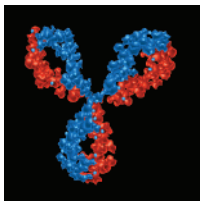
Immunotherapy

Major finding: Anti-CTLA4 antibodies induce an FcγR-dependent depletion of Tregs to promote tumor rejection.

Clinical relevance: A high affinity FcγR polymorphism is linked to ipilimumab response in patients with melanoma.

Impact: Enhancing the Fc effector function of anti-CTLA4 antibodies may improve their antitumor activity.

INCREASING FCγR BINDING ACTIVITY MAY ENHANCE ANTI-CTLA4 EFFICACY



Immune checkpoint blockade with anti-CTLA4 antibodies relieves inhibition of effector T cells to promote antitumor immune responses. In addition, recent preclinical data has suggested that anti-CTLA4 may also deplete regulatory T cells (Treg) via antibody-dependent cell-mediated cytotoxicity (ADCC), but the effects on Tregs are not well understood. Vargas, Furness, and colleagues investigated the role of Treg depletion in anti-CTLA4–mediated antitumor immunity *in vivo* using a mouse model expressing human Fc-gamma receptors (FcγR) treated with anti-CTLA4 monoclonal antibodies. CTLA4 was highly expressed by tumor-infiltrating Treg cells, and treatment with anti-CTLA4 antibodies induced FcγR-dependent cytotoxicity *in vitro* and depleted intratumoral Tregs *in vivo*. This resulted in an increase in the ratio of intratumoral T effector cells to Tregs, thereby enhancing antitumor immunity. In mouse models of fibrosarcoma or colon carcinoma, anti-CTLA4 alone was insufficient to produce a robust antitumor immune response, whereas CTLA4 blockade with an antibody with enhanced affinity for activating FcγRs produced durable tumor regression. However, this effect was not observed in a B16 melanoma model, suggesting that it may be relevant only to inflamed tumors with abundant expression of FcγR-expressing innate effector cells. In patients with advanced melanoma, a single nucleotide polymorphism in the FcγR-activating receptor CD16a (CD16a-V158F) that resulted in an increased affinity for IgG was associated with an increased response to treatment with the anti-CTLA4 antibody ipilimumab in inflamed tumors. Taken together, these findings suggest that enhancing the FcγR binding activity of anti-CTLA4 antibodies may result in superior efficacy, depleting intratumoral Tregs to improve the antitumor activity. ■

Vargas FA, Furness AJ, Litchfield K, Joshi K, Rosenthal R, Ghorani E, et al. Fc effector function contributes to the activity of human anti-CTLA-4 antibodies. Cancer Cell 2018;33:649–63.e4.

Phosphorylation

Major finding: Deregulated histidine phosphorylation may promote tumorigenesis in hepatocellular carcinoma (HCC).

Clinical relevance: LHPP is downregulated in patients with HCC, and the histidine kinases NME1 and NME2 are overexpressed.

Impact: LHPP loss promotes HCC tumorigenesis, and LHPP may be a tumor suppressor in a variety of tumor types.

LHPP IS A HISTIDINE PHOSPHATASE AND A TUMOR SUPPRESSOR

Histidine phosphorylation is less well understood than post-translational phosphorylation of other residues. Hindupur and colleagues uncovered a role for histidine phosphorylation in liver tumorigenesis using a mouse model of mTOR-driven hepatocellular carcinoma (HCC), induced by liver-specific deletion of *Pten* and *Tsc1* (L-dKO mice). Proteomic analysis of 12 mouse tumors revealed an upregulation of the only two known mammalian histidine kinases, NME1 and NME2, as well as downregulation of a putative histidine phosphatase, LHPP. In L-dKO tumors, expression of NME1/2 was mTOR-dependent, whereas LHPP expression was mTOR-independent. *In vitro* experiments confirmed that LHPP is a bona fide histidine phosphatase, and LHPP expression impaired cell proliferation *in vitro* and suppressed tumor formation to maintain normal liver function *in vivo*, indicating that LHPP is a tumor suppressor. Consistent with these findings in mouse tumors, LHPP was expressed at low levels in tumors from patients with HCC compared with adjacent normal tissue, whereas NME1 and NME2 were highly expressed in tumors. Further, in patients with HCC, LHPP downregulation was associated with accelerated disease progression and poorer survival. Analysis of data from The Cancer Genome Atlas and the International Cancer Genome Consortium revealed LHPP mutations in a variety of tumor types, suggesting that the tumor-suppressive role of LHPP may not be limited to HCC. In addition to identifying LHPP as a histidine phosphatase and tumor suppressor, these findings indicate that deregulated histidine phosphorylation is oncogenic in HCC and other tumor types. ■

Hindupur SK, Colombi M, Fuhs SR, Matter MS, Guri Y, Adam K, et al. The protein histidine phosphatase LHPP is a tumour suppressor. Nature 2018;555:678–82.

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