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INTRINSIC OR INDUCED AGGRESSIVENESS-LINKED REGULATION OF VEGFC IN MEDULLOBLASTOMA CELL LINES

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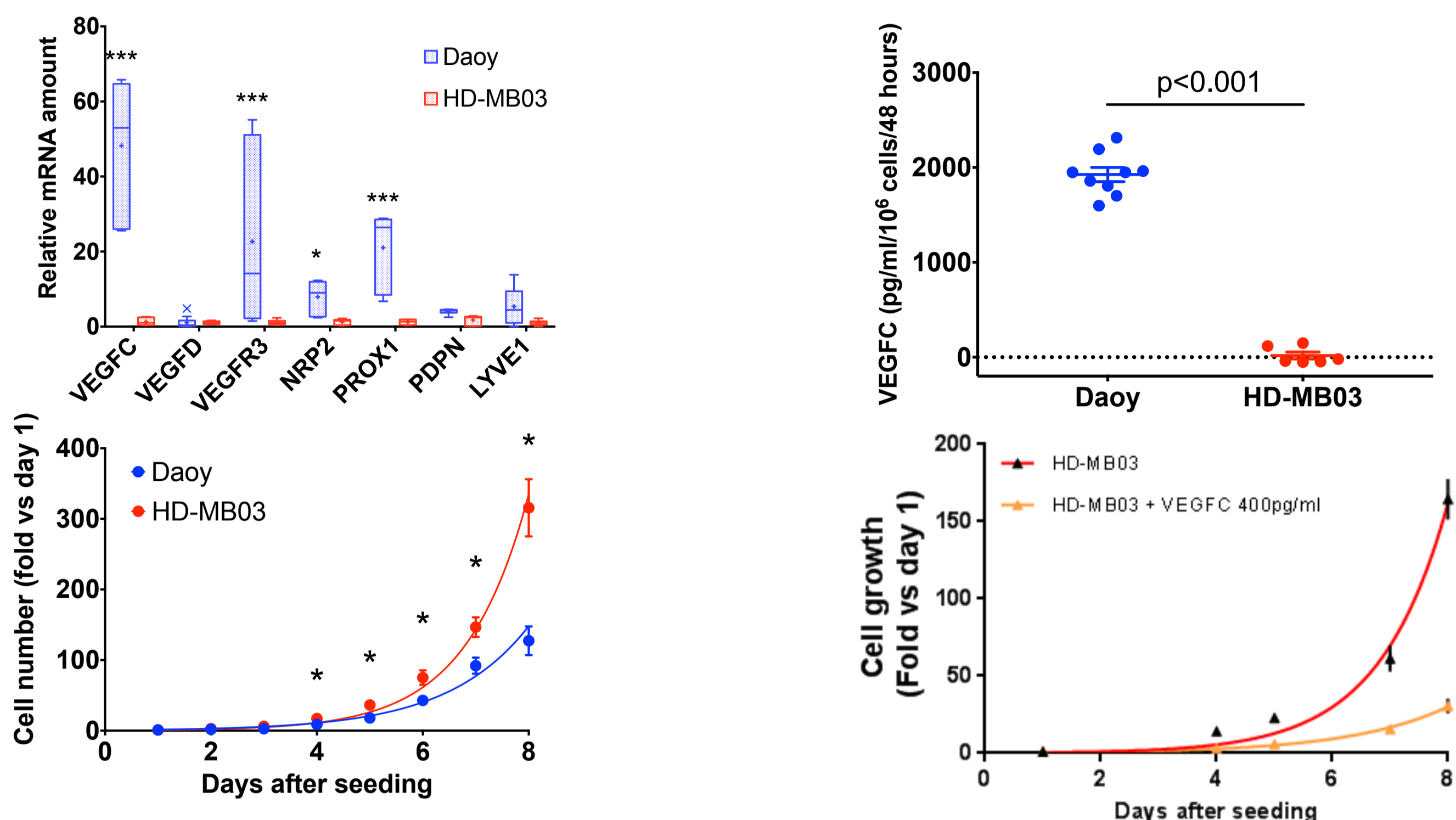
Medulloblastoma (MDB) is the most common pediatric malignant brain tumor. MDB is a very heterogeneous disease that consists of four subgroups, each of them with different molecular profiles, metastasis status and clinical outcomes. Treatment of MDB includes surgery, radiotherapy and chemotherapy. It cures 70% of the patients nevertheless with many side effects. Relapse is always fatal. Understanding the mechanisms of this relapse might lead to the development of new targeted treatments. VEGFC and lymphatic markers are the main actors of the metastatic process in many tumors. We thus meant to determine their role and regulation in MDB-derived cells.

We demonstrated that low-aggressiveness MDB-derived cells, DAOY, expressed high basal amounts of lymphatic marker mRNAs and proteins (VEGFC, PROX1, NRP2). Conversely, highly aggressive cells, HD-MB03, presented low amounts of these markers. X-ray irradiation treatment of the cells induced a rise in VEGFC, at the mRNA and protein levels.

We thus questioned the regulation of lymphatic markers in MDB cells. We observed that in the highly aggressive HD-MB03 cells, VEGFC mRNA amount relies upon a very active NF-κB-dependent promoter, but that the mRNA gets intensely degraded, hence the low level of VEGFC mRNA in these cells. Conversely, DAOY cells present low activity of VEGFC promoter and high stability of the synthesized mRNA. The promoter activity is independent from NF-κB. Moreover, while VEGFC is secreted in DAOY cells, it is retained inside the cytoplasm of HD-MB03 cells.

Since VEGFC is so precisely regulated in MDB cells, it may play an important part in MDB aggressiveness.

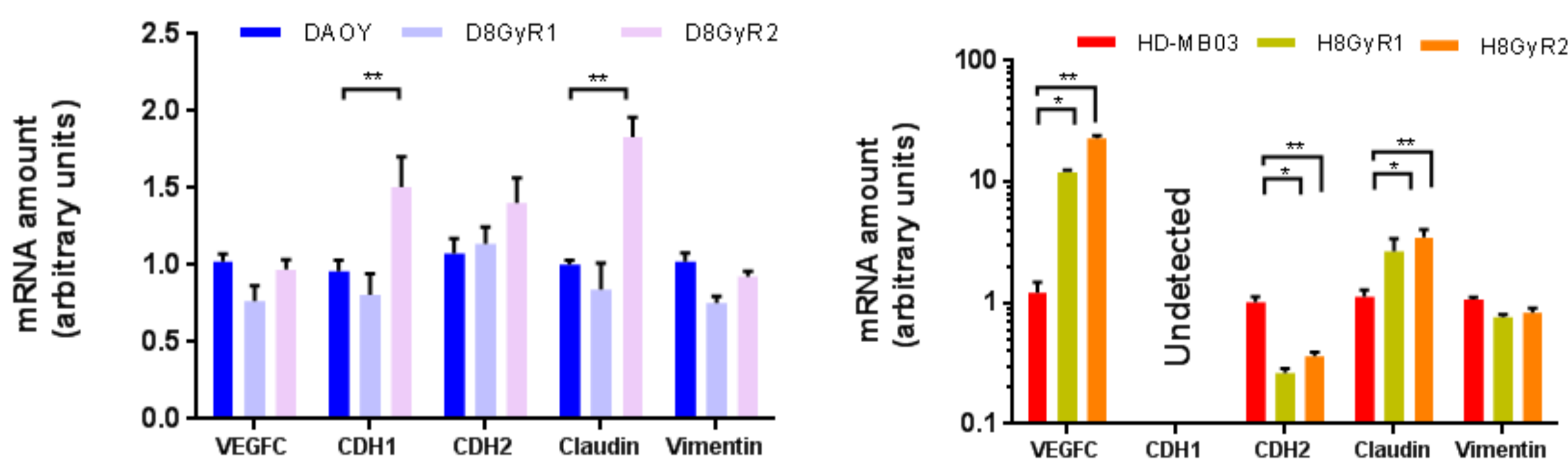
Intrinsic characteristics of MB cell lines



DAOY (SHH): High expression of lymphatic markers and VEGFC
> Low proliferation and high migration rates
HDMB-03 (Grp3): High expression of lymphatic markers and VEGFC
> High proliferation and low migration rates

VEGFC has a impact on the proliferation of HD-MB03 cells.

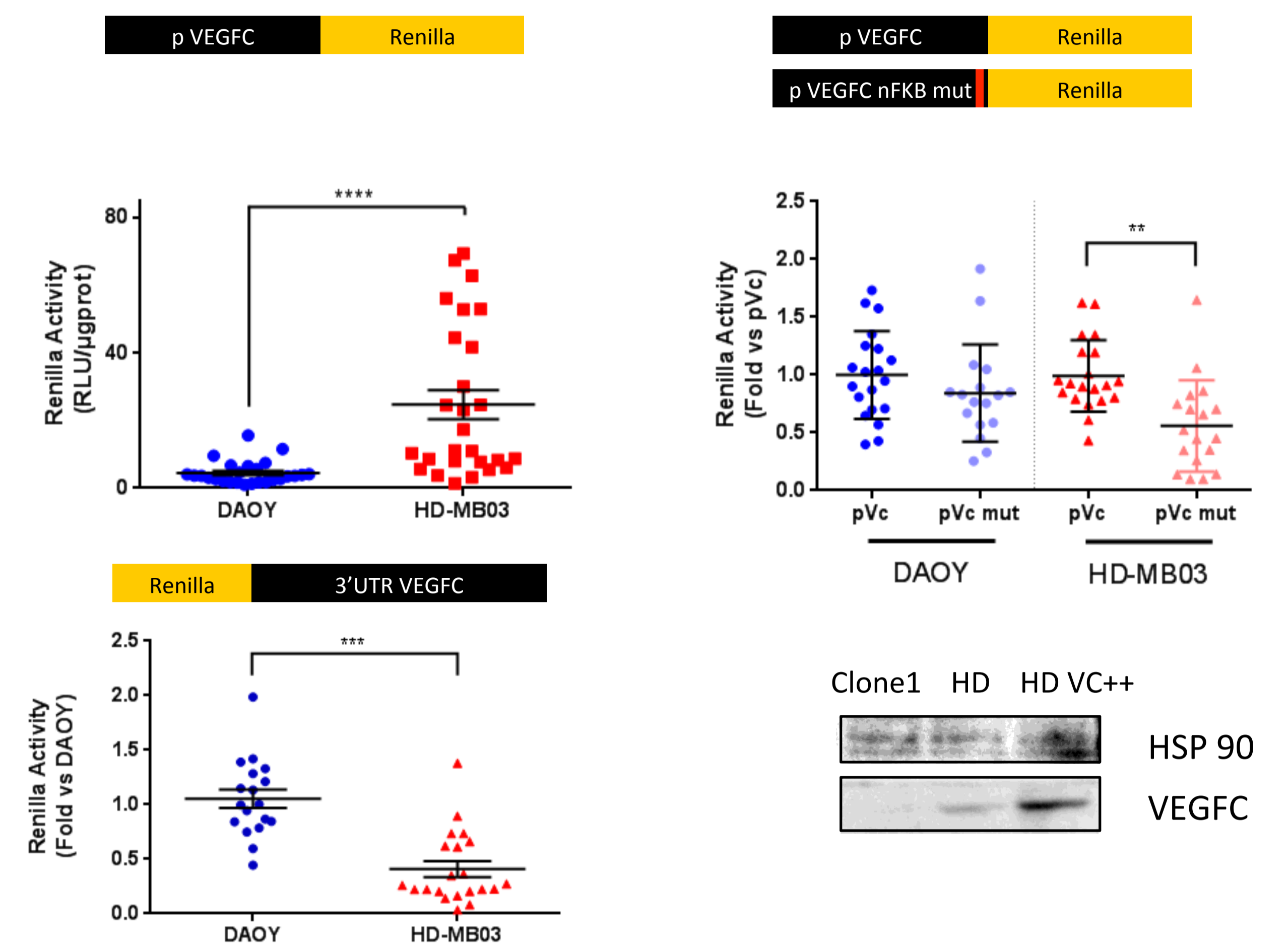
VEGFC is involved in the EMT phenotype of MB cells



Daoy cells (SHH): CRISPR-Cas9 knock-out of VEGFC gene
> Decrease of epithelial phenotype: ↓ Claudin, ↑ N-cadherin
HD-MB03 (Grp3): Transduction of VEGFC gene
> Increase the epithelial phenotype: ↑ Claudin, ↓ N-cadherin

VEGFC increases the mesenchymal-epithelial transition of MB cells

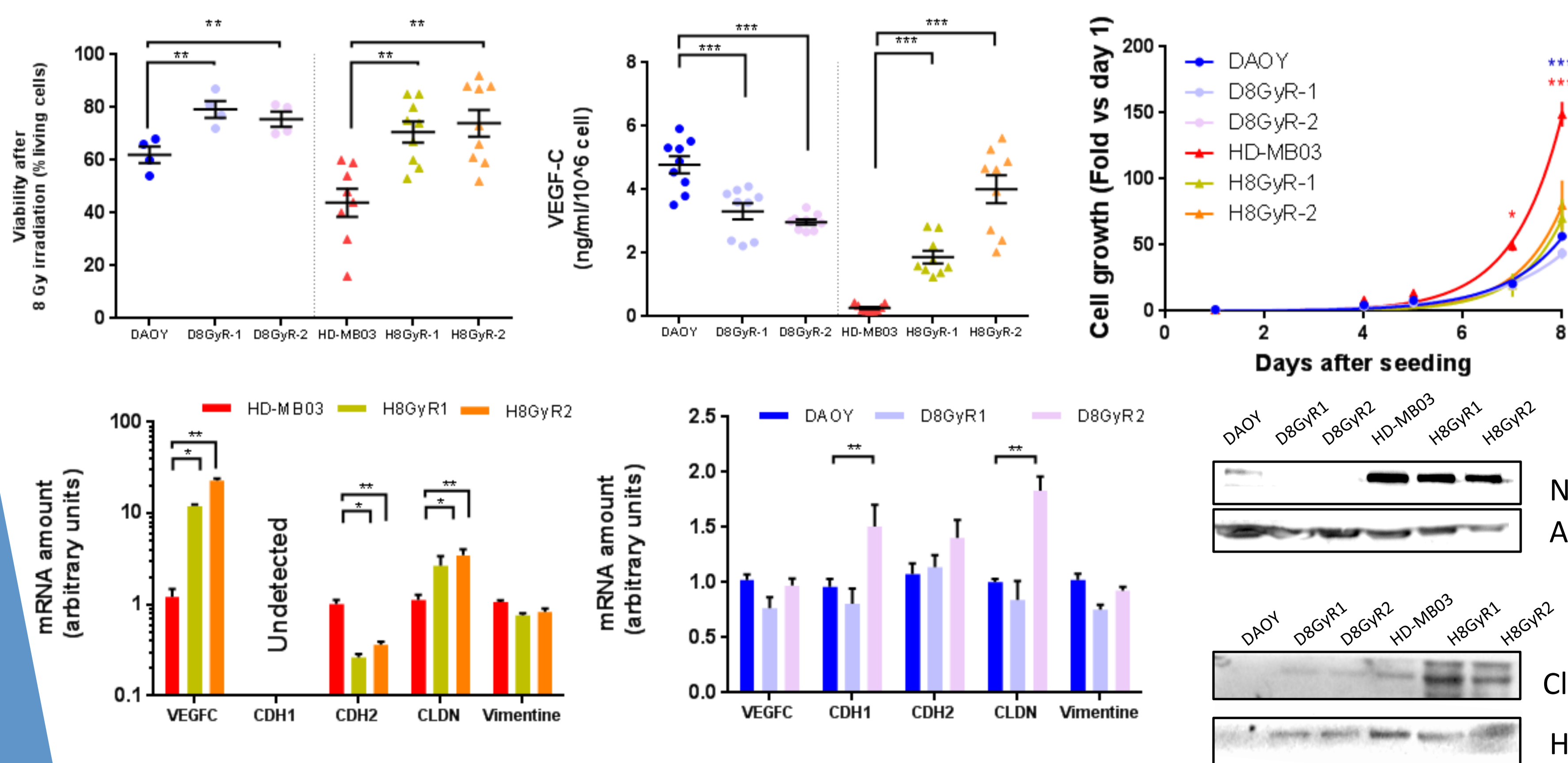
Regulation of VEGFC in medulloblastoma



HD-MB03 (Grp3): High promoter activity, involvement of NF-κB site
VEGFC mRNA less stable in HD-MB03
Lack of VEGFC secretion in HD-MB03

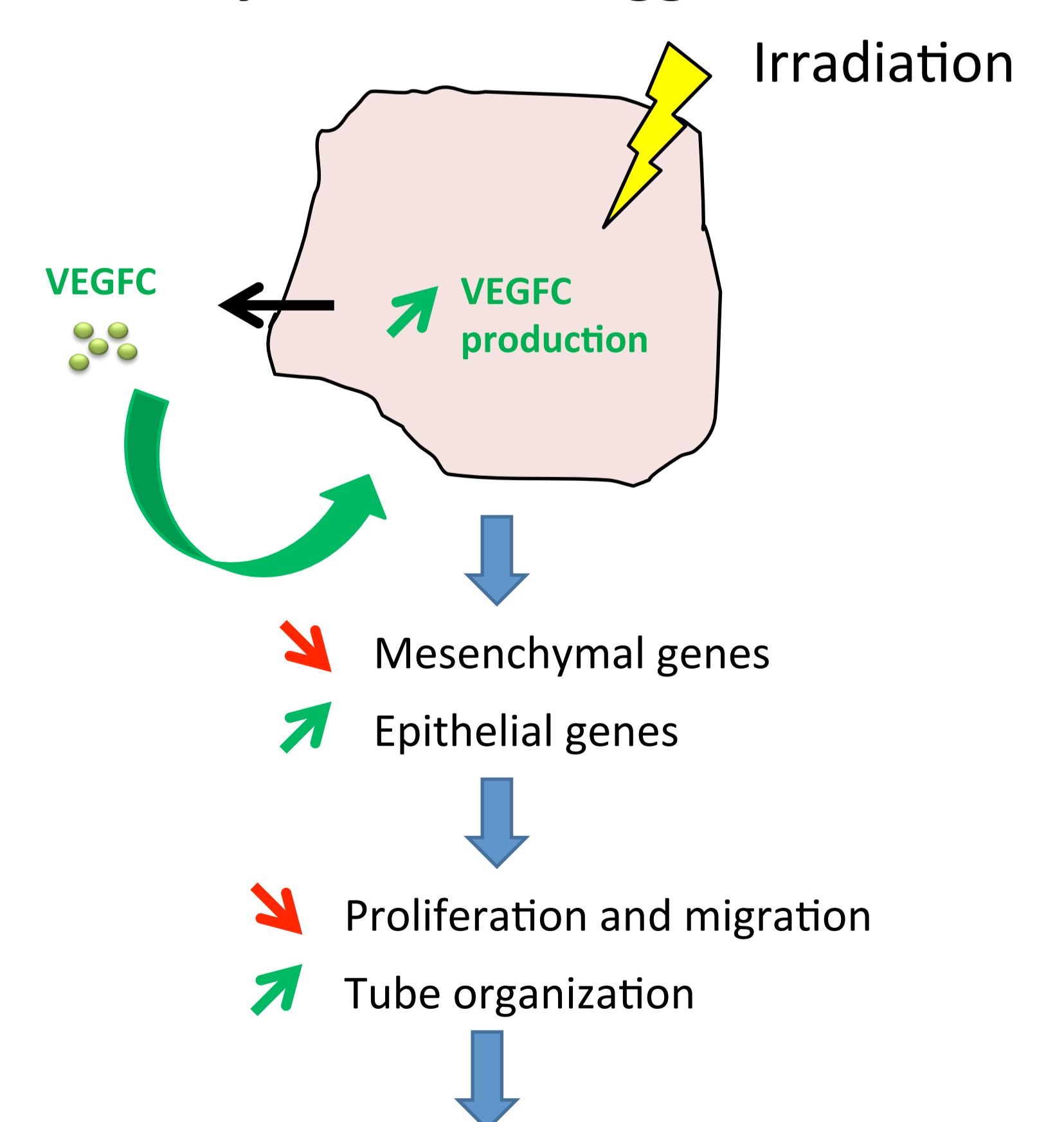
HD-MB03 have a higher ability to regulate their VEGFC production

Multiple irradiations influence MB cell VEGFC production and phenotype



Multiple irradiations influence VEGFC production in MB cells
After irradiation HD-MB03 are more epithelial
Multiple irradiations increase VEGFC and the mesenchymal-epithelial transition of MB cells

VEGFC has a key role in MB aggressiveness



VEGFC is a negative regulator of medulloblastoma aggressiveness, through the mesenchymal-epithelial transition