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"Alcohol-associated impact of sIgA-coated intestinal bacteria on pulmonary host defense during S. pneumoniae pneumonia"

Introduction: Alcohol use disorders (AUDs) are an established risk factor for bacterial pneumonia. The GI microbiota plays a crucial role in the immune response to bacterial and viral respiratory infections. We have previously shown that alcohol consumption causes intestinal dysbiosis and is linked to impaired pulmonary host defense, however, the mechanisms behind this effect are unknown. Immunoglobulin A (IgA) is a critical mediator of mucosal immunity. Response to enteric pathogens can produce T-cell dependent, pathogen specific IgA, which transcytose into the intestinal lumen via the polymeric immunoglobulin receptor (pIgR). Preliminary studies from our group show that alcohol administration changes secretory IgA (sIgA) coating of GI bacteria in association with intestinal dysbiosis. We hypothesized that chronic-binge alcohol administration alters the sIgA-coating of gut bacteria and impairs lung clearance of *Streptococcus Pneumoniae* infection.

Methods: To investigate the relationship between alcohol-associated sIgA-coated bacteria and pulmonary host defense, we used a fecal microbiota adoptive transfer model. Female C57BL/6 mice were fed binge-on chronic alcohol (or isocaloric control) liquid diet for 10 days then assessed for IgA secretion, gene pIgR expression, and plasma cells using ELISA, qPCR and flow cytometry. These also served as donor animals. For microbiota adoptive transfers, a separate group of animals was treated with a cocktail of antibiotics for 12 days to reduce the gut microbial burden. Cecal microbiota from the donor animal experimental group were divided into IgA+/- factions and used to recolonize the microbiota-depleted mice by gavage. Following recolonization, mice were sacrificed 48 hrs after infection with *S. Pneumoniae* intratracheal. Lung bacterial burden, lung and intestinal immunology were measured.

Results: Alcohol exposure reduced circulating IgA levels and reduced the abundance of plasma cells and pIgR gene expression in the gut, suggesting that lower IgA in the intestinal lumen was due to both reduced IgA production and reduced transportation. In mice recolonized with alcohol-fed sIgA+ coated bacteria, there was higher gene expression of S. *Pneumoniae* in the lung as compared to the other groups. There were also reduced numbers of innate immune cells including neutrophils, NK cells and dendritic cells in the intestinal mucosa and the lung.

Conclusions: Alcohol administration reduces IgA in the intestinal lumen, associated with changes in the sIgA coating of specific bacterial taxa, by both reducing production and transport into the lumen. Further, alcohol-associated sIgA-coated bacteria impaired host response against pneumonia, indicating that sIgA-coated bacteria may be mechanistic in the higher prevalence of pneumonia in patients with AUDs. Our experiment could provide novel therapeutic targets to mitigate alcohol-related lung host defense defects.