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Gut microbiota and colon cancer: the carbohydrate link

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Abbreviations: CRC, colorectal cancer; MMR, mismatch repair.

Understanding the complex pathophysiology of colorectal cancer and the interaction between host genetics, the gut microbiome, and diet has attracted significant attention in the last few years. The discovery that gut microbial metabolites may dictate the course of colorectal cancer progression supports the development of microbial-targeted strategies.

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths. Normally associated with numerous genetic alterations, a relatively large proportion of CRC cases are due to a DNA mismatch repair (MMR) deficiency known as hereditary nonpolyposis colorectal cancer or Lynch syndrome, and MMR defects are also observed in approximately 20% of sporadic CRCs.[1] However, based on the known roles of the MMR pathway, it is unclear why MMR inactivation predisposes more to CRC than to other cancers. One possibility is an unusual interplay between MMR deficiency and the colon epithelial cell microenvironment. Gut microbiota and specific diets have been established as key contributors to CRC development.[2-4] In a study published on July 17th in the journal Cell, we revealed a novel link between gut microbiota and colon cancer; specifically, gut microbes metabolize dietary carbohydrates into metabolites that fuel CRC development in MMR-deficient mice.[5] Using different antibiotic treatment regimens that ablate specific members of the gut flora, we achieved a 75% reduction in polyp numbers in MMR-deficient mice. This effect was also reproduced by feeding mice with a diet reduced in carbohydrates. Importantly, antibiotic treatments and the low carbohydrate diet induced significant alterations in the microbial community that attenuated CRC development, but only in MMR-deficient mice. These findings therefore suggest a specific interplay between gut microbiota and the status of the MMR system. In an attempt to understand the nature of this interaction, we found that gut microbes do not affect CRC through inflammatory responses or by inducing genetic mutations. Instead, our results pointed to a more intimate mechanism that is associated with mutations in MMR genes. The discovery that MMR deficiency predisposes to hyperproliferation of colon epithelial cells as a result of deregulated WNT/β-catenin signaling was a key piece of the puzzle. Hence, we hypothesized that metabolism of carbohydrates by specific members of the gut microbiota may provide the fuel that drives aberrant proliferation and accelerated polyp formation in MMR-deficient mice. Indeed, butyrate, a principal carbohydrate-derived metabolite, was the only short chain fatty acid that was significantly diminished by all treatments that led to a reduction in polyps in MMR-deficient mice. In addition, by monitoring the effects of treatments that reduce polyp numbers on the gut microbiota, we found that all of these treatments lead to a reduction of Firmicutes, to which the major butyrate-producing bacteria belong. We further demonstrated that butyrate stimulated the hyperproliferation of MMR-deficient colonocytes. Collectively, these results implicate a role for butyrate-producing gut microbiota in CRC development in MMR-deficient mice and therefore provide a novel link between host genetics, diet, and microbiota.

Carbohydrates account for about half of the daily caloric intake of adults on a western-style diet, and previous studies have linked carbohydrate-rich diets to colorectal cancer in humans.[6–8] Our study further implicates carbohydrates in the etiology of MMR-deficient CRC.[5] Although significant, the relative risk of a carbohydrate-rich diet for CRC is not very high.[7] Since only ~20% of CRCs are defective in MMR, it would be important to test whether the observed relative risk value would be higher if patients were stratified based on the status of the MMR system in their tumors. Indeed, treatment strategies for other cancers are currently being based on genetic findings. Future efforts should also focus on elucidating which type of

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dietary carbohydrates contributes to CRC development, and specifically CRC that harbors mutations in the MMR system. For example, are highly fermentable fibers such as pectin and oat bran more strongly associated with CRC development than poorly fermented fibers such as wheat bran, cellulose, and resistant starches? We also report that butyrate interacts with the MMR-deficient colonocytes in a way that stimulates proliferation and accelerates transformation of the cells although the mechanism of this intimate interaction is not yet understood. It is well known that fiber-derived fermentation products, including short chain fatty acids, that are produced by anaerobic microbiota are essential to maintain normal colonic health and homeostasis. However, the role of butyrate in CRC development has been quite controversial. Many of these discrepancies are thought to be due to the different settings between *in vivo* and *in vitro* experiments and different butyrate doses tested in these experiments. Also, the effects of butyrate will strongly depend on the presence of other microbial metabolites.[9] Recent advances in a number of technologies that could precisely measure the concentrations of butyrate at different parts of the gastrointestinal tract will certainly help to explain the differential effects of butyrate on colon epithelial cells. Furthermore, it is now time to look at the effects of butyrate on CRC development in the context of specific genetic backgrounds. Since butyrate activity in the cells depends on its concentration, the proliferative and energy status of the cells,[10] and the presence of other metabolites,[9] our study adds another level of complexity in which the genetic background dictates the effects of butyrate.[5] Our results also demonstrate that alterations in gut microbial communities through simple changes in diet could significantly affect the course of CRC. Therefore, manipulation of the gut microbiota opens new opportunities for controlling CRC progression. Certainly, development of such microbiota-targeted therapies will be very challenging and will require considerable work to fully elucidate the complex interactions between a given individual's genetic background and microbial community.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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