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Viral evolution in the gut reservoirs from SIV infected long term non-progressing Chinese rhesus macaques on combination anti-retroviral therapy

Binhua Ling, Wenpeng Li, Stefanie Perez, Ann-Marie Johnson, Hong Na, Hope Sansing, Marion Ratterree and Lara Doyle-Meyers
Tulane University, USA

HIV infected long term non-progressors (LTNP) and elite controllers (EC) maintain enduring control of HIV infection without anti-retroviral therapy (ART). Emerging evidence suggests that cells in tissues such as the gut continue to produce low levels of HIV, low level ongoing viral production occurs in the body even with concurrent ART. Whether LTNP/EC receiving ART can completely suppress low level ongoing viral replication is unknown. We have previously found that SIV infection in Chinese rhesus macaque (ChRM) is the closest animal model that mimics HIV infection. We have also shown that gut mucosa is a major reservoir in LTNP/EC of SIV infected ChRM. Here we studied SIV mutation and evolution in the gut associated lymphoid tissue to determine whether ART can fully suppress viral replication in LTNP/EC of SIV infected ChRM. Ten animals were treated with reverse integrase inhibitors (tenofovir and Emtricitabine) daily for up to 24 weeks. PBMCs and lymphocytes were isolated from blood, spleen, lymph nodes and gut tissues of 6 sites (duodenum, jejunum, ileum, cecum, colon and rectum) by the end of ART. Nested PCR and single genome amplification (SGA) was performed. SIV envelope gp120 gene from positive samples was amplified. Sequences from PBMC before and after ART were compared with sequences isolated from the 6 sites of the small and large intestine. Phylogenetic trees were constructed. Viral mutation and evolution were analyzed. The size of reservoirs in PBMC and lymph nodes was evaluated by quantitative co-culture assays. We found that plasma viral loads (pVL) in all animals were suppressed and sustained below 28 copies per ml (limitation of detection) during ART. Two animals had viral rebound after approximately 2 weeks of cessation of ART. Viral DNA loads were detectable in either PBMCs and/or lymphocytes from different gut sections at variant levels by the end of ART. The frequency of detective PCR positives was higher in large intestine than small intestine, indicating large intestine is a major reservoir. A total of 245 sequences were analyzed. While envelope sequences showed limited viral mutations in some animals, viral evolution was observed in different sections of the gut in other animals even received 24 weeks of ART with sustained undetectable pVL. The size of viral reservoirs in blood reduced in LTNPs/ECs after ART. However, spleen and lymph nodes had higher resting CD4+ T cells carrying replication competent SIV than blood by the end of ART. These data suggest that low level of ongoing viral replication may still occur in some LTNP on ART. The SIV/ChRM non-human primate model is excellent for testing novel therapeutic interventions on typical progressors and LTNP/EC for HIV eradication.

bling@tulane.edu

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