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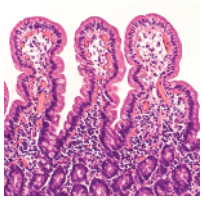
Colon Cancer

Major finding: Farnesoid X receptor is a tumor suppressor linking intestinal self-renewal and bile acid homeostasis.

Mechanism: Bile acids antagonize FXR function to drive transformation of intestinal stem cells.

Impact: Pharmacologic activation of FXR is a potential therapeutic strategy to delay CRC progression.

FARNESOID X RECEPTOR SUPPRESSES Lgr5+ CANCER STEM CELL PROLIFERATION



Among the many risk factors for colorectal cancer (CRC) is elevated serum levels of toxic bile acids (BA) caused by a high-fat diet. Erosion of the crypt-villi architecture is the driving force behind increased BA exposure of Lgr5+ intestinal stem cells (ISC), the cell of origin of colonic neoplasias caused by mutation of the APC tumor suppressor, but how precisely this exposure contributes to initiation and progression of CRC remains unclear. Fu and colleagues showed that increased BA exposure in the $APC^{min/+}$ mouse model inactivates farnesoid X receptor (FXR)–mediated control of Lgr5+ proliferation and contributes to malignant transformation and CRC progression. Mice subjected to a high-fat diet exhibited multiple intestinal abnormalities and increased serum levels of the BAs tauro-β-muricholic acid (T-βMCA) and deoxycholic acid (DCA). T-βMCA inhibited FXR activity, decreased intestinal integrity, increased DNA damage and chromosomal aberrations, and accelerated tumor growth in the intestine and colon. Deletion of FXR in ISCs increased growth and enhanced expression of proliferation marker genes; conversely, treatment with the FXR agonist FexD inhibited basal WNT signaling. Treatment of organoids or $APC^{min/+}$ mice with FexD abrogated T-βMCA–induced proliferation, reduced expression of ISC genes, and derepressed genes in the p53 tumor suppressor pathway. FexD also reduced serum levels of T-βMCA and DCA, restored intestinal integrity and function, increased cellular differentiation, and significantly reduced tumor frequency and delayed tumor progression in both adenoma and adenocarcinoma models. Collectively, these findings identify BAs as antagonists of FXR signaling, whose disruption is critical for intestinal stem cell proliferation and disease progression. Moreover, they highlight the potential for FXR agonists as effective therapeutic agents in limiting CRC initiation and progression. ■

Fu T, Coulter S, Yoshihara E, Oh TG, Fang S, Cayabyab F, et al. FXR regulates intestinal cancer stem cell proliferation. Cell 2019;176:1098–112.

Immunology

Major finding: Inhibition of DPP4 promotes an IL33-driven eosinophil-mediated antitumor response.

Mechanism: DPP4 inhibition promotes migration of eosinophils into tumors by preventing inactivation of CCL11.

Impact: Combination therapy of DPP4i and immune checkpoint blockade may have therapeutic potential.

DPP4 INHIBITION CONTROLS TUMOR GROWTH VIA EOSINOPHIL RECRUITMENT

Post-translational modifications of chemokines can have significant effects on their functions. Dipeptidyl peptidase 4 (DPP4), also known as CD26, cleaves proteins at an amino acid consensus motif that is found on 18 different human chemokines, among them CXCL10. Previous studies have shown that cleavage of CXCL10 by DPP4 reduces migration of T cells and natural killer cells in several tumor models. Additionally, treatment with the DPP4 inhibitor (DPP4i) sitagliptin increases lymphocyte trafficking to tumors and improves tumor immunity and response to T cell–mediated therapy in mouse models. Hollande and colleagues further investigated the mechanism by which inhibition of DPP4 reduces tumor growth in syngeneic and orthotopic models of hepatocellular carcinoma (HCC) and breast cancer and found that eosinophils migrate to the tumor site to facilitate the DPP4i-mediated antitumor effect. Furthermore, profiling cytokine and chemokine expression in DPP4i-treated tumor extracts revealed higher expression of the eosinophil chemoattractant CCL11, which is a known target for DPP4-mediated truncation and inactivation, and the cytokine IL33, known to have a role in activation of eosinophil effector function. Neutralization of CCL11 eliminated the antitumor effect of DPP4i, whereas injection of CCL11 promoted eosinophil migration. In addition, expression of IL33 by tumor cells was a prerequisite for the antitumor effect of eosinophils, with blockade of IL33 resulting in reduced efficacy of DPP4i in *in vivo* models and forced IL33 expression conferring sensitivity to eosinophil targeting that did not previously exist. These findings demonstrate that the CCL11–IL33 axis is crucial for the DPP4i antitumor response mediated by eosinophils. Combined treatment with sitagliptin and anti–PD-1 and anti-CTLA4 also resulted in a significant reduction of tumor growth, indicating that T cells and eosinophils interact in mediating DPP4i antitumor response. Collectively, these results elucidate a mechanism by which eosinophils contribute to intrinsic antitumor immunity and checkpoint inhibitor–induced antitumor immunity. The combination of DPP4 inhibition and immune checkpoint blockade may therefore have therapeutic potential for patients with cancer. ■

Hollande C, Boussier J, Ziai J, Nozawa T, Bondet V, Phung W, et al. Inhibition of the dipeptidyl peptidase DPP4 (CD26) reveals IL-33-dependent control of tumor growth. Nat Immunol 2019;20:257–64.

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AACR American Association for Cancer Research

CANCER DISCOVERY

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