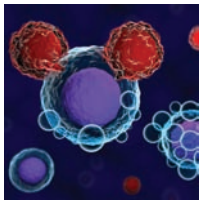
Immunology

Major finding: LXR activation reduces immunosuppressive MDSCs to activate antitumor cytotoxic T cells.

Mechanism: LXR agonism upregulates its transcriptional target ApoE, which binds to LRP8 to impair MDSC survival.

Impact: LXR agonists may relieve immunosuppression to enhance the efficacy of immune checkpoint blockade.

LXR AGONISM DEPLETES MDSCS TO PROMOTE ANTITUMOR IMMUNITY



Immune checkpoint inhibition has had success in some patients with cancer, but the majority of patients do not respond. Many of the nonresponding patients have high levels of circulating myeloid-derived suppressor cells (MDSC) that suppress the innate and adaptive immunity to suppress the antitumor immune response. Thus, strategies to target MDSCs might enhance the efficacy of immune checkpoint blockade. The Liver-X receptors (LXRβ and LXRα) are nuclear hormone receptor family transcription factors, and LXR agonists have been shown to inhibit tumorigenesis, with more potent antitumor effects in immune-competent mice. These findings prompted Tavazoie and colleagues to investigate the effects of LXR antagonism on the antitumor immune response using the LXRβ agonists GW3965 and RGX-104, which is currently being investigated in a phase I clinical trial. LXRβ agonism suppressed tumor growth *in vivo* in mice with lung, ovarian, renal cell, triple-negative breast, or colon cancer, melanoma, or glioblastoma. Further, LXR activation reduced the abundance of tumor-infiltrating and systemic MDSCs and increased tumor-infiltrating activated $CD8^+$ and $CD4^+$ T cells to reverse tumor immune evasion and promote antitumor immunity. Mechanistically, LXR agonism promoted upregulation of its transcriptional target ApoE, which bound to its receptor LRP8 on MDSCs to reduce MDSC survival. In addition to its activity as a single agent, RGX-104 enhanced the efficacy of anti–PD-1 therapy in multiple tumor models, conferring sensitivity to immune checkpoint blockade in poorly immunogenic resistant models. Peripheral blood samples were obtained from patients in the phase I trial of RGX-104, and these samples showed that LXR agonism depletes MDSCs and promotes T-cell activation in human cancer. Collectively, these findings suggest that LXR agonists may enhance the efficacy of immunotherapy in poorly immunogenic tumors by depleting MDSCs and support further investigation of RGX-104 in patients with cancer. ■

Tavazoie MF, Pollack I, Tanqueco R, Ostendorf BN, Reis BS, Gonsalves FC, et al. LXR/ApoE activation restricts innate immune suppression in cancer. Cell 2018;172:825–40.e18.

Clinical Trials

Major finding: Nivolumab plus ipilimumab achieves higher response rates than previously reported for nivolumab alone.

Approach: The phase II CheckMate-142 trial evaluated nivolumab plus ipilimumab in dMMR/MSI-H colorectal cancer.

Impact: Nivolumab plus ipilimumab may be more effective than nivolumab alone in dMMR/MSI-H colorectal cancer.

NIVOLUMAB PLUS IPILIMUMAB ACHIEVES RESPONSES IN dMMR/MSI-H TUMORS

In patients with metastatic colorectal cancer, those with DNA mismatch repair–deficient (dMMR)/microsatellite instability–high (MSI-H) tumors have poorer outcomes and derive less benefit from conventional chemotherapy. However, these patients also demonstrate better responses to immune checkpoint blockade with the anti–PD-1 antibody nivolumab, and it has been previously reported that nivolumab achieves a 31% overall response rate in these patients. In patients with metastatic melanoma, treatment with the anti-CTLA4 antibody ipilimumab plus nivolumab achieved better responses than nivolumab alone, and preclinical studies have demonstrated that ipilimumab can enhance the efficacy of nivolumab. Thus, Overman and colleagues evaluated the safety and efficacy of nivolumab plus ipilimumab in 119 patients with previously treated metastatic dMMR/MSI-H tumors as part of the multicenter, open-label, phase II CheckMate-142 trial. The primary endpoint was overall response rate, and other endpoints included safety, tolerability, progression-free survival, and overall survival. The overall response rate was 55%, with complete responses occurring in 4 (3%) patients and partial responses occurring in 61 (51%) patients. The 12-month progression-free and overall survival rates were 71% and 85%, respectively. Nivolumab plus ipilimumab exhibited a manageable toxicity, with treatment-related grade 3–4 adverse events occurring in 32% of patients. Thirteen percent of patients discontinued treatment due to drug-related adverse events. Taken together, the results of this phase II trial indicate that nivolumab plus ipilimumab achieves high response rates with a manageable safety profile in patients with dMMR/MSI-H metastatic colorectal cancer. Based on indirect comparison with nivolumab alone, combined therapy with nivolumab plus ipilimumab improves therapeutic efficacy, supporting further investigation of this combination in patients with dMMR/MSI-H tumors. ■

Overman MJ, Lonardi S, Wong KY, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018 Jan 20 [Epub ahead of print].