TARGETED THERAPY FOR CHONDROSARCOMA

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Chondrosarcoma is an aggressive primary malignant bone tumor for which there are no effective systemic treatments, resulting in poor survival. Traditional cytotoxic chemotherapy is not effective. Therefore, we have studied metastatic pathways in this tumor with the goal of identifying potential therapeutic targets.

Two such targets are chemokine receptor 4 (CXCR4) and microRNA-181a (miR-181a). Both are overexpressed in human chondrosarcoma cell lines, xenograft and human tumors, and expression is in part driven by hypoxia. CXCR4 blockade with AMD3100 inhibits tumor angiogenesis, tumor growth, and metastasis in a xenograft mouse model. Mir-181a is an oncomiR that promotes tumor progression. Regulator of G-protein signaling 16 (RGS16) is a target of miR-181a. Inhibition of RGS16 expression by miR-181a enhances CXCR4 signaling, which in turn increases MMP1 and VEGF expression, angiogenesis, and metastasis. Delivery of anti-miR-181a with lentivirus to tumor cells reverses these effects. Systemic treatment with anti-miRNA oligonucleotides (AMOs) directed against miR-181a utilizing a nanopiece delivery platform restores RGS16 expression, decreases expression of VEGF and MMP1, MMP activity, tumor volume, metastatic burden, and prolongs survival in a mouse model.

These data suggest that chondrosarcoma metastasis can be inhibited with drug and anti-microRNA approaches directed at CXCR4 signaling. The nanopiece delivery platform can be used for nucleotide based therapeutics.