Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer-related mortality worldwide. CRC has typically been a disease associated with increasing age, and heightened screening has resulted in a decline in CRC incidence in older individuals. However, there has been an alarming increase in early-onset colorectal cancers in individuals less than 50 years of age. Thus, there is a clear need to identify and mitigate risk factors, particularly lifestyle factors, that contribute to colorectal carcinogenesis.

A hallmark of colorectal carcinogenesis is dysregulation of Wnt signaling and expansion of stem-like cells, marked by expression of Lgr5. Obesity and a high-fat diet (HFD) have been associated with increased risk for developing CRC, but the mechanism behind this association remains to be fully understood. Beyaz et al. had previously demonstrated that an HFD can drive Lgr5+ intestinal stem cell (ISC) proliferation and their capacity to self-renew via peroxisome proliferator-activated receptor-delta (PPAR-δ) signaling. A HFD has also been associated with pathologic changes in the composition of the gut microbiota, known as dysbiosis, that can directly contribute to colorectal tumorigenesis. Recently, Beyaz et al. discovered a new mechanism linking diet and CRC risk via gut microbiota-mediated modulation of anti-tumor immunity.

An essential step in immune surveillance is the presentation of tumor antigen via major histocompatibility complex (MHC) class I and MHC class II on the cell surface of antigen-presenting cells for recognition by CD8 and CD4 T cells, respectively, that lead to their activation.

In a recent issue of Cell Stem Cell, Beyaz et al. show that high-fat diets promote tumorigenesis by reducing major histocompatibility complex (MHC) class II expression in intestinal stem cells. Dietary modulation of epithelial MHC II expression is regulated by the gut microbiota.

Although cytotoxic CD8 T cells have been considered the major players in immune surveillance, CD4 T cells also play a critical role in anti-tumor immunity via secretion of effector cytokines and promotion of CD8 cytotoxic T cell responses. Consistently, high MHC class II expression has been associated with better prognosis in CRC patients while loss of expression correlated with reduced tumor-infiltrating T cells and higher metastatic potential. In a kras-driven mouse model of intestinal cancer, a HFD altered the gut microbiome, which, in turn, resulted in reduced MHC class II expression on dendritic cells and increased tumorigenesis.

Beyaz et al. found that HFDs reduced MHC class II expression in intestinal epithelial cells, and in particular, in ISCs, that was independent of PPAR-δ signaling and obesity that was not diet-related. Using an orthotopic mouse model of CRC in which Lgr5+ ISCs with loss of the tumor suppressor Apc were implanted into the colon, Beyaz et al. demonstrated that MHC class II-negative ISCs exhibited greater tumor-initiating capacity than their MHC class II-positive counterparts in HFD-fed mice. Furthermore, in mice that had loss of APC as well as MHC class II expression in Lgr5+ ISCs, larger tumors developed compared with mice that had intact MHC class II expression. MHC class II-related effects in Lgr5+ ISCs were not cell-intrinsic and did not involve stemness, as MHC class II-deficient APC-null Lgr5+ ISCs were still capable of forming tumor organoids in vitro and had similar organoid forming efficiencies to that of their MHC class II-expressing counterparts. Rather, the effects on tumorigenesis required the presence of B and T cells that mediate adaptive immunity. These findings by Beyaz et al. are exciting in that they suggest a role for ISC MHC class II-mediated immune surveillance in suppressing carcinogenesis that can be modulated by the diet.

How MHC class II expression in ISCs is regulated is not entirely known; however, Beyaz et al. demonstrated that the gut microbiota plays a critical role. Numerous studies have highlighted the role of the gut microbiota in colorectal carcinogenesis. Specifically, several bacterial species, such as Fusobacterium nucleatum, enterotoxigenic Bacteroides fragilis, and pks+ Escherichia coli are enriched in human CRC. These oncomicrobes have been shown to promote tumorigenesis in preclinical models via several mechanisms including genotoxicity, dysregulation of Wnt signaling via β-catenin activation, and upregulation of pro-inflammatory signaling pathways. In the study by Beyaz et al., a new mechanism was revealed, namely regulation of ISC MHC class II expression (Figure 1). In particular, Beyaz et al. showed that HFDs resulted in changes in the composition of the gut microbiota, including a significant decrease in the abundance of Helicobacter and Odoribacter spp. Co-housing and fecal transplantation studies using Helicobacter-positive and Helicobacter-negative donors confirmed the direct correlation between Helicobacter abundance and intestinal epithelial MHC class II expression levels. Future work involving monoassociation studies in gnotobiotic mice will be needed to further clarify the role of Helicobacter as well as other bacterial populations whose...
Spotlight of ISCs revealed downregulation of inhibited reduced intestinal interferon-(tide-binding oligomerization domain of Toll-like receptor (Tlr)), which a HFD diet reduced the expression of sensing gut microbes and observed innate immune receptors that are capable of ISC MHC class II associated with decreased abundance of Helicobacter and Odoribacter, decreasing anti-tumor immunity, in addition, HFDs upregulate PPAR-α signaling, which leads to ISCs expansion and tumorigenesis. Bacteria associated with dysbiosis can also contribute to tumorigenesis by promoting DNA damage and oncogenic activation of Wnt/β-catenin signaling.

To determine how the gut microbiota modulates MHC class II expression in ISCs, Beyaz et al. measured levels of innate immune receptors that are capable of sensing gut microbes and observed that a HFD diet reduced the expression of Toll-like receptor (Tlr) 2 and nucleotide-binding oligomerization domain (Nod) 2. In addition, HFD-fed mice exhibited reduced intestinal interferon-γ (IFN-γ) levels, and bulk RNA-seq of ISCs revealed downregulation of IFN-γ-induced genes. Treatment of HFD-fed mice with a dual TLR2/NOD2 agonist or IFN-γ increased MHC class II expression in ISCs. These findings are in line with previous evidence showing that the gut microbiota regulates the intestinal expression of TLR2 and NOD2, and that TLR-mediated expression of MHC class II requires IFN-γ production by lamina propria lymphocytes. Altogether, these findings highlight the interplay between diet, the gut microbiota, and the host immune system on CRC susceptibility and support the incorporation of dietary strategies to promote anti-tumor immunity.

Figure 1. HFD and dysbiosis promote intestinal tumorigenesis
The presence of Helicobacter and Odoribacter is associated with increased ISC expression of MHC class II mediated in part by NOD2, TLR2, and IFN-γ, which promotes immune surveillance. In the presence of dysbiosis and/or chronic ingestion of HFDs, there is reduced expression of NOD2, TLR2, and IFN-γ, and ISC MHC class II associated with decreased abundance of Helicobacter and Odoribacter, resulting in reduced anti-tumor immunity. In addition, HFDs upregulate PPAR-α signaling, which leads to ISC expansion and tumorigenesis. Bacteria associated with dysbiosis can also contribute to tumorigenesis by promoting DNA damage and oncogenic activation of Wnt/β-catenin signaling.

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