Katedry genetiky a biochémie PriF UK
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Autocrine VEGF-VEGFR2/Neuropilin-1 signaling promotes glioma stem-like cell viability and tumor growth

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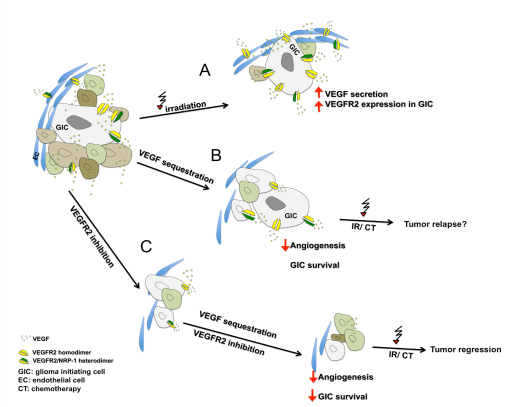
Research focus and talk annotation:



Malignant gliomas, including the most malignant variant glioblastoma multiforme (GBM), are rapidly growing destructive tumors that extensively invade the surrounding brain parenchyma. Robust neoangiogenesis and intratumoral heterogeneity are hallmark features of these brain malignancies, which contribute to their phenotypic plasticity and therapeutic resistance. The latter includes drugs that target the angiogenic interplay between Vascular Endothelial Growth Factor (VEGF) and its receptors, VEGFRs. Recent observations suggest that anti-VEGF compounds (blocking antibodies and tyrosine kinase inhibitors) administered in combination with or before radiation improve the responsiveness of solid tumors through radiosensitizing effects. While Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is traditionally regarded as an endothelial cell protein, evidence suggests that VEGF receptors may be expressed by cancer cells. GBMs are characterized by florid vascularization and aberrantly elevated Vascular Endothelial Growth Factor (VEGF). Anti-angiogenic therapy with Bevacizumab reduces GBM tumor growth, however clinical benefits are transient, invariably followed by tumor recurrence. We have found that the limited impact of Bevacizumab-mediated VEGF blockage may reflect ongoing autocrine signaling through VEGF-VEGFR2/NRP1, associated with VEGFR2/NRP1 recycling and a pool of active VEGFR2 in a cytosolic compartment of human Glioma Initiating Cells (GICs). Whereas Bevacizumab failed to inhibit pro-survival effects of VEGFR2-mediated signaling in our experiments, direct inhibition of VEGFR2 tyrosine kinase activity or shRNA-mediated VEGFR2 or NRP1 knockdown attenuated GIC viability. We propose that direct inhibition of VEGFR2 kinase may block the highly dynamic VEGF-VEGFR2/NRP1 pathway and inspire a GBM treatment strategy complementary to the currently prevalent ligand neutralization approach.

Relevant publications:

1. Knizetova P., Darling JL., Bartek J. (**2007**) Vascular Endothelial Growth Factor in Astroglioma Stem Cell Biology and Response to therapy. J Cell Mol Med 11: 1-15.

2. Hlobilkova A., Ehrmann J., Sedlakova E., Krejci V., **Knizetova P.**, Fiuraskova M., Kala M., Kalita O.,Kolar Z. (**2007**) Could changes in the regulation of the PI3K/PKB/Akt signaling pathway and cell cycle be involved in astrocytic tumour pathogenesis and progression? Neoplasma 54: 334-41.

3. Knizetova P., Ehrmann J., Hlobilkova A., Vancova I., Kalita O., Kolar Z., Bartek J. (**2008**) Autocrine regulation of glioblastoma cell cycle progression, viability and radioresistance through the VEGF-VEGFR2 (KDR) interplay. Cell Cycle 7: 2553-61.

4.Vrzalikova K., Skarda J., Ehrmann J., Murray P.G., Fridman E., Kopolovic J., **Knizetova P.**, Hajduch M., Klein J., Kolek V., Radova L., Kolar Z. (**2008**) Prognostic value of Bmi-1 oncoprotein expression in NSCLC patients: a tissue microarray study. J Cancer Res Clin Oncol 134: 1037-42.

5. Hlobilkova A., Ehrmann J., **Knizetova P**., Krejci V., Kalita O., Kolar Z. (**2009**) Analysis of VEGF, Flt-1, Flk-1, nestin and MMP-9 in relation to astrocytoma pathogenesis and progression. Neoplasma 56: 284-90.

6. Bartkova J.*, **Hamerlik P.***, Stockhausen M., Ehrmann J., Hlobilkova A., Laursen H., Kalita O., Kolar Z., Skovgaard Poulsen H., Broholm H., Lukas J., Bartek J. (**2010**) Replication stress and oxidative damage contribute to aberrant constitutive activation of DNA damage signaling in human gliomas. Oncogene 29: 5095-102. ***equal contribution-shared first author**

7. Bartek J., **Hamerlik P.**, Lukas J. (**2010**) On the origin of prostate fusion oncogenes. Nature Genetics 42: 647–648.

8. Strauss R., Li Z.Y., Liu Y., Beyer I., Sova P., Möller T., Pesonen S., Hemminki A., **Hamerlik, P.,** Drescher C., Urban N., Bartek J., Lieber A. (**2011**) Analysis of epithelial and mesenchymal markers in ovarian cancer reveals phenotypic heterogeneity and plasticity. PLoS One 6: e16186.

9. Patent: Hamerlik P.: Targeting of VEGFR2. Submission number 400001795 and Application number PA 2010 70288.

10. Hamerlik P., Lathia JD., Rasmussen R., Wu Q., Bartkova J., Lee M., Moudry P., Bartek J. Jr., Fischer W., Lukas J., Rich JN. and Bartek J. (**2011**) Autocrine VEGFR2/NRP1 signaling contributes to glioma stem-like cell viability and tumor growth. Journal of Experimental Medicine (under revision).

1.-4. Published under maidens surname Knizetova