TLR9 AGONIST MODULATED INTESTINAL GLYCOGENE EXPRESSION IMPACTS MICROBIOME DIVERSITY

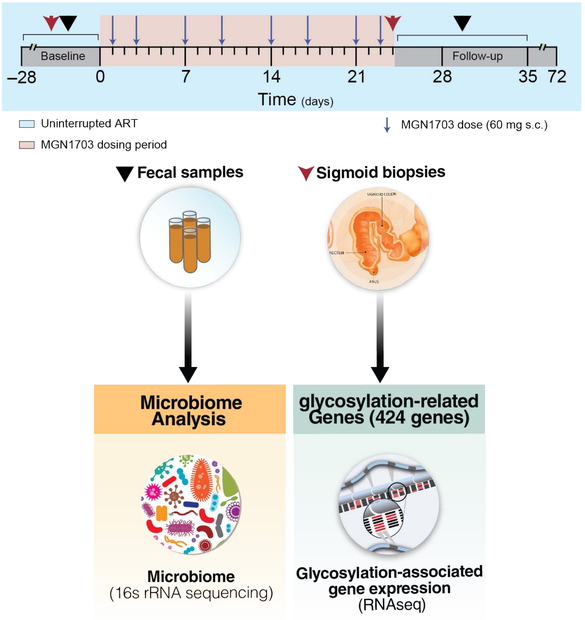
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BACKGROUND

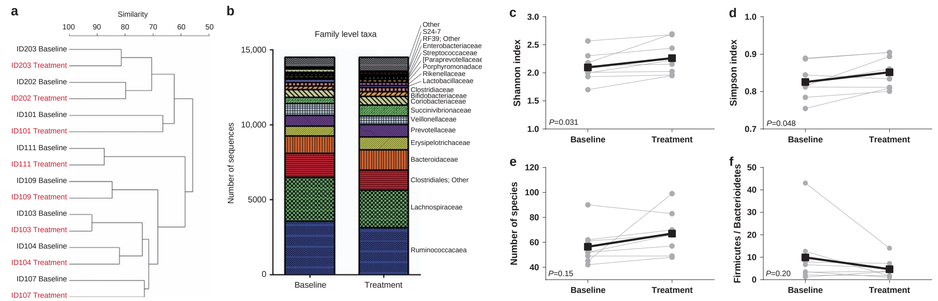
- An emerging paradigm suggests that the gut-associated glycome is critical to the maintenance of a homeostatic relationship between the host and its gut microbiota.
- In HIV infection, alterations in glycan metabolism may contribute to HIV-mediated intestinal damage, microbial translocation, and chronic inflammation.
- Given that we recently found that the TLR9 agonist lefitolimod (MGN1703, Mologen AG) increased microbiome diversity in HIV-1 infected individuals at multiple phylogenetic levels in Shannon and Simpson indices (PMID: 28766555), we hypothesized that lefitolimod-mediated changes in the gut glycome promoted changes in microbiome diversity.

METHODS



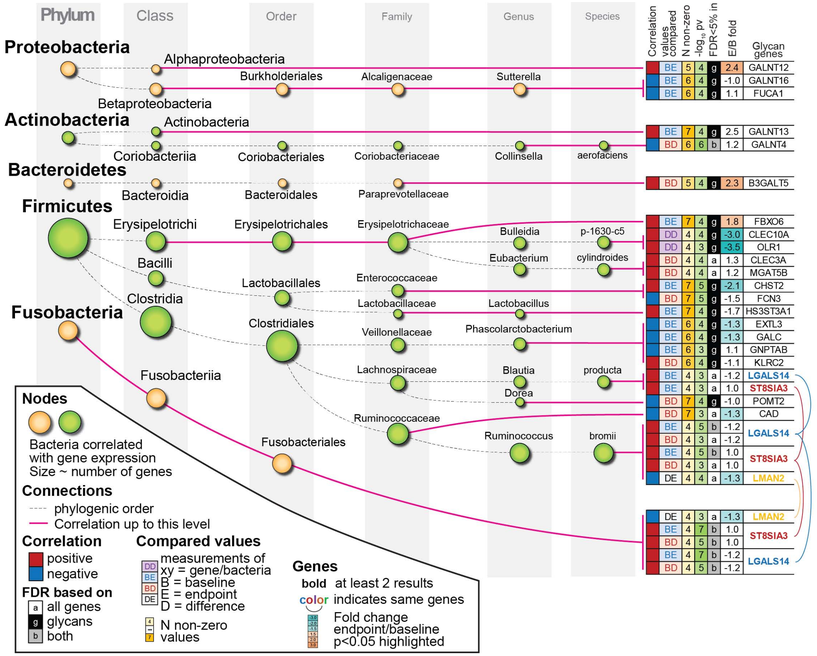
RESULTS

1) Lefitolimod treatment alters the intestinal flora. (A) Group average dendrogram illustrates relationships between samples at the taxonomic level of family. (B) The rarefied number of sequences (14,500) of microbial taxa (family) at baseline and post-treatment is shown. (C-F) Plots show the Shannon diversity (family) index values (C), the Simpson diversity (family) index values (D), the number of bacterial species identified (E), and the fermicutes over bacterioides ratios (F) at baseline and during lefitolimod treatment **[PMID: 28766555]**.



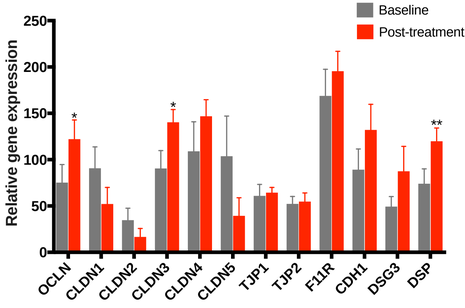
2) The expression of glycosylation-associated genes in the gut correlate with the microbiome composition during suppressed HIV infection.

- When we filtered the data to only the glycogenes that were significantly modulated by lefitolimod, we identified 10 glycogenes with diverse functions including: mucin-type O-glycosylation synthesis (N-acetyl-galactosaminyltransferases); mannose synthesis and metabolism; and anti-microbial C-type lectin-mediated innate immunity.
- The changes in these glycogenes correlated strongly with longitudinal changes in microbiome diversity in multiple taxa including *Alphaproteobacteria* (*Proteobacteria*), *Paraprevotellaceae* (*Bacteroidetes*) and several species of Firmicutes.



RESULTS

3) Lefitolimod-associated changes on gut glycome suggest an increase of mucin synthesis and an impact on gut permeability. This is supported by an induction of tight junction genes. Levels of several tight junction genes were elevated in the gut of HIV+ ART-suppressed individuals after lefitolimod treatment



CONCLUSIONS

- The degree of glycosylation in the gut directly impacts the ability to maintain a functional mucus layer and healthy intestines.
- Our analyses identified a gut glycomic signature associated with lefitolimod treatment that may influence intestinal homeostasis by modulating alpha diversity of the gut microbiome.
- Immunohistochemistry (IHC) and In Situ Hybridization (ISH) analyses will be needed to assess the impact of lefitolimod on gut integrity.
- Comprehensive glycomic profiling of well-characterized cohorts can yield valuable insights into determinants of viral persistence, providing potential targets for pharmacological manipulation.
- Our data highlight that host glycomics is an important tool for evaluating the impact of novel HIV interventions, particularly within the context of HIV eradication.

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