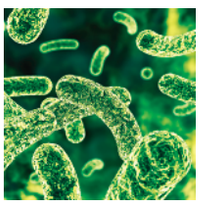
Microbiome

Major finding: Gut microbiota enhance the cytotoxic activity of anticancer immuno- and chemotherapies.

Mechanism: Commensal bacteria promote generation of proinflammatory cytokines, ROS, and pT_H17 cells.

Impact: Manipulation of human gut microbes may improve therapeutic responses to anticancer agents.

INTESTINAL BACTERIA REGULATE ANTICANCER THERAPY RESPONSES



Gut commensal microbiota modulate both local and systemic inflammatory responses, and disruption of the microbial balance, or dysbiosis, has been implicated in chronic inflammation–associated colon cancer. However, whether intestinal bacteria regulate anticancer therapy responses remains unknown. Iida and colleagues found that dysregulation of commensal microbiota via antibiotic treatment or use of germ-free mice impaired inhibition of tumor growth by CpG-oligodeoxynucleotide immunotherapy, suggesting that intestinal bacteria modify anticancer immune responses in the tumor microenvironment. Indeed, commensal microbiota and expression of Toll-like receptor 4 were required for induction of proinflammatory cytokines, including TNF, by tumor-associated myeloid cells. In addition, microbiota were also necessary for the early cytotoxic response to platinum chemotherapeutic compounds; elimination of microbiota reduced myeloid-cell generation of reactive oxygen species (ROS) in response to oxaliplatin, resulting in decreased DNA damage and diminished tumor cell death. In another study, Viaud and colleagues found that cyclophosphamide, which induces antitumor immune responses, stimulated translocation of specific Gram-positive commensal bacteria into lymph nodes and the spleen and dysbiosis in the small intestine of tumor-bearing mice. This subset of bacteria was necessary and sufficient for cyclophosphamide-induced polarization of pathogenic T-helper (T_H) 17 (pT_H17) cells and bacteria-specific T_H1 memory cells in the spleen. Furthermore, pT_H17-cell and T_H1-cell accumulation and cyclophosphamide-mediated inhibition of tumor growth were suppressed in the absence of commensal bacteria in multiple mouse tumor models, whereas adoptive transfer of pT_H17 cells restored the anticancer efficacy of cyclophosphamide in antibiotic-treated mice, supporting a critical role for pT_H17 cells in inducing the cytotoxic effects of chemotherapy. Together, these findings indicate that commensal bacteria mediate efficient therapeutic responses to various anticancer agents via modulation of antitumor immune responses and suggest that manipulation of intestinal bacteria may enhance the efficacy of these treatments. ■

Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 2013;342:967–70.

Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 2013;342:971–6.

Tumor Suppressors

Major finding: USP13 deubiquitinates PTEN to promote its protein stability and suppress tumorigenesis.

Mechanism: USP13 loss enhances glycolysis and tumor growth via PTEN degradation and AKT activation.

Impact: Downregulation of USP13 is positively correlated with PTEN protein loss in human breast cancer.

THE DEUBIQUITINASE USP13 REGULATES PTEN PROTEIN STABILITY

The tumor suppressor *PTEN* is commonly mutated or deleted in human tumors, including breast cancer, but can also be downregulated at the protein level, indicating that posttranslational mechanisms also modulate its expression and function. Indeed, recent studies have shown that ubiquitin ligases and the deubiquitinating enzyme (DUB) ubiquitin specific peptidase (USP) 7 regulate PTEN proteasomal degradation and subcellular localization, respectively; however, it remains unclear which DUBs promote PTEN protein stability. Among a panel of 30 DUBs, Zhang and colleagues identified five DUBs that interacted with PTEN, including USP7 and USP13; of these, only USP13 directly interacted with PTEN via its phosphatase domain, resulting in increased PTEN protein expression and reduced downstream phosphorylation of AKT, forkhead box O1 (FOXO1), and FOXO3 in human breast cancer cells. USP13-mediated regulation of PTEN protein was dependent on the catalytic activity of USP13, which triggered PTEN deubiquitination and stabilized PTEN protein without affecting its subcellular localization. Depletion of USP13 augmented cell proliferation and anchorage-independent growth, stimulated glucose uptake and glycolysis, and enhanced xenograft tumor growth via downregulation of PTEN expression and subsequent induction of AKT signaling. In contrast, USP13 overexpression suppressed cell proliferation and tumor growth and impaired glucose uptake in PTEN-expressing but not PTEN-deficient breast cancer cells, further supporting a tumor-suppressive function for USP13 via positive regulation of PTEN protein stability. Moreover, decreased expression of USP13 protein was positively correlated with PTEN protein downregulation in a panel of human breast cancer samples. These findings identify USP13 as a critical posttranslational regulator of PTEN and suggest that USP13 loss may drive PTEN inactivation and tumorigenesis in a large subset of patients with breast cancer. ■

Zhang J, Zhang P, Wei Y, Piao H, Wang W, Maddika S, et al. Deubiquitylation and stabilization of PTEN by USP13. Nat Cell Biol 2013;15:1486–94.

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