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Review

Overcoming the blood–brain tumor barrier for effective glioblastoma treatment

O. van Tellingen[d,**,1], B. Yetkin-Arik[c,1], M.C. de Gooijer[d,1], P. Wesseling[e,f], T. Wurdinger[a,b], H.E. de Vries[c,*]

[a] Neuro-oncology Research Group, Department of Neurosurgery, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[b] Molecular Neurogenetics Unit, Departments of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Clinical Chemistry/Preclinical Pharmacology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[e] Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands
[f] Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

Gliomas are the most common primary brain tumors. Particularly in adult patients, the vast majority of gliomas belongs to the heterogeneous group of diffuse gliomas, *i.e.* glial tumors characterized by diffuse infiltrative growth in the preexistent brain tissue. Unfortunately, glioblastoma, the most aggressive (WHO grade IV) diffuse glioma is also by far the most frequent one. After standard treatment, the 2-year overall survival of glioblastoma patients is approximately only 25%. Advanced knowledge in the molecular pathology underlying malignant transformation has offered new handles and better treatments for several cancer types. Unfortunately, glioblastoma multiforme (GBM) patients have not yet profited as although numerous experimental drugs have been tested in clinical trials, all failed miserably. This grim prognosis for GBM is at least partly due to the lack of successful drug delivery across the blood–brain tumor barrier (BBTB). The human brain comprises over 100 billion capillaries with a total length of 400 miles, a total surface area of 20 m^2 and a median inter-capillary distance of about 50 μm, making it the best perfused organ in the body. The BBTB encompasses existing and newly formed blood vessels that contribute to the delivery of nutrients and oxygen to the tumor and facilitate glioma cell migration to other parts of the brain. The high metabolic demands of high-grade glioma create hypoxic areas that trigger increased expression of VEGF and angiogenesis, leading to the formation of abnormal vessels and a dysfunctional BBTB. Even though the BBTB is considered 'leaky' in the core part of glioblastomas, in large parts of glioblastomas and, even more so, in lower grade diffuse gliomas the BBTB more closely resembles the intact blood–brain barrier (BBB) and prevents efficient passage of cancer therapeutics, including small molecules and antibodies. Thus, many drugs can still be blocked from reaching the many infiltrative glioblastoma cells that demonstrate 'within-organ-metastasis' away from the core part to brain areas displaying a more organized and less leaky BBTB. Hence, drug delivery in glioblastoma deserves explicit attention as otherwise new experimental therapies will continue to fail. In the current review we highlight different aspects of the BBTB in glioma patients and preclinical models and discuss the advantages and drawbacks of drug delivery approaches for the treatment of glioma patients. We provide an overview on methods to overcome the BBTB, including osmotic blood–brain barrier disruption (BBBD), bradykinin

* Corresponding author at: Department of Molecular Cell Biology and Immunology, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. Tel.: +31 20 4448077; fax: +31 20 4448081.
** Corresponding author at: Department of Clinical Chemistry/Preclinical Pharmacology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 20 5122792; fax: +31 20 5122799.
E-mail addresses: o.v.tellingen@nki.nl (O. van Tellingen), he.devries@vumc.nl (H.E. de Vries).
[1] These authors contributed equally to this work.

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receptor-mediated BBTB opening, inhibition of multidrug efflux transporters, receptor-mediated transport systems and physiological circumvention of the BBTB. While our knowledge about the molecular biology of glioma cells is rapidly expanding and is, to some extent, already assisting us in the design of tumor-tailored therapeutics, we are still struggling to develop modalities to expose the entire tumor to such therapeutics at pharmacologically meaningful quantities. Therefore, we must expand our knowledge about the fundamentals of the BBTB as a step toward the design of practical and safe devices and approaches for enhanced drug delivery into the diseased brain area.

Contents

1. Gliomas

Gliomas account for approximately 80% of all tumors arising in brain tissue, with an incidence of about 7 per 100,000 individuals worldwide. Patients with gliomas may present with several neurological symptoms such as headaches, seizures, focal neurologic deficits, memory loss, personality changes, vomiting, and visual changes (Chandana et al., 2008; Ferguson, 2011; Wen and Kesari, 2008). According to the World Health Organization (WHO), gliomas are classified according to their cell type and malignancy grade (Louis et al., 2007). The vast majority of gliomas in adult patients are so-called diffuse gliomas, *i.e.* tumors that are characterized by diffuse infiltration of tumor cells in the preexistent brain tissue. However, diffuse gliomas may also occur in children. Based on the phenotype of the tumor cells diffuse gliomas are according to the WHO 2007 classification typed as astrocytic, oligodendroglial or oligoastrocytic tumors. Furthermore, a malignancy grade (grade II = low grade diffuse glioma; grade III = malignant/anaplastic diffuse glioma; grade IV = glioblastoma) is assigned to these tumors based on the presence/absence of features like brisk mitotic activity, florid microvascular proliferation and necrosis (Louis et al., 2007; Sanai et al., 2011). Glioblastomas are by far the most common and most malignant type (Nupponen and Joensuu, 2006; Wen and Kesari, 2008). Of note, WHO grade I is reserved for more circumscribed glioma variants such as pilocytic astrocytoma that occur especially in children.

Despite their initially often relatively indolent nature, most low-grade diffuse gliomas eventually progress to anaplastic glioma or glioblastoma (Nupponen and Joensuu, 2006). Glioblastomas can be further subdivided into primary and secondary glioblastoma and are characterized by marked cellular proliferation, necrosis, florid microvascular proliferation (*i.e.* a peculiar form of angiogenesis), resistance to apoptosis, and genomic aberrations (Furnari et al., 2007). Primary glioblastomas comprise the majority of cases (>90%), generally occur in older patients (>50 years) and are considered to be WHO grade IV from the start. In contrast, secondary glioblastomas occur in younger patients and arise from progression of a lower grade glioma (Ohgaki and Kleihues, 2007). Most lower grade diffuse gliomas carry a mutation in the isocitrate dehydrogenase 1 or 2 (IDH1/IDH2) gene, and it was recently proposed to define primary *vs* secondary glioblastoma based on the IDH1/IDH2 mutation status of the tumor (Ohgaki and Kleihues, 2013).

2. Molecular composition of the BBB and implications for drug entry

The human brain comprises over 100 billion capillaries with a total length of 400 miles, a total surface area of 20 m^2 and a median inter-capillary distance of about 50 μm, making it the best perfused organ in the body (Pardridge, 2005). Proper function of the vasculature in the central nervous system (CNS) is essential for adequate brain function, not only to efficiently supply the brain with nutrients and oxygen, but also to protect the brain from potentially neurotoxic compounds. This protective blood barrier known as the blood–brain barrier (BBB), between the blood compartment and the brain is an essential prerequisite to secure correct neuronal functioning of the brain. The BBB is a cellular barrier (Fig. 1 and 2A) that regulates the ionic composition for proper synaptic signaling function, prevents macromolecules and unwanted cells from entering the brain as well as protects the CNS from neurotoxic substances and ensures brain nutrition.

In essence, the BBB is formed by the specialized brain endothelial cells that exert their barrier properties through the continuous interaction with surrounding cells like astrocytes, pericytes, and perivascular macrophages, forming the so-called neurovascular unit (Abbott et al., 2006). Astrocytic endfeet cover the basal lamina of the brain capillaries and provide the cellular connection to neurons. Astrocytes play a key role in the maintenance of the barrier properties of the endothelium (Abbott et al., 2006; Alvarez et al., 2013). Pericytes cover the endothelium and contribute to the structural integrity of the BBB and the induction of barrier properties during development (Daneman et al., 2010; Obermeier et al., 2013). There is increasing evidence that astrocytes and pericytes secrete soluble developmental cues, like sonic hedgehog, retinoic acid and Wnt that control the onset of barrier properties (Alvarez

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