DISSECTING THE INFLUENCE OF HIV INFECTION AND TREATMENT WITH ANTIRETROVIRAL THERAPY ON HUMAN PAPILLOMAVIRUS INFECTION, DISEASE AND IMMUNITY

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HIV positive women suffer from a higher burden of Human papillomavirus (HPV) induced cervical cancer (CC) and premalignant lesions even in the era of ART, yet, the impact of ART on HPV induced cervical disease is still not clear, ART does not seem to fully restore immunity to HPV infection evidenced by the high propensity of HIV+ women on ART to develop cervical cancer. We therefore hypothesized that HIV infection causes dysfunction of HPV-specific T cell and as a consequence increases persistence of high-risk (HR) HPV types, more frequent malignant cell transformation and rapid disease progression; and ART initiation does not fully reconstitute HPV-specific T cell function. Within the on-going 2H case-control study, which enrolled 100 HIV+ and 100 HIV- clinical cases with CC or High grade squamous intraepithelial lesions (HSIL) and 200 controls per HIV strata, we are addressing this hypothesis using IFNg enzyme-linked immunospot assay, flow cytometry and HPV genotyping. HIV infected women had a greater risk for HPV disease progression or persistence as compared to HIV- women (RR 1.5 [95 CI 1.2-1.8], $p<0.001$). Systemic oncogene E6/E7-specific T cell responses targeting the most relevant HR HPV genotypes (16, 18, 45) were selectively depleted in HIV+ CC/HSIL cases as compared to HIV+ controls without cervical lesions ($p < 0.05$). In subjects with a relatively high magnitude of IFNg+ E6/E7-specific T cells responses , we were able to characterize IFNg-specific T cells using polychromatic flow cytometry; In these responders, E6/E7-specific T cell were more often CD8 as compared to CD4 T cells and they were dominated by an exhausted and senescent phenotype (as defined by PD-1, CTLA-4 and CD57). We are currently establishing an immunohistochemistry panel to study T cell infiltration, phenotype and spatial interaction of the infiltrating lymphocytes into the cervix in the presence of HPV disease. Together these results add knowledge to HPV/HIV co-infection pathogenesis.