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[Stem Cell Rev.](#) 2010 Aug 10. [Epub ahead of print]

Glioma Stem/Progenitor Cells Contribute to Neovascularization via Transdifferentiation.

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Abstract

OBJECTIVE: Previous studies suggest that tumor cells might be the progenitor for tumor vasculature. Whether vascular tube formation from transdifferentiation of human glioma stem/progenitor cells (hGSPCs) contribute to angiogenesis of gliomas remain largely uncertain.

METHODS: hGSPCs were isolated from thirteen surgical specimens of gliomas and cultured in medium favored for stem cell growth. In vitro transdifferentiation of hGSPCs was performed under hypoxia. Expression of vascular endothelial cells (VECs) markers CD31, CD34, kinase insert domain receptor (KDR), and von Willebrand factor (vWF) were analyzed with real-time quantitative RT-PCR and immunofluorescence techniques. Vasculogenic mimicry of hGSPCs was evaluated in a tumor stem cell xenograft model in vivo. Relationships between content of hGSPCs and expression levels of both VECs markers and proangiogenic factors in large number of clinical specimens were further investigated in glioma tissue microarray.

RESULTS: In vitro, hGSPCs can transdifferentiate into VECs under hypoxia, they manifested typical "flagstone" pattern when cultivated in medium containing VEGF for a few days; when cultivated on Matrigel they were capable of forming capillary-like structures. Expression of VECs markers including CD31, CD34, KDR, and vWF were significantly up-regulated after transdifferentiation. Human leukocyte antigen (HLA) positively stained vessels were observed inside the xenograft tumors after intracerebral transplantation of hGSPCs in athymic nude mice, implied part of tumor cells with human origin were involved in formation of tumor vessels. In surgical specimens of human glioma, tumor vascular cells coexpressing the markers of early VECs (CD34) and markers of hGSPCs (ABCG2 and nestin) suggest that these vascular cells may stemmed from hGSPCs.

CONCLUSIONS: Our observations suggest the functional role of hGSPCs as endothelial progenitors, which have properties that give rise to VECs, and have the ability to form vascular endothelial tubes. However, unspecific markers (ABCG2, nestin) that stain for both endothelial as well as glioma stem cells, were found to be expressed in tumor vasculature of human specimen, and limit further interpretation of this finding.

PMID: 20697979 [PubMed - as supplied by publisher]

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