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The Involvement of MDSCs-Bacteria Crosstalk in Colitis as a Predisposing Factor for Colitis-Associated Colorectal Cancer

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Abstract

Inflammatory Bowel Disease (IBD), composed of Crohn's Disease (CD) and Ulcerative Colitis (UC), represents a chronic inflammatory condition that is associated, in some cases, with a predisposition of the host to Colitis-Associated Colorectal Cancer (CAC). Both IBD and CAC are characterized by immune system dysregulation and changes in intestinal microbiota composition (dysbiosis). The dysbiotic bacteria invade the intestinal tissue and are found to interact with diverse immune cells of which one key population is represented by Myeloid-Derived Suppressor Cells (MDSCs).

MDSCs are a heterogeneous population of immature myeloid cells that, under normal conditions, give rise to immune cells from the myeloid lineage. However, under pathologies associated with chronic inflammation, these cells become highly polarized with enhanced suppressive activity, suppressing both the innate and adaptive immune systems by different routes.

Our general aim is to better understand the involvement of MDSC-Bacteria crosstalk in colitis as a predisposing factor for CAC development.

Herein, we demonstrate that IBD is characterized by elevated levels of MDSCs with enhanced suppressive activities, which can promote progression to CAC by inducing persistent immunosuppression and a proinflammatory environment in the colon during the IBD stage. In the intestines of IBD individuals, we found that MDSCs can often be seen in close proximity to tissue-invading bacteria, resulting in a polarization of these cells toward a highly suppressive and proinflammatory phenotype.

Suppression mediated by the MDSCs is linked to the secretion of proinflammatory cytokines, nitric oxide, the arrest of T cell proliferation, and downregulated levels of CD247, a key signaling molecule expressed by T cells. Since MDSCs play a major role in the dysregulation of the immune system, different combinatorial therapeutic strategies to recuperate the host's health and regress the disease were tested, aiming at targeting the MDSCs. To this end, we tested different metabolites and identified a potent metabolite inhibiting the bacteria-induced MDSCs polarization. The effects of this metabolite on MDSCs are currently under investigation, using proteomics analysis through the exploration of the downstream mechanism. These studies will help discover novel pathways that mediate the immunosuppression induced by MDSC upon their interaction with bacteria, towards the development of specific anti-MDSC therapeutic modalities.

Our long-run aims are to alleviate intestinal inflammation by manipulating MDSC-induced immunosuppression, combat bacteria-induced MDSC polarization, and study the underlying mechanisms of unique metabolites as MDSC inhibitors.