Vascular microenvironment in gliomas

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Summary

Structural and functional abnormalities of the vascular microenvironment determine pathophysiological characteristics of gliomas, such as loss of blood–brain barrier function, tumor cell invasiveness, or permselectivity for large molecules. Moreover, the effectiveness of various therapeutic strategies critically depends upon the successful transvascular delivery of molecules. In order to shed more light on the vascular microenvironment in gliomas, a variety of experimental and clinical techniques have been applied to study the glioma microvasculature, including histology, vascular corrosion casts, microangiography by injection of dyes, blood flow measurements by autoradiography, tracer washout techniques, magnetic resonance imaging, as well as intravital fluorescence microscopy. This review summarizes the characteristic features of vascular morphology, angio-architecture, tumor perfusion, microvascular permeability, as well as microvessel-related immunological competence in gliomas. An improved understanding of the vascular microenvironment in gliomas will help in the future to optimize glioma imaging and delivery of vectors for gene therapy or encapsulated drug carriers in patients.

Introduction

Despite various therapeutic and diagnostic efforts, high-grade gliomas (anaplastic astrocytoma and glioblastoma multiforme) still represent an unsolved problem of today’s neurooncology. The mean survival time for patients with this tumor entity currently approximates 9–12 months (treated by surgery, radiotherapy and chemotherapy) with 5-year survival rates of 10–35% and near 0% for anaplastic astrocytomas and glioblastoma multiforme, respectively [1,2].

As all neoplastic tissues, gliomas may be subdivided into three compartments, classified as cellular, interstitial and vascular in nature. While earlier experimental studies primarily focused on the biology and pathology of the tumor cells and paid only minor attention to the in vivo environment they exist in, the significance of the vascular microenvironment for glioma progression, invasion, diagnosis, and treatment is now realized in its full significance. Angiogenesis and continuous remodeling of the tumor microvasculature are essential for adequate tumor tissue oxygenation and nutritional supply. The vascular microenvironment determines pathophysiological characteristics of gliomas, such as edema formation [3], tumor cell invasiveness [4,5], or permselectivity for large molecules [6,7]. Moreover, the effectiveness of radiotherapy, chemotherapy, immunotherapy, or gene therapy critically depends upon the successful transvascular delivery of small and large molecules [8–13]. Thus, the understanding of structural and functional characteristics of the vascular microenvironment in gliomas is essential for the design of future therapeutic strategies against this tumor. In the following we will review (i) experimental and clinical techniques to study the glioma microvasculature, (ii) the development of the vascular microenvironment in gliomas, and (iii) its structural and functional characteristics. Since the vasculature of low-grade gliomas closely resembles that of normal brain [14] we will focus on the vascular microenvironment in high-grade gliomas.

Experimental approaches to the vascular microenvironment in gliomas

Our current knowledge on the vascular microenvironment in gliomas has evolved from various experimental
studies applying both morphological and functional techniques. Conventional light microscopic studies and immunohistochemical staining for endothelial cell marker such as factor VIII-related antigen (von Willebrand factor), CD31 (PECAM), or CD34 have identified high-grade gliomas as one of the most intensively vascularized tumors reflecting a high angiogenic activity of these tumors [15–17]. The same techniques allowed to identify tumor vessel density as an independent prognostic parameter for human astroglial tumors [18,19]. Vascular corrosion casts together with scanning electron microscopy have characterized the three dimensional micro-angio-architecture of gliomas [20,21]. Transmission electron microscopic analyses have gained further insight into ultrastructural alterations of the glioma vessel wall and potential transvascular transport mechanisms [6,22].

Initial studies on functional aspects of the glioma microvasculature were performed by angiographic techniques in patients and revealed early results on the origin of glioma vessels and specific perfusion patterns of human gliomas [23,24]. Perfusion studies in experimental tumors using dyes or radioactive tracers [25–27] have provided further informations on the heterogeneity of glioma blood flow. In contrast to the aforementioned ex vivo methods, the advantage of non-invasive imaging techniques is that they allow to assess the vascular microenvironment repeatedly in vivo which enables to analyze the dynamic aspects of glioma microcirculation. Cross-sectional techniques such as computerized tomography and magnetic resonance imaging have been successfully applied to study perfusion and permeability characteristics in human and experimental gliomas [28,29]. The low spatial resolution of these techniques can be overcome by intravital fluorescence microscopy which offers the possibility to adress the dynamic aspects of the tumor microvasculature at the level of individual microvessels as well as microvascular cell–cell-interactions (Figure 1) [30].

**Vascular development in gliomas**

The microvasculature in gliomas is characterized by a constant vascular remodeling where tumor microvessels establish, sustain, and finally regress. This chronic microvascular turnover which is unique to tumor microenvironment has led Dvorak and coworkers to characterize a tumor as ‘a wound that never heals’ [31]. Glioma microvessels appear to have three principal origins: neovascularization by sprouting from pre-existing vessels (i.e. angiogenesis), take over of host vessels by the tumor (i.e. cooption), and partitioning of the vessel lumen by insertion of interstitial tissue columns (i.e. intussusception) [14,24,32,33]. Although the exact biomolecular mechanism responsible for these distinct vascularization mechanisms are still elusive, strong evidence exists that they are mediated by similar growth factors such as vascular

![Figure 1](image-url)