

Abstract

Pseudopalisades (Ps) around necrotic foci are severely hypoxic and overexpress hypoxia-inducible factor (HIF) in glioblastoma (GBM). Hypoxic regions have been proposed as one of several distinct niches for cancer stem cells (CSCs) in GBM, but little is known about the association between Ps features and CSC properties. Herein, we focused on the biological role of Ps lesions. In clinical cases of GBM, expression of hypoxia-related molecules including HIF-1 α , Glut-1, p27^{Kip1} as well as pAkt, was significantly increased in perinecrotic Ps lesions compared with non-necrotic areas and perinecrotic lesions lacking Ps features. Significantly higher expression levels of several CSC-related markers, including CD133, Sox2, CD44s, and aldehyde dehydrogenase (ALDH) 1, were also observed in Ps lesions, which were positively correlated with expression of hypoxia-related molecules and pAkt. Ps lesions also showed increased number of apoptotic cells and decreased bcl-2 and survivin expression compared with the surrounding tissue. Short-term exposure of astrocytoma cell lines to cobalt chloride (CoCl₂), which is known to mimic the effect of hypoxia, caused an increase in expression of both hypoxia- and CSC-related markers, in line with increases in the ALDH^{high} cell population and number of spheroids. Inhibition of endogenous Akt by LY294002 resulted in decreased expression of Sox2, ALDH1, and CD133, leading to enhancement of CoCl₂-mediated apoptotic events due to altered ratio of bcl-2 to bax expression. These findings suggest that Ps lesions within GBM may serve as a specialized hypoxic niche, in which the HIF-1 α /pAkt axis is activated, in response to severe hypoxia.