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Microbiome

Major finding: Colitis-induced inflammation induces the expansion of bacteria that promote tumorigenesis.

Concept: Abnormal expansion of genotoxic *E. coli* leads to increased DNA damage in colon epithelial cells.

Impact: Chronic inflammation creates a tumorigenic environment by affecting both the host and microbiota.

ALTERATIONS IN THE INTESTINAL MICROBIOTA PROMOTE COLORECTAL CANCER

Chronic intestinal inflammation is a risk factor for colorectal cancer, but the underlying mechanism is unclear. Given previous evidence implicating the intestinal microbiota in the development of colitis-associated colorectal cancer in mice, Arthur and colleagues sequenced the bacterial 16S rRNA gene in mucosal biopsies and stool samples to compare the microbial composition of wild-type mice with that of colitis-susceptible *interleukin-10* (*Il10*)-deficient mice that selectively develop colorectal cancer following carcinogen exposure. Microbial diversity was significantly reduced in *Il10*-deficient mice compared with wild-type controls but was not affected by treatment with the colon-specific carcinogen azoxymethane (AOM), suggesting that inflammation, not cancer, causes a shift in the composition of the intestinal microbiota. Specifically, the abundance of *Escherichia coli* was increased 100-fold in *Il10*-deficient mice. The fact that colonization of germ-free *Il10*-deficient mice with commensal *E. coli*, but not commensal *Enterococcus faecalis*, led to invasive mucinous adenocarcinoma in 80% of mice despite a similar host inflammatory response in both groups suggested a selective role of the microbiota on colorectal cancer development. Unlike *E. faecalis*, *E. coli* harbors a pathogenicity island that encodes genotoxic polyketide synthases (*pks*). Notably, *pks* was detected in 40% of patients with inflammatory bowel disease and 66.7% of patients with colorectal cancer, compared with only 20.8% of healthy controls, and was sufficient to induce DNA damage in a rat intestinal epithelial cell line. *In vivo*, the absence of *pks* did not affect *E. coli*-induced colitis or AOM-dependent tumor initiation in *Il10*-deficient mice but led to a significant reduction in tumor burden and invasive carcinomas that was associated with a significant decrease in DNA damage foci in colon epithelial cells. Collectively, these findings provide evidence that host inflammation and expansion of genotoxic bacteria create a favorable microenvironment for the development of colorectal cancer. ■

Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 2012 Aug 16 [Epub ahead of print].

Drug Discovery

Major finding: Increased PKM2 tetramerization and pyruvate kinase activity suppress tumorigenesis.

Concept: Tumor-specific PKM2 expression may be due to selection against high pyruvate kinase activity.

Impact: PKM2 activators promote a metabolic state that is not conducive to biosynthesis and cell proliferation.

PYRUVATE KINASE M2 ACTIVATORS INHIBIT TUMOR GROWTH

Increased nutrient uptake and altered metabolic pathways in cancer cells support the biosynthetic demands of a hyperproliferative state. Cancer cells preferentially express the M2 isoform of pyruvate kinase (PKM2), which catalyzes the last step of glycolysis. The relatively low pyruvate kinase activity of PKM2 compared with other pyruvate kinase isoforms facilitates the diversion of glycolytic metabolites into anabolic pathways that support rapid growth and proliferation. Because PKM2 is specifically expressed in proliferating cells, one possibility is that PKM2 expression is selected for during oncogenic transformation. However, Anastasiou and colleagues hypothesized that there is instead selection against high pyruvate kinase activity associated with the constitutively active PKM1 isoform expressed in many normal cells, suggesting that synthetic PKM2 activators might inhibit cancer cell proliferation. Consistent with this paradigm, forced expression of PKM1 in PKM2-expressing cancer cells increased total cellular pyruvate kinase activity and suppressed xenograft tumor growth. Furthermore, PKM2 activators stabilized the tetrameric active form of PKM2, increased pyruvate kinase activity, and reduced the rate of cancer cell proliferation under hypoxic conditions in association with decreased intracellular concentrations of biosynthetic intermediates. It is notable that one PKM2 activator, TEPP-46, was orally bioavailable and had favorable pharmacokinetic and pharmacodynamic properties in mice. Treatment with TEPP-46 was well tolerated, and similar to the effects seen in cultured cells, treatment of xenograft tumor-bearing mice with TEPP-46 increased tetramerization of PKM2 and decreased intratumoral levels of lactate, ribose phosphate, and serine compared with levels in vehicle-treated mice. Additionally, TEPP-46 treatment safely led to a significant delay in the formation of xenograft tumors and reduction in tumor burden. PKM2 activation may therefore represent a strategy to specifically target the altered metabolic state of cancer cells and suppress tumor growth. ■

Anastasiou D, Yu Y, Israelsen WJ, Jiang JK, Boxer MB, Hong BS, et al. Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis. Nat Chem Biol 2012 Aug 26 [Epub ahead of print].

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AACR American Association for Cancer Research

CANCER DISCOVERY

Pyruvate Kinase M2 Activators Inhibit Tumor Growth

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