1201. Sarcoïdosis Candidate Microbes Identified by Next Generation Sequencing
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Session: P-53. Microbial Pathogenesis

Background. Sarcoïdosis is an autoimmune disease characterized by granulomatous lung disease with very prominent mediastinal adenopathy. Acid-fast bacteria, fungi, and viruses have been considered as possible causes of sarcoïdosis. We used next-generation or deep sequencing to characterize the microbial content of diseased mediastinal lymph nodes from 10 sarcoïdosis patients compared to a set of 10 negative-controls.

Methods. RNA was extracted from fixed paraffinized mediastinal lymph nodes (MLN) from 12 diseased specimens taken from 10 sarcoïdosis patients and 2 positive control subjects (TB, MAI), and normal appearing MLN from 10 negative-control subjects (mostly cancer patients). The extracted RNA was sequenced on the Illumina 2500, yielding 125-bp paired-end reads. These reads were aligned to the human genome, human transcriptome, and a nonredundant panmicrobial database. Each experimental sample was compared against the set of 10 negative-controls using the false discovery rate method (q-value). Directed qPCR was performed on all the samples.

Results. 100-153 million read-pairs were obtained from the 24 sequenced samples (12 sarcoïdosis, 10 negative-control, 2 positive-control). Among these, 0.01-1.32% of the reads were microbial, with a trend towards fewer microbial reads in the sarcoïdosis group compared to controls (means 66K vs. 457K, p<0.09). Mycobacterial sequence was significantly enriched (q<0.05) for the following genera: fungal, Magnaporthe (N=4 samples) and Debaromyces (1); bacteria, Odoribacter (1) and Granulicella (1); and viral, Roseolovirus (6) and Mardivirus (6). Further metagenomic analysis eliminated Magnaporthe as a candidate. qPCR confirmed the presence of Odoribacter in 2 specimens and Debaromyces in 1. Roseolovirus (HHV6) could not be detected by qPCR in any of the samples.

Conclusion. We conclude that sequencing is a feasible method for identifying candidate microbes that might trigger sarcoïdosis in human subjects. Further research is required to establish or refute the pathogenicity of these organisms in patients with sarcoïdosis.

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1202. Subinhibitory Concentrations of Omadacycline Inhibit Staphylococcus aureus Hemolytic Activity in Vitro
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Session: P-53. Microbial Pathogenesis

Background. In animal models of Staphylococcus aureus infection, α-hemolysin has been shown to be a key virulence factor. Treatment of S. aureus with subinhibitory levels of protein synthesis inhibitors can decrease α-hemolysin expression. Omadacycline, a novel aminomethylcycline antibiotic in the tetracycline class of bacterial protein biosynthesis inhibitors, is approved in the United States for treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults. This study was performed to determine the durability of inhibition and effect of subinhibitory concentrations of omadacycline on S. aureus hemolytic activity.

Methods. All experiments used the methicillin-sensitive S. aureus strain Wood 46 (ATCC 10832), a laboratory strain known to secrete high levels of α-hemolysin. Minimum inhibitory concentrations (MICs) of omadacycline and comparator antibiotics (tetracycline, cephalothin, clindamycin, vancomycin, linezolid) were determined. Growth of S. aureus with all antibiotics was determined and the percentage of hemolysis assayed. "Washout" experiments were performed with omadacycline only.

Results. S. aureus cultures treated with 1/2 or 1/4 the MIC of omadacycline for 4 hours showed hemolysis units 10^4 CFU of 47% and 59% of vehicle-treated cultures, respectively (Fig. 1A, 1B). In washout experiments, treatment with as little as 1/4 the MIC of omadacycline for 1 hour decreased the hemolysis units 10^4 CFU by 60% for 4 hours following removal of the drug (Table 1).

Figure 1

Table 1. Summary of omadacycline washout study

| Fold MIC of omadacycline | % Vehicle-treated hemolysis units/10^4 CFU |
|--------------------------|------------------------------------------|
| 0 (vehicle)              | 100.00 ± 18.59                           |
| 0.25                     | 39.85 ± 5.03                             |
| 0.5                      | 55.63 ± 13.40                            |
| 1.0                      | 15.78 ± 4.66                             |
| 2.0                      | 21.07 ± 4.29                             |

CFU, colony-forming unit; MIC, minimum inhibitory concentration.

Data indicate mean ± standard deviation of 3 samples per group.

Conclusion. Omadacycline inhibited S. aureus hemolytic activity in vitro at subinhibitory concentrations and inhibition was maintained for ≥4 hours after removal of extracellular drug (Fig. 2). The suppression of virulence factors throughout the approved omadacycline dosing interval, in addition to the in vitro potency of omadacycline, may contribute to the efficacy of omadacycline for ABSSSI and CABP due to virulent S. aureus. This finding may apply to other organisms and other virulence factors that require new protein synthesis to establish disease.

Figure 2

Figure 2. Hemolytic activity of S. aureus Wood 46 grown for 4 hours with the indicated concentration of omadacycline followed by 4 hours’ growth without drug. Vehicle = 0.0025% DMSO in MH broth. Data represent the mean of 3 cultures; error bars indicate standard deviations.
1203. Systemic, Mucosal Immune Activation And Psycho-sexual Health in HIV-Infected And Uninfected Women: Evaluation of Biomarkers And Environmental Stimuli

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Session: P-53. Microbial Pathogenesis

Background. HIV infection in women in disproportionate ratios as compared to men has been a grave concern over the years. It is in proportion to reproductive and hormonal differences making women more vulnerable. It elicits an immune response which can be monitored by analysing various factors such as mucosal immunity, sexual behaviour, biomarkers in the plasma, serum and vaginal lavage and vaginal infections.

Aim. Evaluating and comparing the systemic and mucosal immune-inflammatory status, the female sexual function (FSF) and generalized anxiety in HIV+ women on successful HAART with healthy women (HW).

Methods. We enrolled 53 subjects (23 HIV+ women on successful HAART and 30 Healthy women (HW)) with no statistical differences in age. The figure (named methodology) below explains the methods applied:

Cytometry and Kit ELISA were used to estimate lymphocytes and all cytokines. Plasma levels of sCD 163, CXCL-10, IL-1, IL-6 and IL-8 were lower in the VL of HIV women. An ASCUS in HW was found for IL-8 (< p=0.004). We enrolled 53 subjects (23 HIV+ women on successful HAART and 30 Healthy women (HW)) with no statistical differences in age.

Results. Higher CD4 and CD8 cell count was observed in HW compared to HIV+ women (p=0.02, p=0.004). Plasma levels of CD63, CXCL-10, IL-1, IL-6 and IL-8 were significantly higher in HIV women as compared to HW (p=0.001), while IL-6 and IL8 were lower in the VL of HIV women. An ASCUS in HW was found for PAP Test. CXCL-10 was correlated to estradiol levels (r=0.8, p=0.02). 57% reported FSD and 43% had a FSFI score≤10. A significant difference between the two groups in the FSFI score (p=0.007) was found, particularly in sexual desire, arousal and pain. A positive correlation between level of testosterone and FSFI score was found (r=0.4, p=0.02). Z-index was associated with orgasm domains (p=0.01; r=-0.4) and CD4+ T cells (p=0.02; r=-0.45).

Conclusion. Higher plasma levels of the cytokines despite successful antiretroviral therapy were observed. At the mucosal level evaluating the balance within pro anti-inflammatory cytokines and micro-biome will be interesting to study; FSD is detected in more than half of HIV infected women and seems to be related to testosterone levels. The comparison with uninfected women underlying a persistent gap in quality of life of young HIV women should be bridged.

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