Angiopoietin 2

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Tumor formation

Microtumor growth initiates angiogenic sprouting with simultaneous expression of VEGF, VEGF receptor-2, and angiopoietin-2 [1)].

The angiopoietins Ang-1 and Ang-2 have been implicated in the regulation of angiogenesis; reports have suggested that a net gain in Ang-2 activity may be an initiating factor for tumor angiogenesis.

The relative increase in angiopoietin-2 activity in brain tumors may result in the creation of a pro-angiogenic environment that enhances the recruitment of putative bone marrow-derived endothelial progenitor cell into the tumor's developing vascular tree [2)].

The expression of Ang-1, Ang-2, VEGF, and Tie 2, a member of the receptor tyrosine kinases and the natural receptor for both Ang-1 and Ang-2, follows a distinct transcriptional profile in vivo. Ang-2 and VEGF were expressed early in tumor formation and their levels increased throughout tumor growth. Their expression coincided with the expansion of the tumor mass and the formation of the vascular tree. There was no significant change in the expression of Tie-2 and Ang-1. The expression of Ang-1 and Tie-2 was more noticeable at the periphery of the tumor. The expression of Ang-2 was more robust at the periphery and within the tumor mass, and VEGF was more concentrated within the center of the tumor. This distinct gene expression profiling may explain the morphology of the newly formed vessels at various times and regions of the tumor. The lack of concomitant expression of Ang-1 may underscore the unopposed endovascular induction by Ang-2 and VEGF resulting in the chaotic appearance and fragility of tumor vessels [3)].

p53 causes tumor regression by suppressing tumor proliferation and indirectly induces involution of tumor vessels by fostering unopposed activity of Angiopoietin 2 in an environment of diminishing VEGF [4)].

High grade glioma

Angiopoietin-2 mRNA expression in cultured human malignant glioma cells (U105, U251, and U373 MG) by reverse transcriptase-PCR. Western blot analysis and immunocytochemical analysis with antihuman Ang2 antibody revealed that Ang2 protein was expressed and secreted by these cells. Furthermore, hypoxia increased the Ang2 protein level in cultured glioma cells. Serial sections of 32 human glioma tissues (14 glioblastomas, eight anaplastic astrocytomas, seven astrocytomas, and three pilocytic astrocytomas) were immunostained against Ang2, vascular endothelial growth factor, Tie2, von Willebrand factor, and alpha smooth muscle actin. The immunoreactivity of each angiogenic factor was higher in malignant gliomas than in low-grade gliomas.

Angiopoietin 2 protein was detected not only in endothelial cells but also in glioma cells, and its expression was prominent in both the area surrounding the necrosis and the periphery of

glioblastomas.

In the area surrounding necrosis, Ang2 was highly expressed and tumor vessels showed regression. In the tumor periphery, Ang2 was highly expressed and many small vessels stained positively for von Willebrand factor but not for alpha smooth muscle actin, suggesting angiogenesis. Statistical analysis revealed that the Ang2 expression was negatively correlated with vessel maturation in malignant gliomas and that vascular endothelial growth factor expression was positively correlated with vessel maturation in low-grade gliomas ($P < 0.05$). These results suggest that glioma cells themselves express Angiopoietin 2 and that expression may be induced by hypoxic stimulation and may play a crucial role in the vessel maturation, angiogenesis, and vessel regression in malignant glioma [5].

ANGPT1/ANGPT2 balance has prognostic value in patients with primary glioblastomas (GBMs). This findings support the need for further studies of the feasibility of antiangiogenic therapy in primary GBMs, with a special focus on the normalization of tumor vasculature [6].

Combining VEGF blockade with inhibition of Angiopoietin 2 may potentially overcome resistance to bevacizumab therapy [7].

Arteriovenous malformation

Up-regulated VEGF in part of brain and Tie-2, Angiopoietin 2 high expression in endothelial cells (EC) of some vessels may be one of major factors for cerebral arteriovenous malformation (CAVM) formation growth, and rupture in the embryonic period [8].

Traumatic brain injury

Ang-1/2 evaluation in plasma, serum and cerebrospinal fluid may provide new therapeutic modalities which can modify 'secondary' forms of brain injury after TBI and SAH [9].

Chronic subdural hematoma

Persistent activation of the angiopoietin and their receptor Tie 2 system in addition to high levels of VEGF may keep the vasculature in a destabilized condition and may account for the continuous formation of new and immature blood vessels resulting in massive plasma extravasation and repeated bleeding episodes. This provide new evidence in favor of pro-angiogenic mechanisms playing an important role in the pathophysiology of chronic subdural hematoma (CSH) [10].

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