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

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

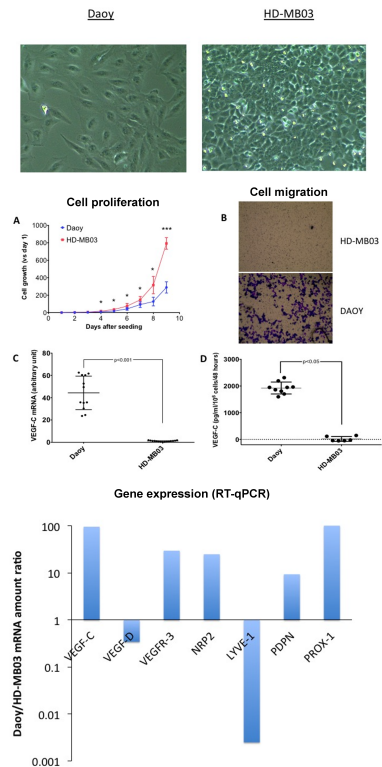
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Tumor angiogenesis is considered a major target in the treatment of cancer. However, anti-angiogenesis therapies (AAG), only used for metastatic patients, prolong survival but are not curative. After a first decrease in tumor burden, the remaining 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. Neurotrophin 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.

Intrinsic characteristics of Daoy and HD-MB03 cell lines



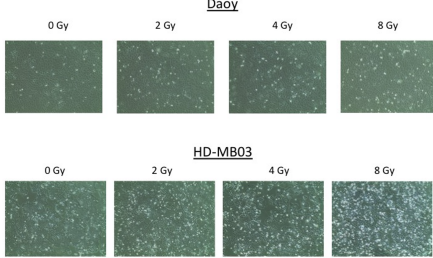
Daoy cells (SHH group) are big, fibroblast-like cells. They grow slower than their group 3 counterpart (HD-MB03 cells), but are able of fast migration and invasion in Boyden chambers.

HD-MB03 cells are small, fast-growing, but non-migrating cells.

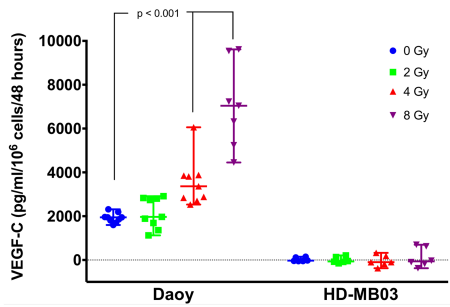
Daoy cells express 100-fold more *vegfc*, at the mRNA level, and produce 40-fold more VEGF-C, at the protein level, than HD-MB03 cells.

Several other genes of the lymphangiogenesis axis are overexpressed in Daoy cells when compared to HD-MB03 cells (with the exception of *vegfd* and *lyve1*).

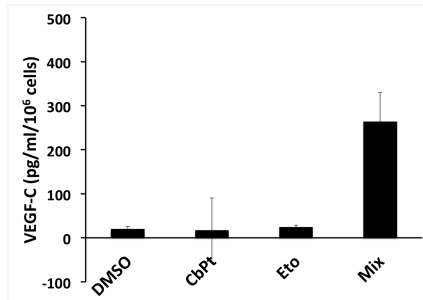
X-ray irradiation effect on MDB cells: acute measurement



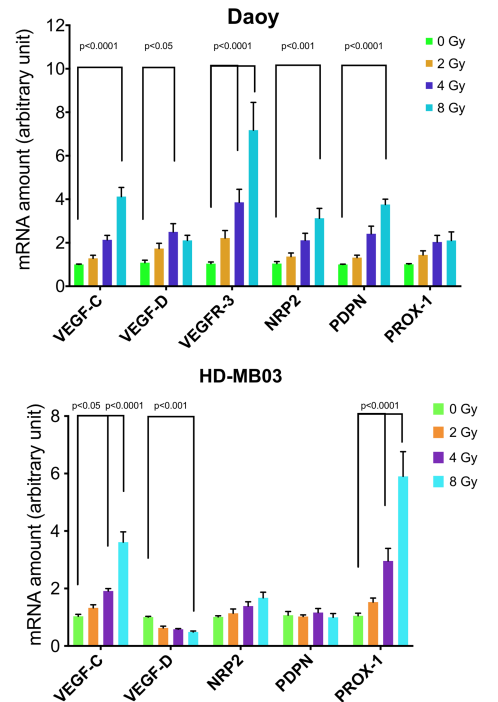
Average X-ray irradiation effect on VEGF-C production by MDB cells



Average X-ray chemotherapeutic treatment effect on VEGF-C production by MDB cells



Average X-ray irradiation effect on *vegfc* expression by MDB cells

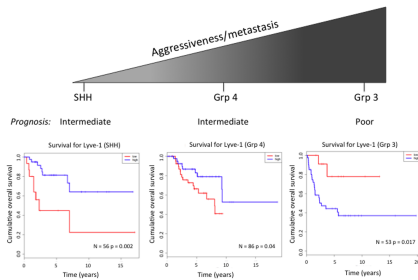


Reference treatment of medulloblastoma includes maximal resection of the tumor, followed by high energy X-ray irradiation and adjuvant chemotherapy, i.e. carboplatin (CbPT), etoposide (Eto) or a mix of both.

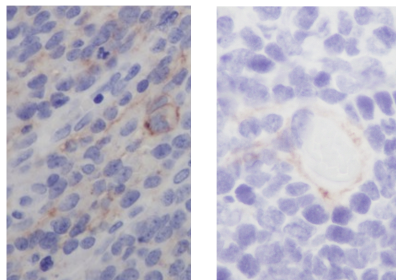
We show that photon irradiation (at 2, 4, or 8 Gy) and chemotherapeutic agents have differential effects on our two models of medulloblastoma cells, as for the expression of *vegfc* and of several genes of the lymphangiogenesis axis. Furthermore, we demonstrate an increase in the production of VEGF-C, the main lymphangiogenic factor.

We conclude that medulloblastoma treatment may result in an increase in tumor aggressiveness, via the development of the lymphatic system.

Correlation between Lyve-1 expression and patient survival



Expression of podoplanin in MDB tissue and lymphatic vessels



We correlated our *in vitro* experiments by the *in vivo* detection of *lyve1* and *podoplanin* genes in patient's tumors.

RNA-seq dataset analysis for *lyve1* gene demonstrates that a high amount of *lyve1* is a marker of good prognosis in MDB groups of low aggressiveness (presenting little metastasis rate, SHH and Group 4). On the contrary, in the most aggressive cases (Group 3), high amount of *lyve1* testify for bad prognosis.

Immunohistochemistry labeling of patients' tumors demonstrates that both tumor cells and lymphatic vessels were labeled by podoplanin antibody.

Conclusion:

MDB cell resistance and MDB aggressiveness seem to be mediated by the lymphangiogenesis axis and, more precisely, by VEGF-C.

The next step is to study the involvement of the VEGF-C / VEGFR-3 pathway (ongoing).