Angiogenic Factors in Plasma of Brain Tumour Patients

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Abstract. *Background: Angiopoiesis and angiopoietic growth factors are of considerable importance in the development and progression of intracranial tumours. However, knowledge of the plasma detectability of distinct angiogenic factors in patients with brain tumour is very limited. This study evaluates the plasma concentrations of the angiogenic factors angiopoietin-2 (Ang-2), vascular endothelial growth factor (VEGF) and platelet-derived growth factor BB (PDGF-BB) in patients with brain tumour. Patients and Methods: Plasma samples of 78 patients suffering from various types of intracranial tumours (glioblastoma multiforme, GBM, n=22; astrocytoma, n=12; meningioma, n=16; and intracranial metastasis, n=28) were analysed. For determination of plasma concentrations of angiogenic factor, highly specific enzyme-linked immuno sorbent assays (ELISAs) were used. Results: Ang-2 plasma concentration in GBM patients was significantly lower when compared with that in patients with meningioma and intracranial metastasis. Highest levels of VEGF concentrations were detected in plasma derived from patients suffering from meningioma. Interestingly, VEGF plasma levels depended on the number of intracranial lesions, with significantly higher concentrations in patients with 3 or more lesions when compared with those with 2 or fewer lesions. However, no correlation between the survival time of the patients and the plasma levels of the tested growth factors was obtained. Plasma levels of PDGF-BB did not differ between the individual tumour groups. Conclusion: The detectability of the angiogenic factors Ang-2 and VEGF, as well as of PDGF-BB, in the plasma of patients suffering from various types of brain tumours is described. The plasma detectability of the individual angiopoetic factors seems to depend at least partly on the tumour type as well as on tumour progression. This might be of prognostic and therapeutic relevance.*

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Primary brain tumours are classified into 4 malignancy groups as defined by the World Health Organisation (WHO) (1). The most malignant tumour is the glioblastoma, also known as glioblastoma multiforme (GBM). Although chemotherapy, radiotherapy and surgical methods have progressed enormously in recent years, the prognosis of GBM patients is still very limited (2).

Angiogenesis plays a crucial role in tumour growth, particularly in GBM. The unique structure of brain vessels, consisting of endothelial cells (EC), pericytes and astrocytes, is abnormal in these tumours. There are many growth factors and cytokines involved in the complex mechanism of angiogenesis. Vascular endothelial growth factor (VEGF) is a secreted dimer with characteristic kinase domain receptor binding sites (3, 4). Based on its potential to increase vascular permeability, Senger and colleagues were the first to hypothesize an involvement of VEGF in angiogenesis (5). Development of abnormal vascular structures in mice lacking VEGF has encouraged this hypothesis (6). Endothelial expression of VEGF was detected in all angiogenesis stages, namely survival, proliferation, migration and permeability, underlining the central role of this growth factor in new vessel formation (7). Up-regulation of VEGF transcription in tumour cells due to hypoxia (8, 9) represents a stimulus for angiogenesis. Notably, in gliomas, expression levels of VEGF and its receptor highly correlate with their malignancy grade (10).

Angiopoietins have been identified as one of the most important growth factors involved in the VEGF signalling pathway (11, 12). Upon stimulation, angiopoietin-1 and -2 (Ang-1 and -2) are secreted and act *via* the Tie 2 tyrosine kinase receptor (13). In mice, alterations of the expression levels of angiopoietins and their receptor Tie 2 resulted in a high extent of vessel malformations. Thus the potential role of the angiopoietin/Tie 2 receptor system in angiogenesis has been suggested (11, 14-16). Ang-1 induces auto-phosphorylation of the tyrosine kinase-dependent Tie 2 receptor, whereas Ang-2 is a natural antagonist (16). In GBM, Ang-1 was highly expressed in tumour cells and Ang-2 was predominantly present in ECs (17-19). It is hypothesized that Ang-1 promotes angiogenesis in GBM (20, 21), whereas Ang-2 serves as an early marker of tumour angiogenesis in astrocytomas (22).