged 13 times intravaginally with low dose of SHIV162p3. Up to w13 post-challenge, 5/5 animals vaccinated by the combined i.m./i.n. routes were fully protected against SHIV162p3 (undetectable viremia, anti-HIV IgG seronegative), as compared to the 6/6 infected control group, or the 5/6 infected animals vaccinated by only the i.m. route. Protection was correlated to gp41-specific IgA in vaginal secretion with *in vitro* neutralizing activities against transcytosis and CD4+ cell infection. These results highlight the high potential of virosome-based vaccines targeting gp41 in inducing a mucosal protection against sexual HIV transmission.

OR.108. A Broadly Conserved Epitope of HIV-1 gp41, QARILAVERY, is a Potent Inducer of IgA

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Eliciting effective systemic and mucosal immunity against HIV-1 is a critical goal for the success of future vaccines.

However, thus far, very few studies have aimed to induce HIV-specific IgA responses which can play an important role in mediating protection by preventing virus transmission at the mucosa. We have designed novel chimeric Gag virus-like-particles (VLPs) that encode epitopes from the C- and N-termini of gp41. The VLPs are expressed *in vivo* via DNA vectors (given intra-muscularly followed by electroporation) or adenovirus vectors (intra-nasally). In previous studies we have shown that our unique epitope insert design and optimized immunization regime (choice of adjuvants, selected administration routes and heterologous prime-boost) elicit high titres of IgG and IgA in both systemic (serum) and mucosal compartments (vaginal washes/ fecal pellets) of C57bl/6 mice. Of particular interest is the N-teminus epitope QARILAVERY which induces significantly high levels of IgA when compared to the C-terminus epitopes (-ELDKWAS--NWFDIT-) in both systemic and mucosal compartments. Furthermore the ratio of IgG:IgA elicited by QARILAVERY in the serum is nearly 1:1 in mice given homologous (DNA alone or Ad alone) or heterologous (DNA+Ad) immunizations. A similar ratio is observed when Ad is administered via different routes (intra-nasal/ intra-peritoneal/ intra-muscular. Our future work involves the characterization of the function of anti-QARILAVERY IgG/IgA in vitro as well as to understand how/why such unusually high levels of IgA are elicited against this epitope in our model. We are also characterizing the QARILAVERY-specific reactivity of antibodies obtained from serum and vaginal-lavage samples of HIV exposed-uninfected sex workers from a Kenyan cohort, to determine the clinical relevance of such a response.