

RESEARCH WATCH

Lymphoma

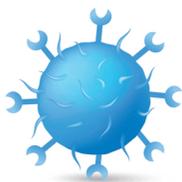
Major finding: HVEM loss drives B-cell proliferation and promotes a pro-tumorigenic microenvironment.

Mechanism: Loss of the HVEM-BTLA interaction drives BCR signaling and increases stroma-activating cytokines.

Impact: Immune cells can be modified to deliver anticancer proteins as a targeted therapeutic approach.

CAR-T CELLS RESTORE TUMOR SUPPRESSOR FUNCTION IN LYMPHOMA

Somatic mutations of the tumor suppressor tumor necrosis factor receptor superfamily member 14 (HVEM, encoded by *TNFRSF14*), which frequently occur in follicular lymphomas (FL), disrupt the interaction between HVEM and the immune checkpoint protein B and T lymphocyte associated (BTLA), resulting in the inhibition of T-cell immune responses. To elucidate the role of HVEM in germinal center (GC) lymphomagenesis, Boice, Salloum, Mourcin, and colleagues evaluated the interaction between HVEM and BTLA in FLs. Genomic and immunohistochemical analyses of human FLs identified *HVEM* mutations in 28% (40 of 141) of patient samples and the mutually exclusive loss of either HVEM or BTLA expression in 73% (145 of 198) of patient samples. Depletion of B cell-specific *Hvem* or *Btla* in a genetically engineered mouse model of FL resulted in enhanced lymphomagenesis in *Hvem*-deficient mice and *Btla*-deficient mice compared to control mice. Further, the morphology and activated status of the B-cell receptor (BCR) signaling pathway in *Hvem*-deficient lymphomas and *Btla*-deficient lymphomas closely resembled those of GC FLs, and *Hvem*-deficient lymphomas exhibited increases in stroma-



activating cytokines and follicular T helper cell infiltration compared to controls. The soluble HVEM ectodomain protein (solHVEM), which retains BTLA binding activity, inhibits activated BCR signaling in lymphoma B cells and partially reversed aberrant cytokine production by HVEM-deficient lymphoma B cells. Moreover, solHVEM ablated growth of BTLA^{hi} lymphomas compared to BTLA^{lo}

lymphomas and controls, respectively, *in vitro* and *in vivo*. Anti-CD19 chimeric antigen receptor (CAR)-T cells modified to express and secrete solHVEM displayed greater antitumor efficacy than control anti-CD19 CAR-T cells against lymphomas *in vivo*. Taken together, these results provide new insights into the tumor suppressor function of HVEM by elucidating the BTLA-dependent mechanism by which HVEM inhibits BCR signaling and activation of the tumor microenvironment, and provide evidence that immune cells can be engineered for the local delivery of anticancer therapies. ■

Boice M, Salloum D, Mourcin F, Sanghvi V, Amin R, Oricchio E, et al. Loss of the HVEM tumor suppressor in lymphoma and restoration by modified CAR-T cells. *Cell* 2016;167:405–18.e13.

Drug Discovery

Major finding: Blocking the MDM2 protein-XIAP mRNA interaction reduces MDM2 and XIAP levels and activates p53.

Approach: A high-throughput protein-RNA fluorescence polarization assay identified MDM2-XIAP inhibitors.

Impact: MDM2-XIAP inhibition may be a potential strategy to induce apoptosis in tumors.

DUAL INHIBITION OF MDM2 AND XIAP INDUCES CANCER CELL APOPTOSIS

MDM2 and X-linked inhibitor of apoptosis (XIAP) promote cancer cell survival by binding p53 and promoting its degradation and by inhibiting caspase activation to prevent apoptosis, respectively. Further, the RING domain of MDM2 can bind to the internal ribosome entry site (IRES) of *XIAP* mRNA transcripts to promote *XIAP* translation, increase MDM2 protein expression, and enhance resistance to apoptosis, suggesting a potential p53-independent role for MDM2 in enhancing cell survival. Gu and colleagues hypothesized that disrupting the interaction between MDM2 and *XIAP* would decrease expression of both proteins and enhance cancer cell apoptosis. A fluorescence polarization assay was developed for high-throughput screening of small-molecule inhibitors of *XIAP* IRES binding to the MDM2 RING domain. Of 141,394 small-molecule compounds tested, 8 candidates disrupted MDM2-XIAP binding, and 3 compounds selected for further study (MX3, MX11, and MX69) reduced protein expression of both MDM2 and XIAP when added to cancer

cells. MX11 and MX69, which bound to the MDM2 RING, and MX3, which bound to the *XIAP* IRES, induced the self-ubiquitination and degradation of MDM2, which not only led to the stabilization and activation of p53 but also inhibited XIAP, resulting in activation of caspases 3, 7, and 9. In a panel of acute lymphoblastic leukemia (ALL) and neuroblastoma cell lines, MX3 and MX69 induced apoptosis in an MDM2-, p53-, and XIAP-dependent manner. MX69 had little effect on normal hematopoiesis, and was thus tested *in vivo* in mice bearing ALL xenografts. Treatment with MX69 reduced disease burden, increased survival, and was well tolerated in mice. Altogether, these findings support further investigation of MX69 and dual MDM2/XIAP inhibitors as therapies to induce apoptosis in cancer cells. ■

Gu L, Zhang H, Liu T, Zhou S, Du Y, Xiong J, et al. Discovery of dual inhibitors of MDM2 and XIAP for cancer treatment. *Cancer Cell* 2016;30:623–36.

CANCER DISCOVERY

CAR-T Cells Restore Tumor Suppressor Function in Lymphoma

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