630. Identification of a Depressed Mucosal Immune Environment in HIV Infection
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Background. Among patients with human immunodeficiency virus (HIV), pulmonary complications are a common cause of morbidity and mortality. Emerging evidence suggests that respiratory viruses contribute to this disease burden. Although HIV is known to alter other mucosal surfaces including the GI tract and vagina, its effect on the upper respiratory mucosa, the primary target of respiratory viruses, has not been well described. We sought to characterize the effect of HIV on the upper respiratory mucosal immune environment.

Methods. Ten HIV-infected patients and 10 sex-matched uninfected controls were enrolled. Subjects were ages 18–49, non-smokers, and otherwise healthy. HIV-infected subjects had complete viral load suppression for at least 6 months prior to participation. Subjects provided serum samples and underwent nasal mucosal sampling procedures—epithelial lining fluid (ELF) collection, nasal lavage (NLF) and nasal biopsy. Serum, ELF, and NLF were analyzed using ELISAs targeted at pro-inflammatory cytokines. NLF was analyzed by flow cytometry for nasal-specific immune cells.

Results. T-cells in NLF, including both CD8 and CD4 populations, were significantly decreased in HIV-infected compared with uninfected subjects. We also found decreased numbers of neutrophils. Additionally, we identified diminished levels of IL-16 in ELF, a T-cell chemoattractant in HIV-infected subjects; however, all other cytokines and chemokines were similar between the two groups. These findings were in contrast to an earlier study we had done in six HIV-infected men with variable levels of HIV control and age-matched control subjects which also demonstrated decreased levels of other pro-inflammatory cytokines, including IL-1β, IL-5, and IL-5 in those with HIV.

Conclusion. The mechanism underlying the morbidity and mortality of respiratory viruses in HIV-infected patients is unclear. However, we identified that HIV infection does result in relative upper respiratory immune suppression, including in both CD4 and CD8 T-cell populations, despite otherwise excellent systemic control of HIV. We hypothesize that this suppression persists in viral infection leading to an impaired immune response and prolonged respiratory virus replication, contributing to the observed burden of disease in this population.

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631. Markers of Immune Response in Patients with Acute, Chronic and Fatal Infection with Chikungunya Virus in Colombia During the 2015 Epidemic
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Background. After 2014 Chikungunya virus (CHIKV) became in public health problem in west world with disability and deterioration in the quality of life that it generates and fatal complications. The objective of this study was, to determine the markers of immune response in patients with acute, chronic and fatal infection by CHIKV in Colombia, during the epidemic in 2015.

Methods. Cross-sectional study, carried out in serological samples of patients with laboratory-confirmed diagnosed for acute cases (AC), chronic cases (CC) and fatal CHIKV cases (FC). The samples were supplied by the virology laboratory of the National Health Institute and through commercial kit 13 cytokines were processed.

Results. One hundred sixty-four samples were analyzed. 50 from patients with AD, 25 from FC due to CHIKV and 89 from patients with CC. The average age was 48.2 years ± 24.4 SD. AC were more prevalent in the extreme ages of life (<10 years and >70 years), and the CC in young adults and intermediate adults (20–60 years) (P < 0.05). The median time taken for the sample was 4.5 [IQR3] days for acute cases and 7 days [IQR1.75] for FC. Ten plasma cytokinas (INF-gamma, IL-10, IL-17a, IL-2, IL-4, IL-5, IL-6, TGF-a, TNF-a) were significantly elevated in patients deceased compared with patients with acute infection (P < 0.005). In patients with FC, IL-6 was the pro-inflammatory cytokines with the highest median value and among the anti-inflammatory cytokines, IL-10. Exception of GM-CSF and IL-12, the comparison of medians between FC and patients with CC (INF-gamma, IL-10, IL-13, IL-17a, IL-2, IL-4, IL-5, IL-6, IL-12/TNF-β, TGF-a, TNF-a) presented statistically significant differences (P < 0.05). The median of IL-6 was >8 ng/mL and the IL-10 was >2 ng/mL in patients with AC than in the group with CC.

Conclusion. This is the first study conducted in Colombia, which provides evidence on cytokine levels in the acute, fatal and chronic outcome of patients with CHIKV. AC had an increase in INF-gamma, IL-10, IL-17a and IL-23 cytokines, which if persisted elevated for more than 3 months with some decreased levels of INF-γ and IL-6, maybe progression to chronic phase. If in addition of acute phase cytokines, IL-2, IL-4, IL-13, IL-12/TNF-β, TGF-a increase, the disease maybe in chronic and fatal. Cytokines, especially IL-6, is becoming a tool for monitoring, evolution and prognosis of CHIKV disease.

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632. Recurrent Pneumococcal Meningitis in Adults
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Background. Recurrent pneumococcal meningitis is uncommon in adults. Underlying disorders include humoral immune deficiency, cerebrospinal fluid (CSF) leaks, asplenia or cochlear implants. We evaluated two women who each had two separate episodes of Streptococcus pneumoniae meningitis. Both had histories of systemic lupus erythematosus (SLE).

Methods. Immune evaluations were negative except for occasional Howell-Jolly bodies on their blood smear. Immunoglobulins were normal and their post vaccine responses to pneumococcal polysaccharide vaccine-23 (Pneumovax). Complement levels: C3, C4 and CH50 were normal. Lab but not clinical markers of SLE were present. In both patients, the spleen was anatomically present. In both, there was near absent splenic function on a heat damaged RBC spleen scan. A literature search was carried out using Medline/PubMed and Google.

Results. Streptococcus pneumoniae infections make up about 6–18% of all bacterial infections in SLE, most are pneumonia. Although several cases of pneumococcal sepsis/shock have been reported in such patients, we could not find similar cases of recurrent pneumococcal meningitis in patients with inactive, untreated SLE.

Conclusion. Recurrent pneumococcal meningitis is uncommon in adults and is usually associated with humoral immune deficiency, CSF leaks or cochlear implants. Complement deficiency (primary) is rarely found. Sickle cell disease and other hemoglobinopathies have also been associated with pneumococcal sepsis and meningitis. SLE and other autoimmune connective tissue disorders are associated with functional asplenia, even when clinically inactive. These patients are at increased risk for invasive pneumococcal disease. Functional asplenia in adult patients is often overlooked in patients with severe or recurrent infections caused by polysaccharide encapsulated bacteria. We report on two patients with recurrent pneumococcal meningitis and SLE. Functional asplenia and complement deficiency are the primary factors when such patients develop invasive or recurrent infections. Demonstration of a poorly functional spleen by a TC 99 heat denatured RBC spleen scan when the spleen is anatomically present confirms the diagnosis.

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633. HIV-1 Vpu Immune Correlates in a Narrow-Source Infection Cohort: Impact of ADCC and KIR-Associated Pressure
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Background. We investigated vpu diversity and immune correlates of sequence variation in a unique cohort of former plasma donors (FPDs) from rural China who were infected with a very narrow range of clade B HIV-1 strains.
Methods. Plasma viral RNA was sequenced from a convenience sample of 90 SM cohort samples, and then analyzed for polymorphisms associated with HLA class I and KIR genotypes. An ADCC assay was employed to detect responses to Env and Vpu peptides. An ELISA-based approach was optimized to identify potential Vpu epitopes. Finally, responders from the ADCC assay were assessed in an ADCVI assay.

Results. In keeping with the lack of CTL targets, no HLA class I associated polymorphisms were identified in Vpu. KIR analysis, however revealed evidence of a strong association between KIR2DS1 and a single amino acid at position 14 of Vpu. 59% of HIV-1 sequences derived from KIR2DS1+ individuals encoded a valine (V) at this position whereas the corresponding allele (A) was found at this position in the majority (76%) of KIR2DS1-individuals. ADCC responses to Env were found in 37% of the SM cohort, with only five subjects also showing responses to Vpu peptides. Plasma from all five Env/vpu responders showed potent inhibition of virus replication, nearing 95%, in the ADCCVI assay.

Conclusion. We demonstrate a significant association between an activating KIR, KIR2DS1, and a polymorphism at amino acid position 14 of HIV-1 Vpu, which is consistent with selection by Natural Killer (NK) cells expressing this KIR. We also demonstrate Env and ADCC responses that are associated with potent virus inhibition in vitro in responders. These data help to shed light upon the immune selection pressures exerted on the HIV-1 virus gene and may provide insights into the role of this protein in immune evasion.

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634. Transcriptional Stimulation of Antiviral Response Components by the Structural and Accessory Human coronavirus OC43 Proteins
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Background. In human coronavirus OC43 (HCoV-OC43) causes 25–30% of common cold, and 8.8% of respiratory infections in hospitalised patients. It is also associated with severe respiratory symptoms in infants, elderly, and immunocompromised patients. Our previous studies showed that the expression of antiviral genes in human embryonic kidney (HEK) 293 cells is downregulated in the presence of HCoV-OC43 proteins. To understand the role of HCoV-OC43 proteins in antagonizing antiviral responses of the host, we investigated the effect of HCoV-OC43 structural and accessory proteins on the transcriptional activation of interferon-stimulated response element (ISRE), interferon-β (IFN-β) promoter, and nuclear factor kappa B response element (NF-kappab-RE).

Methods. HCoV-OC43 n2a, n5a, membrane (M), and nucleocapsid (N) mRNA were extracted and cloned into the pACGP1-3X expression vector, followed by transfection in HEK-293 cells. Two days post-transfection, the cells were co-transfected with a reporter vector containing firefly luciferase under the control of ISRE, IFN-β promoter, or NF-kappab-RE. Renilla luciferase vector was used as an internal control for transfection efficiency. Following 24 hours of incubation, the cells were treated with either IFN or tumour necrosis factor (TNF) for 6 hours. Thereafter, promoter activity was assayed using the dual-luciferase reporter assay system. Intracellular NS1 protein was used as positive control for antagonism.

Results. The transcriptional activity of ISRE, IFN-β promoter, and NF-kappab-RE was downregulated in the presence of n2a, n5a, M, or N protein as there was a sharp fall in firefly luciferase levels. Overall, HCoV-OC43 proteins reduced firefly luciferase levels for ISRE and IFN-β promoter by at least ten fold, whereas for NF-kappab-RE the firefly luciferase levels were reduced by at least five fold.

Conclusion. HCoV-OC43 has the ability to block the activation of different anti-viral signaling pathways.

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635. In HIV-Infected Patients Killing of Latently HIV-Infected CD4 T Cells by Autologous CD8 T Cells Is Modulated by Nef
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Background. The PBMC of HIV-infected patients contain HIV-specific CD8 T cells and their potential targets, CD4 T cells latently infected by HIV. The role of HIV-specific CD8 T cells in the course of HIV infection and the way they affect the virus that resides in the latent reservoir, the resting memory CD4 T cells, is unknown. The association between HIV-1 and the cellular ASK1 protein protects the HIV-infected CD4 T cells from killing by CD8 T cells.

Methods. CD8 and autologous CD4 T cells procured from PBMC of acute, chronic untreated, treated and AIDS patients were isolated by magnetic beads and co-incubated. Resting memory CD4 T cells (CD25+, CD69+ and HLA-DR-) were isolated from activated CD4 T cells using a two-step bead depletion purification procedure. Formation of CD8-CD4 T-cell conjugates was observed by fluorescence microscopy and in situ PCR of HIV LTR DNA. Both conjugation and apoptosis were observed and quantified by imaging flow cytometry (ImageStream) using anti-human activated caspase 3 antibody and TUNEL assay. Formation of immunological synapse was observed by using anti-PerCP eCD3, anti-vtau-1, and anti-IL2 antibodies.

Results. Following co-incubation we observed that CD8 T cells conjugate with and induce apoptosis of autologous CD4 T cells. In patients with acute infection or AIDS the conjugation activity and apoptosis were much higher compared with chronic HIV-infected patients. In patients on anti-retroviral therapy (ART) low grade conjugation of CD4 T cells was observed by fluorescence microscopy (2.3 ± 0.3%), by in situ PCR of HIV DNA (3 ± 0.6%) and by ImageStream analysis (2.5 ± 0.5%). After co-incubation with autologous CD8 T cells 2.1 ± 0.4% of the CD4 T cells procured from patients on ART were undergoing apoptosis. Resting memory CD4 T cells were conjugated (1.9 ± 0.3%) and killed (2.2 ± 0.3%) by autologous CD8 T cells. Delivering a peptide that interferes with the Nef-ASK1 interaction, into the CD4 T cells, resulted in twofold enhancement of their apoptosis by the autologous CD8 T cells (from 2.1 ± 0.5% to 4.0 ± 0.4%), with no effect on conjugation.

Conclusion. CD8 T cells conjugate with and kill HIV-infected CD4 T cells throughout the course of HIV infection. We suggest that Nef inhibition may result in the elimination of the latent reservoir CD4 T cells by CD8 T cells.