O16.3 CYTOKINE IMMUNE RESPONSE AGAINST NATURAL HUMAN PAPILLOMAVIRUS INFECTION AMONG MEN IN KISUMU, KENYA

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Background Human papillomavirus (HPV) is strongly associated with ano-genital and cervical cancer. Persistence of oncogenic HPV genotypes is required for development and progression of HPV-associated malignancies. Although, >70% of women clear incident HPV infections, data on natural history and HPV immunology among men is limited.
Methods To evaluate cell-mediated immune response against natural HPV infection among men, we assessed cytokine (IFN-γ, TNF-α, IL-2, IL-4, IL-6, IL-10 and IL-13) responses in peripheral-blood-mononuclear cells (PBMCs) collected from 135 men enrolled in a prospective HPV cohort study. PBMCs were stimulated by HPV L1 gene viral-like-particles (VLP) and cytokine responses measured using a multiplex Luminex assay.
Results Of 135 men included in this analysis, 41 men had persistent HPV infection, 44 men cleared HPV infection and 50 were HPV uninfected. Their mean (SD) ages were 28.9 (6.79), 27.6 (6.49) and 26.4 (4.81) years respectively. Immune response was induced in 22% (95% CI: 12.8–35.2) of HPV uninfected men, 64% (95% CI: 48.9–76.2) of men with HPV clearance and 51% (95% CI: 36.5–65.8) of men with HPV persistence. Men with HPV clearance and HPV persistence were significantly ($p<0.01$) at increased odds [OR = 6.20 (95% CI: 2.29–17.19) and OR = 3.72 (95% CI: 1.37–10.25) respectively] of mounting cytokine responses compared to HPV uninfected men. T-helper type 1 (Th1) cytokines IFN-γ (5.1 mean-fold increase) and IL-2 (4.2-fold) were significantly ($p<0.0001$) upregulated among men with HPV clearance and not in men with HPV persistence, compared to HPV uninfected men. Among men with HPV clearance compared to those with persistent HPV infection, IFN-γ (2.4–fold) and IL-2 (3.0-fold) were the only cytokines significantly ($p<0.0001$) upregulated. In the three groups of men, there were no significant changes in Th1 cytokine TNF-α, and Th2 cytokines: IL-4, IL-6, IL-10 and IL-13.
Conclusion In this study, Th1 cell-mediated cytokine immune response was associated with HPV clearance in men.
Disclosure No significant relationships.

O16.4 STRUCTURAL SIMILARITY OF *TREPONEMA PALLIDUM* PROTEIN TP0225 WITH HUMAN TOLL-LIKE RECEPTOR 2

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Background The causative agent of syphilis, *Treponema pallidum*, is a highly invasive chronic pathogen. Here we used bioinformatics and structural biology to characterize the sole LRR-containing protein in *T. pallidum*, Tp0225. In other bacterial pathogens, Leucine-Rich Repeat (LRR)-containing proteins contribute to chronicity by mediating attachment, invasion and immune evasion.
Methods A phylogenetic tree was constructed to determine the evolutionary relationship between Tp0225 and LRR homologs from pathogenic and non-pathogenic treponemes. The size and organization of Tp0225 protein domains were analyzed by comparing them to the domains of the treponemal homologs. For structure determination, the full-length recombinant protein was purified, crystallized, and the three dimensional structure determined using X-ray crystallography.
Results Bioinformatic analyses showed that Tp0225 has diverged more from non-pathogens compared to pathogens during evolution. The structure of Tp0225 demonstrated that the protein adopts a non-classical LRR fold and contains a hydrophobic pocket on the surface of the structure. This unusual LRR characteristic is similar to the hydrophobic pocket found on the surface of the human Toll-like Receptor 2 (TLR2) LRR domain that recognizes *T. pallidum* during infection.
Conclusion We have determined the structure of the only LRR-containing protein in *T. pallidum* and have shown that it contains an unusual LRR structural feature that is shared with the host innate immune signaling molecule TLR2. This structural mimicry may be involved in subversion of normal host processes during *T. pallidum* infection.
Disclosure No significant relationships.

O16.5 TARGETING COMPLEMENT RECEPTOR 3 ON PRIMARY HUMAN CERVICAL CELLS HAS THE POTENTIAL TO CURE *NEISSERIA GONORRHOEAE* INFECTION

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Background Complement receptor 3 (CR3) is a leukocytic, pattern recognition receptor that plays a pivotal role in innate immunity. CR3 is also uniquely expressed by human cervical epithelial cells where it is the key receptor mediating *Neisseria gonorrhoeae* (*Ng*) cervicitis. Binding of the *Ng* surface appendage, pilus, to the I-domain region of CR3 (CR3ID) is critical to cervical cell adherence and modulates the host response to infection. Thus, the pilus-CR3ID interaction may pose a novel target for critically-needed, new strategies to treat or prevent *Ng* disease in women.
Methods To identify potential inhibitors of the *Ng*-CR3 interaction, recombinant human I-domain or purified CR3 were immobilized on biosensor chips. Interactions between these immobilized proteins and a library of 3141 drugs were investigated by surface plasmon resonance (SPR). Drugs that bound the CR3ID were further examined by competitive SPR studies and in *Ng*, primary human cervical epithelial (Pex) cell infection assays.
Results Using SPR, we identified fourteen drugs that bound to the CR3ID with disassociation constants in the nanomolar range. Competitive SPR analysis demonstrated that six of these fourteen drugs blocked the pilus-CR3ID interaction. Moreover, these drugs also blocked *Ng* adherence to Pex cells as well as to Chinese hamster ovary cells expressing CR3 (CHO-CR3). One drug, carbamazepine, was chosen for further analysis using a panel of low-passage and multidrug-resistant *Ng* strains. Carbamazepine blocked adherence to Pex and CHO-CR3 cells for all strains tested and also could cure Pex cells