Published OnlineFirst September 28, 2018; DOI: 10.1158/2159-8290.CD-RW2018-168

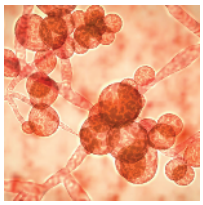
Microbiome

Major finding: Card9$^{-/-}$ mice had an increased fungal burden, and an antifungal reduced colitis-linked tumorigenesis.

Mechanism: CARD9-deficient myeloid cells exhibit defective inflammasome activation and IL18 maturation.

Impact: CARD9 signaling promotes maintenance of the microbial ecology to prevent colitis-associated tumorigenesis.

CARD9 DEFICIENCY PROMOTES COLITIS-ASSOCIATED TUMORIGENESIS



Dysregulation of the gut microbiome has been linked to tumorigenesis as well as to inflammatory bowel disease and colitis. Fungi are a significant component of the gut microbiome, and fungal recognition receptors induce downstream innate immune signaling through the common adaptor protein CARD9. However, the role of CARD9-dependent innate immunity in tumorigenesis has not been elucidated. Malik and colleagues found that *Card9*$^{-/-}$ mice had an increased susceptibility to colitis-associated colon cancer and an impaired immune response during tumorigenesis. *Card9*$^{-/-}$ mice had an increased fungal burden in the feces, and transferring the microbiota from tumor-bearing *Card9*$^{-/-}$ mice to wild-type mice increased the rate of colitis-associated tumorigenesis, demonstrating a role for the microbiota in CARD9 deficiency–induced tumorigenesis. *Card9*$^{-/-}$ macrophages displayed impaired fungicidal abilities in the gut, and *Card9*$^{-/-}$ mice had an increase in intestinal myeloid-derived suppressor cells (MDSC), which reduced the antitumor immunity. Antifungal treatment suppressed tumorigenesis and reduced MDSC number. Consistent with these findings, in patients with colon cancer, abundance of the commensal fungus *C. tropicalis* was linked to MDSC proportion. Similarly, in a related study, Wang and colleagues found that CARD9 expression reduced the susceptibility to colitis-associated cancer. CARD9 promoted inflammasome activation in the colon, and CARD9 deficiency reduced IL18 production by myeloid cells to restrict colitis. Mechanistically, CARD9 interacted with the SYK kinase in myeloid cells to promote the production of IL18 and IFNγ by intestinal CD8^{+} T cells. Adding IL18 or transferring wild-type myeloid cells was sufficient to reduce the tumor burden in *Card9*$^{-/-}$ mice. Conversely, antifungal treatment suppressed tumorigenesis. Collectively, these findings support a model whereby CARD9 deficiency results in impaired fungal clearing, MDSC accumulation, and suppression of effector T cells, suppressing antitumor immunity to promote colon tumorigenesis. ■

Malik A, Sharma D, Malireddi RK, Guy CS, Chang TC, Olsen SR, et al. SYK-CARD9 signaling axis promotes gut fungi-mediated inflammasome activation to restrict colitis and colon cancer. Immunity 2018;49:515–30.

Wang T, Fan C, Yao A, Xu X, Zheng G, You Y, et al. The adaptor protein CARD9 protects against colon cancer by restricting mycobiota-mediated expansion of myeloid-derived suppressor cells. Immunity 2018;49:504–14.

Clinical Trials

Major finding: A phase II trial evaluated lurbinectedin in patients with *BRCA1/2*-mutant and wild-type tumors.

Clinical relevance: Lurbinectedin achieved a 41% response rate in metastatic breast cancer with germline *BRCA1/2* mutation.

Impact: Lurbinectedin warrants further investigation for the treatment of patients with *BRCA1/2* mutations.

LURBINECTEDIN IS ACTIVE IN PATIENTS WITH *BRCA1/2* MUTANT BREAST CANCER

Germline mutations in *BRCA1* or *BRCA2* occur in 3% to 5% of patients with metastatic breast cancer and impair homologous recombination repair (HRR) of double-strand breaks, thereby sensitizing tumor cells to the antitumor agent trabectedin. The trabectedin analogue lurbinectedin is a selective inhibitor of active transcription that promotes irreversible stalling of RNA polymerase II, resulting in recruitment of DNA repair factors and induction of double-strand breaks. HRR deficiency enhances these effects, suggesting that *BRCA1/2*-mutant tumors may be sensitive to lurbinectedin treatment. Cruz and colleagues evaluated the safety and efficacy of lurbinectedin in a phase II trial of patients with metastatic breast cancer. Patients were treated in two arms, with 54 patients with germline *BRCA1/2* mutations treated in arm A and 35 patients with wild-type *BRCA1/2* or unknown status treated in arm B. The primary endpoint was objective response rate, and resistance mechanisms were investigated via exome sequencing and in patient-derived xenografts. The overall response rate was 41% in arm A and 9% in arm B, indicating that lurbinectedin has antitumor activity in patients with germline *BRCA1/2* mutations. In patients with *BRCA2* mutations, the overall response rate was 61%, the median progression-free survival was 5.9 months, and median overall survival was 26.6 months. The safety profile of lurbinectedin was acceptable. Exome sequencing of five paired pre- and post-treatment samples identified multiple mutations in the nucleotide excision repair pathway in three patients, and these mutations were linked to resistance in patient-derived xenograft models. Taken together, the results of this phase II trial indicate that lurbinectedin has antitumor activity and warrants further investigation in patients with metastatic breast cancer with *BRCA1/2* mutations. ■

Cruz C, Llop-Guevara A, Garber JE, Arun BK, Pérez Fidalgo JA, Lluch A, et al. Multicenter phase II study of lurbinectedin in BRCA-mutated and unselected metastatic advanced breast cancer and biomarker assessment substudy. J Clin Oncol 2018 Sep 21 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

CARD9 Deficiency Promotes Colitis-Associated Tumorigenesis

Cancer Discov 2018;8:1345. Published OnlineFirst September 28, 2018.