OS2966

OS2966 is a therapeutic antibody blocking a cell surface receptor governing fundamental biological processes that allow cancer cells to grow, spread, and become resistant to cancer treatment.

Inhibition of β1 in tumor cells with stable gene knockdown or treatment with OS2966, a neutralizing β1 integrin monoclonal antibody, attenuated aggressive tumor phenotypes in vitro and blocked the growth of bevacizumab-resistant tumor xenografts in vivo. Thus, β1 integrins promote resistance to antiangiogenic therapy through the potentiation of multiple malignant programs facilitated by interactions with the tumor microenvironment. The elucidation of this mechanism creates an outstanding opportunity for improving patient outcomes in cancer [1)].

Lee et al. tested the therapeutic potential of OS2966-mediated integrin β1 blockade to enhance the efficacy of oncolytic herpes simplex virus-1 (oHSV) through evaluation of virus replication, tumor cell killing efficiency, effect on the antiviral signaling pathway, co-culture assays of oHSV-infected cells with macrophages, and in vivo bioluminescence imaging on mammary fat pad triple-negative breast cancer xenograft and subcutaneous and intracranial glioma xenografts. OS2966 treatment decreased interferon signaling and proinflammatory cytokine induction in oHSV-treated tumor cells and inhibited migration of macrophages, resulting in enhanced oHSV replication and cytotoxicity. OS2966 treatment also significantly enhanced oHSV replication and oHSV-mediated antitumor efficacy in orthotopic xenograft models, including triple-negative breast cancer and glioblastoma. The results demonstrated the synergistic potential of the combinatory treatment approach with OS2966 to improve antitumor efficacy of conventional oHSV therapy [2)].

Lau et al. previously identified a complex between receptor tyrosine kinase c-Met and Integrin beta 1 in metastases. Using novel cell culture and in vivo assays, they found that c-Met/β1 complex induction promotes intravasation and vessel wall adhesion in triple-negative breast cancer cells, but does not increase extravasation. These effects may be driven by the ability of the c-Met/β1 complex to increase mesenchymal and stem cell characteristics. Multiplex transcriptomic analysis revealed upregulated Wnt and hedgehog pathways after c-Met/β1 complex induction. A β1 integrin point mutation that prevented binding to c-Met reduced intravasation. OS2966, a therapeutic antibody disrupting c-Met/β1 binding, decreased breast cancer cell invasion and mesenchymal gene expression. Bone-seeking breast cancer cells exhibited higher c-Met/β1 complex levels than parental controls and preferentially adhered to the tissue-specific matrix. Patient bone metastases demonstrated a higher c-Met/β1 complex than brain metastases. Thus, the c-Met/β1 complex drives intravasation of triple-negative breast cancer cells and preferential affinity for bone-specific matrix. Pharmacological targeting of the complex may prevent metastases, particularly osseous metastases [3)].

Upregulation of β1 integrin (ITGB1) occurs in some bevacizumab-resistant glioblastomas (BRG) whereby, mediating tumor-microenvironment interactions, we hypothesized that it may mediate a mesenchymal-type resistance to antiangiogenic therapy. Immunostaining analyses of β1 integrin and its downstream effector kinase FAK revealed upregulation in 75% and 86% of BRGs, respectively,

compared with pretreatment paired specimens. Furthermore, flow cytometry revealed eight-fold more β1 integrin in primary BRG cells compared with cells from bevacizumab-naïve glioblastomas (BNG). Fluorescence recovery after photobleaching of cells engineered to express a β1-GFP fusion protein indicated that the mobile β1 integrin fraction was doubled, and half-life of β1 integrin turnover in focal adhesions was reduced markedly in BRG cells compared with bevacizumab-responsive glioblastoma multiforme cells. Hypoxia, which was increased with acquisition of bevacizumab resistance, was associated with increased β1 integrin expression in cultured BNG cells. BRGs displayed an aggressive mesenchymal-like phenotype in vitro. We found that growth of BRG xenograft tumors was attenuated by the β1 antibody, OS2966, allowing a 20-fold dose reduction of bevacizumab per cycle in this model. Intracranial delivery of OS2966 through osmotic pumps over 28 days increased tumor cell apoptosis, decreased tumor cell invasiveness, and blunted the mesenchymal morphology of tumor cells. We concluded that β1 integrin upregulation in BRGs likely reflects an onset of hypoxia caused by antiangiogenic therapy and that β1 inhibition is well tolerated in vivo as a tractable strategy to disrupt resistance to this therapy [4].

1)

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2)

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3)

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4)

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