GUT MICROBIOTA AND ITS METABOLITES ARE IMPORTANT DETERMINANTS OF THE IMMUNE RESPONSE TO THE MUC1 VACCINE IN THE SETTING OF COLON CANCER PREVENTION

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Background We conducted a clinical trial testing MUC1 vaccine in individuals with colonic polyps. The vaccine was immunogenic in some individuals but not others. We postulated that one of the reasons might be a difference in the gut microbiota. Lacking fecal samples, we tested pre-vaccination plasma from all participants for differences in gut microbiota metabolites Kynurenine (Kyn) and indole-3-aldehyde (I3A). We then recapitulated the clinical trial in human MUC1 transgenic mice to check for differences in their response to the vaccine that could be attributed to gut microbiota.

Methods Human: We measured with mass spectrometry Kyn and I3A levels in 88 plasma samples from polyp patients and compared with plasma from 22 colorectal cancer (CRC) patients. We phenotyped by flow cytometry PBMC from 64 polyp patients and 9 age-matched CRC patients for expression of Kyn and I3A receptor AhR on T cells, NKT and NK cells, and expression of Lag-3, PD-1 and Tim3. Treg and MDSC were also measured. Mouse: We collected fecal samples pre-vaccination. Mice were vaccinated with the MUC1 vaccine at DayXX and XX and boosted at Day Y. Mice were sacrificed and sera, spleens (S) and mesenteric lymph nodes (MLN) collected for the immune response to the vaccine. Using sequencing of V3-V4 Variable Regions of 16S rRNA, we investigated the microbiota and using flow we phenotyped S and MLN immune cells.

Results We found higher levels of I3A in plasma of polyp patients compared to cancer patients. There was no correlation between I3A levels and vaccine response. There were similar percentages of AhR⁺ CD8⁺T effector memory (TEM) cells, the primary AhR⁺ T cell population in the PBMC. Exhausted phenotype was characteristic of CD4 TEM and correlated with non/low immune response to the vaccine. Mouse studies revealed an increase in lactic acid bacteria (LAB) post MUC-1 vaccination. This was accompanied by statistically significant reduction in the total frequency of AhR⁺ and PD-1⁺ CD8⁺ TEM and Treg in the spleen of vaccinated mice. There was also statistically significant reduction in AhR⁺ PD-1⁺ CD8⁺FoxP3⁺ cells in the spleen of high responders compared with low responders. Several differentially expressed genes associated with dietary tryptophan metabolism were significantly increased in the fecal microbiota of high responders compared with low responders.

Conclusions Together, our studies provide a deeper understanding of how gut microbiota and microbial metabolites affect vaccine responses and suggests that interventions with LAB or indole derivatives could complement immunoprevention strategies for CRC.

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