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CANCER

New path to improving immunotherapy

Cancer patients with high levels of circulating myeloid-derived suppressor cells (MDSCs) have been found to respond poorly to checkpoint blockade. Accordingly, there is significant interest in therapeutically targeting these immunosuppressive innate immune cells. Writing in *Cell*, lead author Masoud Tavazoie and colleagues now report that activation of the liver X nuclear receptor-β (LXRβ) and its transcriptional target apolipoprotein E (APOE) reduces MDSC abundance and increases cytotoxic T cell activation in mouse cancer models and patients. Furthermore, LXRβ agonists enhanced immunotherapy efficacy in mice.

Previously, the authors reported that pharmacological activation of LXRβ inhibits tumour progression and metastasis in mouse melanoma models, through effects on APOE. Notably, LXRβ activation elicited more pronounced antitumour effects in immunocompetent compared with immunodeficient mice. Given these observations, Tavazoie and colleagues set out to further investigate the breadth of antitumour efficacy of LXRβ agonism as well as potential immune-dependent effects.

The authors first orally treated several mouse cancer models with the LXRβ agonists, GW3965 or the more potent RGX-104, and reported strong antitumour therapeutic responses across a wide spectrum of malignancies. Notably, LXRβ activation significantly reduced growth of a syngeneic colon carcinoma in immunocompetent mice but less so in immunodeficient mice, indicating that the antitumour effects of LXRβ activation may be partly immunological in nature.

LXRβ agonist treatment also reduced levels of both intratumoural and circulating MDSCs in multiple mouse cancer models, including melanoma, ovarian cancer, glioblastoma and lung cancer. This LXR-mediated MDSC depletion was associated with an increase in tumour-infiltrating activated $CD8^+$ and $CD4^+$ T cells.

Mechanistically, LXR activation was shown to affect the survival of MDSCs, promoting their apoptosis *in vitro* and in mice. Studies using knockout mouse models revealed that APOE was mediating LXR-dependent MDSC depletion through the APOE LRP8 receptor. APOE-deficient tumour-bearing mice exhibited higher levels of circulating and intratumoural MDSCs and the growth of melanoma and glioblastoma tumours was accelerated.

Next, the effects of LXR activation were explored in several mouse immunotherapy models. In a mouse model of adoptive T cell therapy, co-administration of RGX-104 with tumour antigen-specific cytotoxic T lymphocytes substantially increased antitumour activity and survival. Similarly, the combination of RGX-104 with an immune checkpoint blockade inhibitor (anti-programmed cell death protein 1 (PD1)) yielded synergistic antitumour activity in mouse models of lung cancer and melanoma, significantly increasing tumour-infiltrating cytotoxic T cell abundance. In addition, in a mouse melanoma model in which anti-PD1 therapy was ineffective in combination with a GVAX regimen, the addition of GW3965 resulted in reduced tumoural MDSCs and impaired tumour growth.

Finally, the authors report on the early findings of a phase I trial of RGX-104 in patients with metastatic solid cancers or lymphomas that have progressed on standard-of-care regimens, including anti-PD1 therapy. Analysis of peripheral blood samples taken from the first six patients in the study revealed that oral LXRβ agonist therapy depletes MDSCs and activates $CD8^+$ T cells. Importantly, RGX-104 was well tolerated, with no dose-limiting toxicities.

In summary, these findings have uncovered a crucial role for LXR-APOE signalling in the regulation of antitumour immunity and revealed a novel target for enhancing the efficacy of cancer immunotherapy. Rgenix is currently initiating a phase Ib expansion study with RGX-104 as a single agent, as well as in combination with a PD1 inhibitor, in various cancer indications.

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