Autophagy

Major Finding: Autophagy-mediated MHC-I degradation facilitated immune evasion in pancreatic ductal adenocarcinoma.

Concept: Autophagy inhibition reduced tumor growth and increased tumor infiltration by $CD8^+$ T cells.

Impact: Autophagy inhibition plus immune-checkpoint blockade is worth investigating in pancreatic cancer.

AUTOPHAGY INHIBITION SYNERGIZES WITH IMMUNOTHERAPY IN PANCREATIC CANCER

Downregulation of the major histocompatibility complex class I (MHC-I) is common in pancreatic ductal adenocarcinoma (PDAC) and may contribute to immune evasion, but inactivating mutations affecting MHC-I are rare in this disease. Yamamoto, Venida, and colleagues found that, compared with nontransformed human pancreatic ductal epithelial cells, PDAC cells exhibited reduced localization of MHC-I on cell surfaces and increased localization of MHC-I in lysosomes and autophagosomes. The trafficking of MHC-I to lysosomes was dependent on the autophagy cargo receptor protein NBR1, which selectively targets substrates that are ubiquitylated—such as MHC-I in PDAC—for degradation. *In vitro*, genetic inhibition of autophagy increased MHC-I–mediated antigen presentation by PDAC cells, promoting proliferation and activation of and tumor cell killing by cytotoxic $CD8^+$ T cells. In mice injected with the autophagy-impaired PDAC cells, tumor growth was reduced, MHC-I expression on PDAC cells was increased, and greater numbers of tumor-infiltrating $CD8^+$ T cells were observed. Results from experiments in a liver metastasis mouse model supported these findings and demonstrated that autophagy inhibition led to lower metastatic burden. Knockdown of a critical component of MHC-I abolished the effects of autophagy inhibition in PDAC, demonstrating that the increased cell-surface expression of MHC-I upon autophagy inhibition is required for the observed increase in tumor infiltration by $CD8^+$ T cells and tumor cell killing. Genetic autophagy inhibition sensitized mouse PDAC to dual immune-checkpoint blockade (ICB) with anti–PD-1 plus anti-CTLA4 and increased the number of tumor-infiltrating $CD8^+$ T cells, a notable finding given that PDAC is notoriously refractory to ICB. Highlighting a potential means to exploit this finding clinically, treatment with the autophagy inhibitor and antimalarial drug chloroquine also synergized with dual ICB in mice. In summary, this study demonstrates that selective autophagy and lysosome degradation of MHC-I is a means by which PDAC may escape immune detection and provides evidence supporting further investigation of autophagy inhibition with ICB in PDAC treatment. ■

Yamamoto K, Venida A, Yano J, Biancur DE, Kakiuchi M, Gupta S, et al. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. Nature 2020;581:100–5.

Clinical Trials

Major Finding: Neoadjuvant immunotherapy was safe and showed evidence of efficacy in stage I–III colon cancer.

Concept: Counterintuitively, the treatment was active in mismatch repair–deficient and –proficient disease.

Impact: The major pathologic responses shown should be evaluated in larger trials with longer follow-up.

IMMUNOTHERAPY IS ACTIVE IN MMR-DEFICIENT AND MMR-PROFICIENT COLON CANCER

In advanced-stage colorectal cancer, immune-checkpoint blockade (ICB) with anti–PD-1 plus anti-CTLA4 has shown efficacy in mismatch repair (MMR)-deficient but not MMR-proficient disease. Hypothesizing that ICB might be effective in colon cancer at earlier stages—during which there is lower T-cell impairment, immunosuppression, and tumor burden as well as an absence of distant metastases—Chalabi and colleagues initiated a clinical trial of neoadjuvant ipilimumab (anti-CTLA4) plus nivolumab (anti–PD-1) in 40 patients with treatment-naïve stage I, II, or III colon cancer. Twenty-one patients had MMR-deficient tumors and 20 patients had MMR-proficient tumors, with one patient having both an MMR-deficient and an MMR-proficient tumor. Due to the lack of benefit from ICB previously observed in patients with MMR-proficient tumors, these patients also received the COX2 inhibitor celecoxib, which has been suggested to synergize with ICB. All patients underwent planned radical resections within six weeks of study inclusion. Treatment was generally well tolerated, with most side effects being grade 1 or 2, and no patients died due to treatment-related adverse effects. Of patients with MMR-deficient tumors, 100% had a pathologic response, of which 95% were major pathologic responses (defined as ≤10% residual viable tumor) and 60% were complete pathologic responses. Among patients with MMR-proficient colon cancer evaluable for response, 27% exhibited pathologic responses of any degree, with 20% experiencing major pathologic responses, a finding that contrasts with the lack of efficacy observed with ICB in advanced MMR-proficient colorectal cancer. Interestingly, biomarker analysis revealed that lower tumor mutational burden—suspected to be a cause of ICB failure—did not correlate with lack of response in patients with MMR-proficient disease. Instead, the analysis showed that greater $CD8^+PD\text{-}1^+$ T-cell infiltration was associated with a higher chance of response in these patients. Limitations of this study include the small number of patients enrolled and the short postoperative follow-up, which prevents evaluation of whether neoadjuvant ICB affects overall survival. However, the promising results presented in this work warrant follow-up in larger trials. ■

Chalabi M, Fanchi LF, Dijkstra KK, Van den Berg JG, Aalbers AG, Sikorska K, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med 2020;26:566–76.