Angiogenesis in glioblastoma: just another moving target?

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Inhibition of angiogenesis as a concept has experienced a renaissance in Neuro-Oncology in 2009. Based on encouraging phase II data suggesting increased response rates and improved quality of life including a steroid-sparing effect (Friedman et al. 2009, Kreisl et al. 2009), bevacizumab, an antibody to vascular endothelial-derived growth factor (VEGF), was approved for the treatment of recurrent glioblastoma in the US and, e.g., in Switzerland, although not in the European Union (Weller and Stupp 2009). Further, the results of a 2:1:2 randomized trial comparing the VEGF receptor antagonist, cediranib (Batchelor et al. 2007), with the alkylating agent, lomustine, and the combination of cediranib and lomustine in patients with recurrent glioblastoma are awaited for the ASCO meeting June 2010. Finally, not only bevacizumab (and probably soon cediranib, too), but also another antiangiogenic agent, the integrin antagonist, cilengitide (Stupp et al. 2010), are currently evaluated in registration trials for patients with newly diagnosed glioblastoma.

Theoretical support for the therapeutic approach of angiogenesis inhibition in glioblastoma stems from the idea that the endothelial cell is the only stable, reliable element in an increasingly heterogenous, chaotic tumor microenvironment. Genetic instability of glioma cells might drive rapid selection processes resulting in the generation of multiple diverse resistant tumor cell clones. In contrast, it has commonly been assumed that (true) endothelial cells, which are non-neoplastic host cells recruited by the growing tumors, would be essentially resistant to the development of resistance. Yet, clinical experience has taught us already that such views are oversimplified.
First, not all vessel formation in gliomas depends on VEGF as illustrated by the response rates defined by classical neuroradiological response criteria in the range of 30-50% (Batchelor et al. 2007, Friedman et al. 2009, Kreisl et al. 2009). While it was appropriate to welcome these data as promising, it must not escape our notice that at least half of the glioblastomas do quite well in the presence of bevacizumab or cediranib, indicating that not all glioblastoma-related angiogenesis is VEGF-related. Second, the responses to antiangiogenic agents targeting VEGF are commonly transient, suggesting that there are effective escape mechanisms of blood vessel formation, contradicting the wishful thinking of endothelial resistance to the development of resistance. In fact, numerous other molecules including other VEGF family members as well as placental-derived, hepatocyte and fibroblast growth factor have been implicated in the primary or acquired resistance to VEGF-antagonistic treatments.

Third, in the current issue of Brain, El Hallani and colleagues (2010) address a largely neglected phenotype of maintaining tumor perfusion, the formation of vessel-like structures by the tumor cells themselves, referred to as vasculogenic mimicry of the tubular type. They identified a subset of glioblastomas characterized by “blood vessels” that were lined by non-endothelial cells. This interpretation was based on the presence of collagen IV, a marker of blood vessel basement membranes, in the absence of the expression of CD34, a universal marker for endothelial cells. To support the idea that the vessel-lining cells were tumor cells, the authors demonstrated the amplification of epidermal growth factor receptor in these cells in a tumor known to harbour this molecular phenotype. Some of the tumor cells expressed smooth muscle actin, indicating that these tumor cells had transdifferentiated into vascular smooth muscle-like cells. Intriguingly, the authors
provide one example of a tissue section where there appears to be an anastomosis between an endothelially lined vessel and a tumor-derived “vessel”. Finally, the authors analysed the subpopulation of glioma-initiating cells by CD133 sorting from two tumors, one with and one without putative tumor-derived blood vessels. CD133+ cells from the former tumor generated vessel-like structures in tube formation assays whereas the latter did not. An expression of endothelium-associated genes was observed in both populations of glioma-initiating cells. These observations led the authors to propose that the subpopulation of glioma-initiating cells may even possess the plasticity to form blood vessels. Taken together, this study indicates that some glioblastomas may grow in the absence of endothelial cell recruitment, suggesting that they may exhibit primary refractoriness to therapeutic approaches targeting, e.g., VEGF. Admittedly, further studies need to clarify the overall frequency of this phenotype and its contribution to the perfusion of glioblastomas in a larger sample of tumors.

The introduction of novel antiangiogenic agents has already imposed some new challenges on clinical neuro-oncologists, some of which have been faced and almost solved whereas others require new approaches. Thus, the response criteria devised by Macdonald and colleagues (1990) had to be modified to rely less on contrast enhancement, to include the necessity for a confirmation of a response as well as to consider tumor extensions on T2-weighted magnetic resonance imaging (Van den Bent et al. 2009). The latter became necessary when it was recognized that some patients treated with bevacizumab exhibited an altered patterns of recurrence reminiscent of gliomatosis cerebri which was attributed to a change from vessel- and VEGF-dependent growth to a vessel- and VEGF-independent growth (Norden et al. 2008). Future clinical trials will aim at identifying prospectively biomarkers associated
with response or lack of response to antiangiogenic agents and such analyses should start with a careful neuropathological and neuroradiological characterization of the pretreatment vascularisation of these tumors.

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References


