

# Clinical Cancer Research

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## Cancer Therapy: Preclinical

# Targeting Hyaluronan Interactions in Malignant Gliomas and Their Drug-Resistant Multipotent Progenitors

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**Purpose:** To determine if hyaluronan oligomers (o-HA) antagonize the malignant properties of glioma cells and treatment-resistant glioma side population (SP) cells *in vitro* and *in vivo*.

**Experimental Design:** A single intratumoral injection of o-HA was given to rats bearing spinal cord gliomas 7 days after engraftment of C6 glioma cells. At 14 days, spinal cords were evaluated for tumor size, invasive patterns, proliferation, apoptosis, activation of Akt, and BCRP expression. C6SP were isolated by fluorescence-activated cell sorting and tested for the effects of o-HA on BCRP expression, activation of Akt and epidermal growth factor receptor, drug resistance, and glioma growth *in vivo*.

**Results:** o-HA treatment decreased tumor cell proliferation, increased apoptosis, and down-regulated

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activation of Akt and the expression of BCRP. o-HA treatment of C6SP inhibited activation of epidermal growth factor receptor and Akt, decreased BCRP expression, and increased methotrexate cytotoxicity. *In vivo*, o-HA also suppressed the growth of gliomas that formed after engraftment of C6 or BCRP+ C6SP cells, although most C6SP cells lost their expression of BCRP when grown *in vivo*. Interestingly, the spinal cord gliomas contained many BCRP+ cells that were not C6 or C6SP cells but that expressed nestin and/or CD45; o-HA treatment significantly decreased the recruitment of these BCRP+ progenitor cells into the engrafted gliomas.

**Conclusions:** o-HA suppress glioma growth *in vivo* by enhancing apoptosis, down-regulating key cell survival mechanisms, and possibly by decreasing recruitment of host-derived BCRP+ progenitor cells. Thus, o-HA hold promise as a new biological therapy to inhibit HA-mediated malignant mechanisms in glioma cells and treatment-resistant glioma stem cells.

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