Enhancement of microbiota in healthy macaques results in robust beneficial modulation of mucosal and systemic immune function

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Background: With more than thirty million HIV-infected individuals worldwide, developing an effective vaccine to prevent new HIV infections remains a top priority in contemporary biomedical research. Given the critical role of mucosal surfaces in susceptibility of HIV infection, it is imperative that we induce effective mucosal responses. However, current approaches to enhance mucosal immunity have not been successful in preventing HIV acquisition. Modulating the microbiota in the GI tract is a safe and well-tolerated approach to enhance mucosal and overall health. We hypothesized that altering TLR signaling via microbiome enhancement may improve mucosal immunity.

Methods: Five macaques (SIV-) were treated with the probiotic (PBio) VSL3. Colon, rectum, blood and LN were sampled prior to PBio treatment and at days 28 and 80 post-treatment. Indicators of cellular and humoral immunity and inflammation were assessed.

Results: PBio therapy resulted in significantly increased T follicular helper cells (Tfh; CD4+PD-1\textsuperscript{high}CXCR5\textsuperscript{high}, p=0.0085). Immunohistochemistry confirmed that LN had increased follicles after PBio treatment. As Tfh induce B cell responses, surface IgA and IgG expression on B cells was assessed. Increased frequencies of B cells expressing IgA in the LN (p=0.0151) and colon (p=0.0072) were identified. IL-23 production by antigen presenting cells (APCs) was measured and increased frequencies of IL-23+APCs in the colon (p=0.0173) were found, which correlated with the frequency of LN Tfh (p=0.0358). Finally, VSL3 significantly down-modulated the response of TLR3, TLR4 and TLR9-expressing HEK293 cells to stimulation with Poly(I:C), LPS and ODN2006, respectively.

Conclusions: These data have potential implications for using PBio therapy to alter mucosal immunity in the context of vaccination or preventative approaches. In particular, the immunomodulatory properties of probiotic therapy in conjunction with HIV vaccination may provide an opportunity for enhanced mucosal HIV vaccine responses that could improve protection from infection by improving immune defenses at the mucosal portal of entry.