RESEARCH WATCH

Targeted Therapy

Major finding: GBMs depend on exogenous cholesterol released from normal brain parenchyma via LXR-mediated efflux.

Concept: An LXR agonist with high CNS penetrance, LXR-623, was tested for *in vivo* efficacy against GBMs.

Impact: LXR-623 is a potential therapy for patients with GBM and other brain cancers.

GLIOBLASTOMAS EXHIBIT A TARGETABLE DEPENDENCY ON EXOGENOUS CHOLESTEROL

The blood–brain barrier (BBB) protects the internal microenvironment of the brain from systemic fluctuations in order to maintain normal brain homeostasis, which includes *de novo* cholesterol synthesis, for proper neural function. However, the BBB is also one of the major obstacles to the development of efficacious therapies for the treatment of brain tumors because it limits systemic drug delivery to intracranial tumors such as glioblastoma multiforme (GBM). Villa and colleagues, who had recently shown that activated EGFR signaling upregulates the expression of the cholesterol receptor low-density lipoprotein receptor in GBM cells, evaluated *de novo* cholesterol metabolism in GBM to ascertain whether GBMs exhibit a potentially exploitable dependency on exogenous cholesterol. GBM cells exhibited significantly decreased expression of the enzymes which drive *de novo* cholesterol synthesis and levels of oxysterols, which are oxidized cholesterol derivatives that bind to the liver X receptors (LXR) to induce the efflux of excess intracellular cholesterol, suggesting that LXR agonists may be efficacious against GBMs. The LXR agonist LXR-623, which had demonstrated favorable central nervous system (CNS) penetrance in a phase I trial, induced cell death in GBM cells and a breast cancer cell line derived from a brain metastasis but did not exhibit toxicity against normal human astrocytes. Consistent with these findings, systemic delivery of LXR-623 upregulated the expression of LXR target genes in normal cortex and induced cell death in various intracranial GBM xenograft models, including patient-derived xenografts, but not in peripheral tissues. Further, LXR-623 activated the beta isotype of LXR, which was the primary LXR isotype in GBM, resulting in the depletion of intracellular cholesterol in GBM cells. Taken together, these findings show that an activator of intracellular cholesterol efflux with high BBB penetrance and CNS selectivity is an efficacious therapy for GBM and potentially other types of brain cancer. ∎

Villa GR, Hulce JJ, Zanca C, Bi J, Ikegami S, Cahill GL, et al. An LXR-cholesterol axis creates a metabolic co-dependency for brain cancers. Cancer Cell 2016;30:683–93.

Extracellular Matrix

Major finding: Anti-VEGF therapy upregulates HA and sGAG to increase tumor stiffness and promote acquired resistance.

Concept: Anti-VEGF therapy induces hypoxia that drives extracellular matrix remodeling and reduces tumor perfusion.

Impact: Targeting ECM components may potentiate chemotherapy in patients receiving anti-VEGF therapy.

TARGETING VEGF REMODELS THE ECM IN COLORECTAL CANCER LIVER METASTASES

Antiangiogenic therapy with the VEGF antibody bevacizumab provides a modest survival benefit in combination with chemotherapy in patients with metastatic colorectal cancer, but the effectiveness is limited by the development of acquired resistance. Hypoxia resulting from antiangiogenic therapy has been shown to increase collagen expression in tumors, but the effect on other extracellular matrix (ECM) components such as hyaluronic acid (HA) and sulfated glycosaminoglycans (sGAG), compression-resistant molecules that could potentially contribute to solid stress–induced blood vessel collapse and reduced drug delivery to tumors, are not well understood. Rahbari and colleagues found that patients treated with bevacizumab and chemotherapy had elevated expression of HA in colorectal cancer liver metastases. Accordingly, in two syngeneic mouse models of metastatic colorectal cancer, treatment with a VEGF-blocking antibody increased the stiffness and solid stress of metastatic liver lesions and reduced the cell-to-matrix ratio, altogether indicating that antiangiogenic therapy induces desmoplasia to alter the mechanical properties of liver metastases. In mouse liver metastases, anti-VEGF therapy increased expression of the HA receptor CD44 in addition to HA, and also increased accumulation of sGAG, whereas collagen deposition was largely unchanged. Bevacizumab treatment also increased sGAG levels in patients with metastatic colorectal cancer. HA expression was localized to hypoxic regions, and culturing hepatic stellate cells (HSC) in hypoxic conditions increased HA synthesis, suggesting that hypoxia drives activated HSCs to produce HA after anti-VEGF therapy. Based on these findings, HA was targeted with polyethylene glycol–conjugated hyaluronidase (PEG-HAse) in mice with liver metastases treated with anti-VEGF therapy. PEG-HAse increased tumor perfusion and enhanced the efficacy of chemotherapy, resulting in prolonged survival. These findings suggest a mechanism by which anti-VEGF therapy remodels the ECM to reduce perfusion and induce acquired resistance, and indicate that targeting ECM components may enhance the effects of combined anti-VEGF therapy and chemotherapy in patients with metastatic colorectal cancer. ∎

Rahbari NN, Kedrin D, Incio J, Liu H, Ho WW, Nia HT, et al. Anti-VEGF therapy induces ECM remodeling and mechanical barriers to therapy in colorectal cancer liver metastases. Sci Transl Med 2016;8:360ra135.

AACR American Association for Cancer Research

CANCER DISCOVERY

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