GUT MICROBIOME DYSBIOSIS PROMOTES IMMUNE SUPPRESSION AND LUNG CANCER DEVELOPMENT

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Background The interplay between the gut microbiome and immune responses in cancer remains poorly understood. We showed that gut microbiome changes are closely associated with development of lung adenocarcinoma (LUAD) in a human-relevant, tobacco-associated mouse model (Gprc5a−/−; G). Knockout of the antimicrobial protein Len2 (Gprc5a−/−/Lcn2−/−; GL) further reduced microbial diversity while enhancing inflammation and tumor development. We thus hypothesized that microbial dysbiosis in the gut, such as that incurred by loss of Lcn2, may exacerbate LUAD development and influence response to immune checkpoint blockade (ICB).

Methods We used fecal microbiota transfer (FMT) in syngeneic and tobacco carcinogenesis models. Gut microbiome composition was assessed using 16S rDNA-Seq analysis, chemokines were quantified in murine sera, and the tumor immune microenvironment (TIME) and gut immune milieu were comprehensively studied using single-cell RNA-sequencing and flow cytometry.

Results Syngeneic G mice receiving FMT from GL donors (G < GL) exhibited significantly increased tumor growth compared to G < G mice. This effect was recapitulated in an independent syngeneic model (KrasG12D/LKR13 cells in wild-type mice) and tobacco carcinogen-exposed G < GL mice. Analysis of fecal pellets using 16S rDNA-Seq revealed significant differences in gut beta diversity between G < G and G < GL mice, with elevated abundance of tumor-promoting Alistipes and reduced levels of immunotherapy-favorable taxa Ruminococcus and Akkermansia. Flow cytometry analysis of the colonic lamina propria demonstrated an inflamed environment in G < GL mice with increased inflammatory immune cell frequency. This local gut inflammation was accompanied by a systemic inflammatory response, as indicated by elevated inflammatory chemokines in the sera. Single-cell RNA-sequencing and flow cytometry analysis of tumors revealed an enhanced immunosuppressive phenotype in the TIME of G < GL mice, including increased fractions of T regulatory and exhausted T cells, along with reduced levels of activated T cells. Flow cytometry confirmed enhanced immunosuppression in G < GL mice, including increased fractions of myeloid-derived suppressor cells in the TIME. The dysbiotic gut, with its associated systemic inflammation and immunosuppression of the TIME, significantly impacted the response to ICB, with G < GL mice demonstrating reduced response and sensitivity to anti-PD1 treatment compared to G < G mice.

Conclusions Our findings show that gut microbiome dysbiosis fosters lung cancer development by promoting immunosuppression, perhaps via a local and systemic gut microbiota-immune system crosstalk (figure 1). Modulating the gut microbiome may offer promising strategy for interception or early treatment of lung cancer.

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REFERENCES