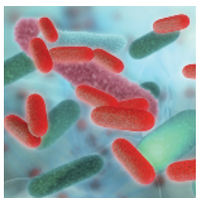
Microbiome

Major finding: A high-fat diet alters the composition of the gut microbiome to promote intestinal tumorigenesis.

Concept: Oncogenic *Kras* and diet-induced changes in gut microbiota impair immune-mediated antitumor function.

Impact: Modulation of dietary-induced dysbiosis may reduce the risk of intestinal cancer in patients.

DIET-INDUCED DYSBIOSIS INFLUENCES SUSCEPTIBILITY TO INTESTINAL CANCER



Multiple studies have linked a high-fat diet (HFD) and changes in the gut microbiome composition independently with increased risk for intestinal cancer. However, although an HFD has been shown to induce alterations in the intestinal microbiota, the mechanisms by which HFD-induced dysbiosis promotes tumorigenesis are poorly understood. To study the molecular effects of HFD on tumorigenesis, Schulz, Atay, Heringer, and colleagues utilized a genetically susceptible mouse model of serrated hyperplasia driven by oncogenic *Kras* and exposed these mice to an HFD regimen. Compared with control mice, HFD-fed mice displayed a higher percentage of low-grade and high-grade dysplasia and invasive carcinoma in the small intestine, and an HFD accelerated tumor progression independent of obesity. HFD-fed mice exhibited an altered gut microbiota composition relative to mice fed a normal diet, supporting the importance of microbial dysbiosis in tumor susceptibility. Analysis of duodenal samples from HFD-fed mice showed a significant reduction in host immune signaling pathways, including decreased expression of genes involved in antigen recognition, impaired antimicrobial function of Paneth cells, and diminished MHC class II presentation by dendritic cells. Systemic deletion of the immune adaptor protein myeloid differentiation primary response 88 (MYD88), antibiotic treatment, or supplementation with the short-chain fatty acid butyrate protected HFD-fed mice against tumor progression; the tumor-protective effect of butyrate was associated with a shift in microbiota composition to that of normal mice and partial restoration of immune function. Interestingly, colonization of healthy *Kras*-mutant mice with fecal samples from HFD-fed mutants resulted in intestinal tumor formation, suggesting that transfer of HFD-modulated microbiota is sufficient to transmit disease. Overall, these data support the hypothesis that diet-induced changes in gut microbiota composition play a major role in oncogene-driven intestinal tumor formation. Moreover, this study highlights the importance of personalized dietary intervention in genetically and environmentally susceptible patients, which may alter the gut microbiome to reduce the risk of intestinal tumorigenesis. ■

Schulz MD, Atay C, Heringer J, Romrig FK, Schwitalla S, Aydin B, et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. Nature 2014 Aug 31 [Epub ahead of print].

Bladder Cancer

Major finding: Inactivation of the NOTCH pathway drives bladder tumorigenesis.

Mechanism: NOTCH signaling suppresses proliferation and ERK1/2 phosphorylation by inducing expression of DUSPs.

Impact: Reactivation of NOTCH signaling may be therapeutically beneficial in patients with bladder cancer.

THE NOTCH PATHWAY PLAYS A TUMOR SUPPRESSIVE ROLE IN BLADDER CANCER

NOTCH signaling regulates a number of cellular processes, including proliferation, differentiation, and apoptosis, and has been implicated as either an oncogene or a tumor suppressor in various tumor types. Using full-exon sequencing, Rampias and colleagues identified somatic loss-of-function mutations in NOTCH pathway components, in particular the NOTCH1 and NOTCH2 receptors, in 43% of human bladder transitional cell carcinoma (TCC) samples examined. In addition, the *NOTCH1* locus was subject to frequent copy-number loss, which was associated with *NOTCH1* mutation in several cases, suggestive of LOH. Inactivation of the NOTCH pathway was associated with decreased expression of NOTCH target genes and correlated with shorter overall survival in patients with superficial or muscle-invasive bladder cancer. Sequencing of known bladder cancer oncogenes, including *FGFR3*, *RAS*, and *PIK3CA*, showed only partial overlap with NOTCH pathway mutations and *NOTCH1* copy-number loss. Furthermore, tumors with NOTCH inactivation, either alone or in combination with *FGFR3* or *RAS* mutations, exhibited increased phosphorylation of ERK1/2, suggesting that NOTCH negatively regulates ERK1/2 activation. Consistent with this idea, activation of NOTCH signaling inhibited the proliferation of TCC cell lines and diminished the phosphorylation of ERK1/2, but not upstream signaling components, by directly inducing the transcription of several dual-specificity phosphatases (DUSP), which mediate dephosphorylation of ERK1/2. Genetic inactivation of NOTCH signaling in mice promoted the development of high-grade invasive urothelial carcinomas characterized by ERK1/2 phosphorylation and expression of basal cell markers, similar to the aggressive basal subtype of bladder cancer in humans, whereas overexpression of activated NOTCH1 reversed the cancer phenotype. Similarly, urothelium-specific loss of NOTCH signaling also resulted in the formation of bladder tumors with basal characteristics. In sum, these data implicate loss of NOTCH signaling as a driver event in bladder cancer and suggest that reactivation of the NOTCH pathway may be therapeutically beneficial. ■

Rampias T, Vgenopoulou P, Avgeris M, Polyzos A, Stravodimos K, Valavanis C, et al. A new tumor suppressor role for the NOTCH pathway in bladder cancer. Nat Med 2014;20:1199–205.