

DECIPHERING THE MECHANISMS OF MEDULLOBLASTOMA RESISTANCE TO RADIO/CHEMOTHERAPY: TOWARD PERSONALIZED TREATMENTS?

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Tumor angiogenesis is considered a major target in the treatment of cancer. However, anti-angiogenesis therapies (AAG), only used for metastatic patients, prolong survival but are not curative. After a first decrease in tumor burden, **the remaining cells evade the treatment** and ultimately proliferate and metastasize. We demonstrated that AAG and radiotherapy induce VEGF-C production and lymphangiogenesis in renal cell carcinomas (RCC) and oral squamous cell carcinomas (OSCC). **VEGF-C, a major growth factor for lymphatic endothelial cells and subsequent lymphangiogenesis might represent a common thread** to all tumors submitted to reference treatments.

To extend this paradigm observed on adult/elderly tumors to pediatric tumors, we questioned the role of VEGF-C for the aggressiveness of medulloblastoma (MDB), the most frequent high-grade pediatric brain tumor. The current standard of care for MDB associates surgical resection, irradiation and adjuvant chemotherapy. This procedure leads to a survival of up to 70%. However, most patients suffer long-term side effects and relapse is fatal in all cases. Neuropilin 2 (NRP2), a co-receptor of VEGF-C is overexpressed in MDB cell membranes. It promotes autocrine proliferation and extravasation in lymphatic vessels and metastasis of RCC cells. We hypothesized **a similar mechanism involving VEGF-C/NRP2 in MDB**. Hence, we aimed at deciphering the mechanisms of resistance to radio/chemotherapy in MDBs. Cell lines derived from MDB subgroups of increasing aggressiveness (DAOY, HD-MB03) were irradiated (8 Gy photon or proton irradiation) and exposed to several adjuvant chemotherapies: carboplatin, vincristin, etoposide (current reference treatments) or vismodegib, an inhibitor of the Sonic Hedgehog pathway (major tumor driver in MDB).

VEGF-C was induced in MDB cells, after treatment by the different agents. Therefore, VEGF-C may be considered as a universal stress marker that stimulates cell proliferation and metastasis. **Knocking-out VEGF-C resulted in increased cell proliferation.** Moreover, expression of VEGF-C, NRP2, LYVE-1 mRNAs was detected in different samples of MDB, suggesting that in the brain, lymphatic vessels may pave the path for tumor metastasis. Therefore, targeting VEGF-C in addition to conventional treatments may improve MDB patients' outcome, especially at relapse.

Medulloblastoma, tumor resistance to treatment, VEGF-C, lymphangiogenesis, alternative treatments