GUT DYSBIOSIS SUPPRESSES ANTI-TUMOR ILC2S IN PANCREATIC CANCER

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Background Symbiotic microbes that colonize gut promote host immunity. Cancer disrupts this homeostasis to alter microbial populations (“dysbiosis”) that suppresses anti-cancer immunity. Yet, the mechanisms of how dysbiosis suppresses anti-tumor immunity remain unclear. Group 2 innate lymphoid cells (ILC2s) are innate lymphocytes that reside in tissues including the gut, respond to the alarmin interleukin-33 (IL-33), and maintain microbial homeostasis in barrier surfaces. ILC2s also activate anti-tumor immunity in multiple cancers. Yet, links between dysbiosis, ILC2s, and anti-tumor immunity, remain unexplored.

Methods To investigate if cancer dysbiosis modulates ILC2s, we examined dysbiosis in pancreatic ductal adenocarcinoma (PDAC), where dysbiosis correlates with fewer intratumoral T cells and worse survival. PDAC is also infiltrated by anti-tumor ILC2s. Briefly, we analyzed dysbiosis by 16S-rRNA gene sequencing in fecal samples of PDAC mice deficient or not for ILC2s or IL-33. To study the effect of dysbiosis on ILC2s, we ablated dysbiosis using antibiotics or reconstituted it in germ-free mice, we explored ILC2 migration using parabiosis.

Results We found that PDAC induced Bacteroidetes overgrowth, thus phenocopying PDAC dysbiosis in patients. Interestingly, PDAC-dysbiosis suppressed intestinal ILC2s frequencies, as dysbiosis ablation with antibiotics increased, and fecal transplantation in germ-free mice conversely decreased intestinal ILC2 frequencies. Reciprocally, we found that ILC2 and IL-33-deficient mice evidenced Bacteroidetes overgrowth at steady state, thus phenocopying the PDAC-induced dysbiosis. Interestingly, ILC2 and IL-33-deficient mice also evidenced accelerated PDAC growth, and worse survival compared to wild-type mice (WT). Thus, PDAC-dysbiosis suppresses intestinal ILC2s that serve to maintain optimal gut homeostasis.

We next investigated how dysbiosis-induced ILC2s suppression modulates tumor growth. We previously reported that IL-33-responsive ILC2s infiltrate PDAC to activate antigen-specific CD8+ T cells. We identified these anti-tumor ILC2s as unique migratory ILC2s that traffic to tumors. We thus hypothesized dysbiosis may promote tumors by modulating ILC2 migration from the intestine reservoir. Consistently, in parabiotic mice, recombinant IL-33 (rIL-33) induced ILC2s to migrate hematogenously to PDACs in different tissues, and antibiotic ablation of dysbiosis lowered donor-derived ILC2s frequencies in recipient blood and intestine. Thus, dysbiosis modulates anti-tumor ILC2 frequencies in circulation and gut reservoirs. Interestingly, in WT PDAC mice, rIL-33 expanded intestinal ILC2s, restored microbiome composition, increased tumor-infiltrating ILC2s, and reduced PDAC growth.

Conclusions We find that cancer dysbiosis suppresses anti-tumor immunity by suppressing gut-derived ILC2s. Moreover, rIL-33 expands ILC2s in the gut and circulation to restore dysbiosis-suppressed ILC2s and controls PDAC. We thus introduce the therapeutic potential of IL-33-based immunotherapies to reverse the dysbiotic state in cancer.

REFERENCES