Machine Learning Modeling of Gut Microbiome-Metabolome Profile Links Alcohol & HIV-Associated Dysbiosis to Immune Senescence

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Background: Despite antiretroviral therapy, People with HIV (PWH) experience premature aging-related diseases, an effect often compounded by alcohol misuse. Evidence suggests that the precocious onset of aging-related diseases in PWH is partially mediated by gut dysbiosis contributing to inflammation and immune senescence. Our prior work found gut microbiome remodeling in PWH is associated with CD8 T cell senescence. In this study, we assess gut microbiome and metabolome remodeling in relation to T cell senescence and measures of intestinal leak.

Methods: The V4 region of the 16S gene was amplified and sequenced from fecal samples of HIV+ participants in the New Orleans Alcohol and HIV (NOAH) cohort using an Illuminia Miseq V2. Sequence variants were identified using the DADA2 workflow and taxonomically classified using the SILVA database (v138). Fecal Metabolomics was performed using UHPLC-MS. Senescent T cells were quantified from cohort participant's PBMCs using flow cytometry (n = 223). Artificial neural networks (ANN) were generated using Tensor flow (version 2.16) and keras (version 2.15). Shap analysis was performed using the python package SHAP (version 0.44) to determine feature importance and to explain how features are used by the model. MintTea (v 1.0.0) was used to generate networks of microbes and metabolites predictive of participants' T cell senescence. Funding for this work was supported by the following grants: P60AA009803, T32AA007577.

Results: Network analysis with MintTea identified networks predictive of intestinal leak marker abundance (sCD14, AUROC = 0.68; A1AT gradient AUROC = 0.65) and senescent CD38+ T cell abundance (AUROC = 0.65). Preliminary ANN modeling achieved an accuracy of 75% on training data and 74% validation data for classifying participants as having high or low concentrations CD38+ senescent T cells category. Shap analysis found the most important features to model predictions included the immune regulatory metabolite, indole, as well as metabolites involved in redox regulation and nucleotide metabolism. Microbial taxa associated with intestinal inflammation and aging were also important to predictions such as *Klebsiella*.

Conclusions: Integrated multi-omic analysis of the fecal microbiome in PWH predicts senescent T cell abundance and identifies gut-derived features that inform senescent T cell abundance and intestinal leak**.** These findings highlight how alcohol-associated gut dysbiosis relates to immune senescence, offering potential targets for interventions aimed at reducing immune senescence and intestinal leak in this vulnerable population.