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## Endothelial factors in the cancer stem-cell maintenance in high grade brain tumors

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Glioblastoma are one of the most lethal forms of adult cancer with a median survival of around 15 months. A new strategy suggests targeting the glioblastoma stem-like cell population (GSC). These GSCs constitute a self-autonomous reservoir of malignant cells able to initiate, maintain, and repopulate the tumor mass. *In situ*, GSCs reside within the vascular niche in tight interaction with brain endothelial cells. Interestingly, this vital dialogue might be required upon tumor regeneration following treatment and could also be maintained outside the niche upon colonization of brain tissues at early stage of tumor formation. These so-called glioblastoma stem-like cells retain the ability to expand *ex vivo* as tumorspheres and recapitulate tumor ontogenesis in mice, whilst they sustain radio- and chemo-resistance. Although their identity and fate are regulated by external cues emanating from endothelial cells, the nature of such angiocrine signals is still unknown. Here, we deployed a mass spectrometry proteomic approach to characterize the factors released by brain endothelial cells. We report the identification of the vasoactive peptide apelin as a central regulator for endothelial-mediated self-renewal of patient-derived glioblastoma stem-like cells. Genetic and pharmacological targeting of apelin cognate receptor APLNR abrogates apelin- and endothelial-mediated pro-self-renewal effects on glioblastoma stem-like cells and suppresses tumor initiation and growth. Functionally, selective competitive antagonists of APLNR were shown to be safe and effective in lengthening the survival of intracranially xenografted mice. Therefore, the APLN/APLNR signaling nexus may operate as a paracrine signal that sustains tumor cell expansion and progression, suggesting that apelin is a druggable factor in glioblastoma. We anticipate that our results will increase our knowledge on signaling mechanisms involved in tumor initiation, progression and resistance, and could help the design of new strategies to face this devastating human cancer.

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