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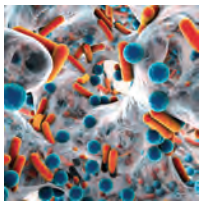
Microbiome

Major finding: Colonic biofilms may accelerate tumorigenesis in patients with familial adenomatous polyposis (FAP).

Concept: Biofilms of *E. coli* and *B. fragilis* secrete oncotoxins that increase IL17 and promote DNA damage.

Impact: Tumorigenic bacteria in the colon may accelerate tumorigenesis in patients with FAP.

TUMORIGENIC COLONIC BACTERIA MAY PROMOTE EARLY NEOPLASIA



In the colon a dense mucus layer separates the colonic epithelium from the gut microbiome. However, in patients with sporadic colorectal cancer, gut microbiome abnormalities can develop including the formation of biofilms in the normal mucus layer, which is linked to a pro-oncogenic state. This suggests that biofilm formation may promote colon cancer progression, but this has not yet been investigated in hereditary colon cancer. Dejea and colleagues studied the colonic mucosal bacteria in patients with familial adenomatous polyposis (FAP), a hereditary condition caused by germline *APC* mutations that results in benign precursor lesions that can progress to colorectal cancer. In patients with FAP, bacterial invasion through the mucus layer was observed, with patchy biofilms comprised primarily of *E. coli* and *B. fragilis* scattered along the entire length of the colon. Mucosal bacterial enrichment was also observed in a mouse model of FAP driven by mutant APC, indicating that *Apc* mutations may promote mucosal bacterial adherence. *E. coli* containing the polyketide synthase (*pks*) genotoxic island produce the colibactin (*clbB*) genotoxin, which induces DNA damage and colon tumorigenesis, and enterotoxigenic *B. fragilis* (termed ETBF) produce the *B. fragilis* toxin (*bft*), which is linked to sporadic colorectal cancer. Cultures of mucosal tissues from 25 patients with FAP revealed that 68% had *pks*$^+$ *E. coli*, compared with 22% of healthy controls, and 60% had ETBF, compared with 30% of healthy controls, and *bft* and *clbB* were present in the mucus layer of FAP biofilms in direct contact with the FAP epithelium. In two mouse models of FAP, cocolonization with *pks*$^+$ *E. coli* and ETBF accelerated colon tumorigenesis and reduced survival. Cocolonization was associated with an IL17-mediated increase in colon inflammation that was necessary, but not sufficient, for tumorigenesis. Further, cocolonization enhanced DNA damage in the colonic epithelium. Collectively, these findings indicate that tumorigenic bacteria in the colon may promote early tumorigenesis in patients with FAP. ■

Dejea CM, Fathi P, Craig JM, Boleji A, Taddese R, Geis AL, et al. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. Science 2018;359:592–7.

Metastasis

Major finding: Asparagine depletion reduces breast cancer invasion and metastasis without affecting primary tumor growth.

Mechanism: Asparagine content is selectively elevated in proteins that drive epithelial-to-mesenchymal transition.

Impact: Therapies that alter asparagine levels may potentially inhibit breast cancer metastasis.

ASPARAGINE BIOAVAILABILITY DRIVES BREAST CANCER METASTASIS

Metastatic relapse is the main cause of mortality in patients with breast cancer; recently, it has been shown that clonal subpopulations of primary mouse mammary 4T1 tumors that are equally proficient at generating circulating tumor cells (CTC) exhibited variable metastatic potential. To identify drivers of breast cancer metastasis, Knott, Wagenblast, and colleagues performed gene expression analysis of two CTC-proficient 4T1 subclones, the highly metastatic subclone 4T1-T and the nonmetastatic subclone 4T1-E. Candidate drivers, which were overexpressed in 4T1-T cells compared with 4T1-E cells, were enriched for metastasis-associated genes and overexpressed in primary breast tumors that subsequently exhibited relapse of disseminated breast cancer. *In vitro* and *in vivo* screening of 4T1-T cells with candidate drivers targeted by pools of shRNAs identified asparagine synthetase (*Asns*) as the most clinically relevant candidate driver of breast cancer metastasis. Although *Asns* depletion in 4T1-T cells did not affect primary tumor growth *in vivo*, *Asns*-depleted 4T1-T cells had decreased invasive potential *in vitro* and metastatic potential *in vivo*. Metastases were nearly undetectable after treatment with L-asparaginase, which degrades asparagine, in ASNS-silenced 4T1 or MDA-MB-231 orthotopic tumor models, although in these models primary tumor growth was also suppressed. Similarly, parental 4T1 cells grown in medium supplemented with asparagine, but not other nonessential amino acids, exhibited increased invasive potential *in vitro*, and mice harboring 4T1 tumors treated with L-asparaginase or fed a low-asparagine diet experienced a decrease in metastasis with no effect on primary tumor growth. Asparagine silencing resulted in the depletion of proteins associated with epithelial-to-mesenchymal transition (EMT), and proteomic analysis revealed that EMT-associated proteins had higher asparagine content compared with the proteome as a whole. Similarly, *Asns*-depleted 4T1-T tumors and metastases exhibited decreased expression of EMT markers. These results describe a role for asparagine bioavailability as a driver of metastasis in breast cancer and suggest potential antimetastatic therapeutic approaches. ■

Knott SR, Wagenblast E, Khan S, Kim SY, Soto M, Wagner M, et al. Asparagine bioavailability governs metastasis in a model of breast cancer. Nature 2018;554:378–81.

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AACR American Association for Cancer Research

CANCER DISCOVERY

Asparagine Bioavailability Drives Breast Cancer Metastasis

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