Biochimica et Biophysica Acta 1846 (2014) 560–575

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Mechanisms of intimate and long-distance cross-talk between glioma and myeloid cells: How to break a vicious cycle

Thomas Wurdinger [a,b,*], Katrin Deumelandt [b,c], Hans J. van der Vliet [c], Pieter Wesseling [d,e], Tanja D. de Gruijl [c,**]

[a] *Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[b] *Department of Neurosurgery, Neuro-oncology Research Group, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*
[c] *Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands*
[d] *Department of Pathology, Neuro-oncology Research Group, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*
[e] *Department of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands*

ARTICLE INFO

Article history:
Received 28 August 2014
Received in revised form 12 October 2014
Accepted 13 October 2014
Available online 20 October 2014

Keywords:
Glioblastoma
Cross-talk
Immune response
Monocytes
Glioma-associated macrophages and microglia
Myeloid-derived suppressor cells

ABSTRACT

Glioma-associated microglia and macrophages (GAMs) and myeloid-derived suppressor cells (MDSCs) condition the glioma microenvironment to generate an immunosuppressed niche for tumour expansion. This immunosuppressive microenvironment is considered to be shaped through a complex multi-step interactive process between glioma cells, GAMs and MDSCs. Glioma cells recruit GAMs and MDSCs to the tumour site and block their maturation. Glioma cell-derived factors subsequently skew these cells towards an immunosuppressive, tumour-promoting phenotype. Finally, GAMs and MDSCs enhance immune suppression in the glioma microenvironment and promote glioma growth, invasiveness, and neovascularization. The local and distant cross-talk between glioma cells and GAMs and MDSCs is regulated by a plethora of soluble proteins and cell surface-bound factors, and possibly via extracellular vesicles and platelets. Importantly, GAMs and MDSCs have been reported to impair the efficacy of glioma therapy, in particular immunotherapeutic approaches. Therefore, advancing our understanding of the function of GAMs and MDSCs in brain tumours and targeted intervention of their immunosuppressive function may benefit the treatment of glioma.

Contents

---

* Correspondence to: T. Würdinger, Massachusetts General Hospital, Harvard Medical School, Building 149, 13th Street, Charlestown, 02129 MA.
** Correspondence to: T.D. de Gruijl, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
E-mail addresses: twurdinger@mgh.harvard.edu (T. Wurdinger), td.degruijl@vumc.nl (T.D. de Gruijl).

http://dx.doi.org/10.1016/j.bbcan.2014.10.003
0304-419X/

1. Introduction

Malignant gliomas form a family of highly aggressive brain tumours. Amongst these, glioblastoma represents the most frequent and most malignant type [1]. Despite great efforts to improve treatment, the median overall survival of patients treated with aggressive therapy is still below 15 months [2]. In 2005, the standard treatment for newly diagnosed glioblastoma changed from radiotherapy alone to a combination treatment of radiotherapy and temozolomide [3]. However, the median survival of patients treated with the combination therapy over surgery only increased from only 12.0 to 14.2 months [3]. It is well established that natural immunity is not effective in suppressing glioma growth. Immunotherapeutic approaches aimed at provoking anti-tumour immune responses achieved significant survival advantages for other tumour types, including prostate cancer for which it is currently used as standard treatment [4,5]. In the past decades, different immunotherapeutic strategies were tested in glioma patients participating in clinical trials, including passive approaches based on either cytokines or antibodies and adoptive cell transfer, and active immunotherapy using anti-tumour vaccines [6–8]. Most of the strategies involved administration of antigen-presenting cells (APCs), e.g. dendritic cell (DC) vaccines loaded with tumour peptides or whole tumour lysates [9]. However, although many of these approaches seemed to be promising *in vitro*, they demonstrated only limited success or significant side effects in animal models and clinical trials [7, 10–12].

Tumours of the central nervous system (CNS) raise challenges for immunotherapy because of the unique immune environment of the CNS. The CNS has long been regarded as an immune privileged site [13,14], due to its blood brain barrier (BBB), controversially lacking a connection to the lymphatic system and the apparent inability of microglia (the so-called resident brain histiocytes) to induce a T-cell response [15]. However, over the years this principle of CNS immune privilege in glioma patients has been challenged in several ways: 1) in high-grade glioma patients the BBB is leaky; 2) connections exist between cerebrospinal fluid (CSF) and cerebral interstitial fluid (CIF) compartments and cervical lymphatics; 3) microglia can fulfill the role of resident APCs within the CNS; 4) 'professional' APCs, i.e. DCs, are present in the meninges and choroid plexus; 5) active trafficking of immune cells to and from the brain is observed [7].

Glioma antigens are released into the CSF and CIF fluids, and although the brain does not contain specialized lymphatic vessels, there is efficient drainage of CSF and CIF to the deep cervical lymph nodes allowing for initial immune activation. In these lymph nodes glioma antigens encounter cognate B lymphocytes and are processed and presented to circulating naive T-cells by professional APCs such as DCs, leading to immune infiltration of the glioma tissue [7]. It thus becomes increasingly clear that the immune privilege of the CNS in the context of glioma is not defined by the absolute absence and ineffectiveness of immune cells in the CNS, but rather is a consequence of the tight regulation of the immune balance in this system [16]. It is now well established that, beyond this unique immune environment of the brain, glioma cells can actively mediate immune suppression and thereby also influence the effectiveness of immunotherapy [17,18]. Immune suppression and immune evasion is established by glioma cells via multiple mechanisms, such as the down-regulation of HLA class I molecules [19], up-regulation of inhibitory HLA molecules [20–22], and secretion of immunosuppressive factors [23,24]. Moreover, glioma cells directly and indirectly interact with myeloid and lymphoid immune cells. These interactions can result in the inhibition, apoptosis, and anergy of immune cells as well as in their skewing to immature, functionally compromised or immunosuppressive phenotypes [18]. Furthermore, tumour-associated immune cells can in turn promote tumour growth, angiogenesis and invasiveness, and further support immune suppression in the tumour microenvironment [25–27]. The contribution of myeloid cells to immune evasion and tumour progression is achieved by the production of matrix metalloproteases (MMPs), growth factors, cytokines and chemokines, reactive oxygen species and other mediators [28].

The diversity and complexity of CNS tumours has been described as unrivalled by tumours elsewhere in the human body [29]. Systematic histopathological analysis for over more than a century resulted in a World Health Organization (WHO) scheme of CNS tumours that now functions as the global gold standard for classification of these neoplasms [30]. CNS tumours are at the top of the list of 'average number of years of life lost' by cancer [31]. This can be explained by two important facts, i.e. 1) the most frequent primary brain tumour is glioma, and most gliomas show very extensive, diffuse infiltrative growth in the surrounding CNS parenchyma precluding curative therapy [32], and 2) CNS tumours are relatively frequent in children, and many of those are highly aggressive. Gliomas are considered to originate from glial cells or their precursors, and may show astrocytic, oligodendroglial, or ependymal differentiation or a combination thereof. In adult patients, most gliomas are astrocytic, oligodendroglial or mixed oligoastrocytic in nature. A malignancy grade can be assigned to these tumours based on histopathological parameters like marked mitotic activity, a peculiar form of angiogenesis such as 'florid' or even 'glomeruloid' microvascular proliferation, and/or necrosis. The least malignant diffuse glioma is designated as WHO grade II, the most malignant and most frequent astrocytic tumour is glioblastoma (WHO grade IV). The category of anaplastic/WHO grade III diffuse gliomas falls in between these grades. Both low (WHO grade II) and high grade (WHO grade III and IV) diffuse gliomas occur in all age groups, but young adults are more often diagnosed with a diffuse low grade glioma (which can however progress to a high grade glioma), while glioblastomas are relatively frequent in patients over fifty years of age.

Over the last decade insight into the molecular aberrations underlying CNS oncogenesis has increased in a revolutionary way. A combination of morphological and molecular characteristics may soon allow for a much more robust and clinically meaningful 'taxonomy' (typing and grading) of CNS tumours, especially of gliomas. In order to successfully survive and develop into a tumour, malignant cells generally need to sustain proliferative signalling, evade growth suppressors, resist cell death, enable replicative immortality, induce angiogenesis, and activate invasion and metastasis [33]. More recently, conceptual progress resulted in the addition of two hallmarks: evasion of immune destruction and reprogramming of energy metabolism. In addition, it was acknowledged that inflammation and genome instability in tumour cells are characteristics facilitating or even enabling these hallmarks [34].Using gene expression data from The Cancer Genome Atlas Project, glioblastomas can now be divided in four subclasses. These four subtypes, classical, neural, proneural and mesenchymal, can be separated according to different patterns of gene expression and aberrations of EGFR, NF1, PDGFRA, and IHD1 [35]. With the growing recognition that immune escape contributes to tumour growth, tumour immunologists have been taking inventory of the significance of immune infiltration for the prognosis of solid tumours. Most notably, Galon and colleagues have shown for Stage I-III colon cancer that memory CD8$^+$ T cell infiltration is more predictive for survival than classic AJCC staging [36,37]. This astonishing finding has led to a world-wide task force with the aim to validate these results in large patient cohorts and to promote the notion that T-cell infiltration rate (the so-called Immunoscore) should be incorporated into a new staging system for colon cancer and possibly also for other solid umours [38,39]. There are indications that also for glioma CD8$^+$ T-cell infiltration rate holds prognostic significance, even in the face of clear immunosuppression in the microenvironment [40].

In this review we will further focus on the infiltration of gliomas by myeloid cells, i.e. glioma-associated microglia and macrophages (GAMs) and myeloid-derived suppressor cells (MDSCs) (Fig. 1). GAMs are considered to represent the most prominent glioma-infiltrating immune cells, constituting up to 30% of all immune cells within the tumour microenvironment [41]. Their presence in the glioma