VEGF-C

Glioblastoma ranks among the most lethal cancers with current therapies offering only palliation. Paracrine vascular endothelial growth factor (VEGF) signaling has been targeted using anti-angiogenic agents, whereas autocrine VEGF/VEGF Receptor 2 (VEGFR2) signaling is poorly understood. Bevacizumab resistance of VEGFR2-expressing glioblastoma cells prompted interrogation of autocrine VEGF-C-VEGFR2 signaling in glioblastoma.

METHODS: Autocrine VEGF-C/VEGFR2 signaling was functionally investigated using RNA interference and exogenous ligands in patient-derived xenograft lines and primary glioblastoma cell cultures in vitro and in vivo. VEGF-C expression and interaction with VEGFR2 in a matched pre- and post-bevacizumab treatment cohort were analyzed by immunohistochemistry and proximity ligation assay.

RESULTS: VEGF-C was expressed by patient-derived xenograft glioblastoma lines, primary cells and matched surgical specimens before and after bevacizumab treatment. VEGF-C activated autocrine VEGFR2 signaling to promote cell survival, whereas targeting VEGF-C expression reprogrammed cellular transcription to attenuate survival and cell cycle progression. Supporting potential translational significance, targeting VEGF-C impaired tumor growth in vivo, with superiority to bevacizumab treatment.

CONCLUSIONS: Our results demonstrate VEGF-C serves as both a paracrine and autocrine pro-survival cytokine in glioblastoma, promoting tumor cell survival and tumorigenesis. VEGF-C permits sustained VEGFR2 activation and tumor growth, where its inhibition appears superior to bevacizumab therapy in improving tumor control [1].

1)
Michaelsen SR, Staberg M, Pedersen H, Jensen KE, Majewski W, Broholm H, Nedergaard MK, Meulengracht C, Urup T, Villingshøj M, Lukacova S, Skjøth-Rasmussen J, Brennum J, Kjær A, Lassen U, Stockhausen MT, Poulsen HS, Hamerlik P. VEGF-C Sustains VEGFR2 Activation under Bevacizumab Therapy and Promotes Glioblastoma Maintenance. Neuro Oncol. 2018 Jun 25. doi: 10.1093/neuonc/noy103. [Epub ahead of print] PubMed PMID: 29939339.