Published in final edited form as:
J Clin Neurosci. 2010 January ; 17(1): 6–10. doi:10.1016/j.jocn.2009.05.006.

The Role of Microglia in Central Nervous System Immunity and Glioma Immunology

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Abstract

The central nervous system (CNS) historically has been considered an immune-privileged organ, lacking a lymphatic system and shielded from the circulatory system by the blood-brain barrier. Microglia are an abundant portion of the CNS cell population, comprising 5% to 20% of the total glial cell population, and are as numerous as neurons. A crucial function of microglia is the ability to generate significant innate and adaptive immune responses. Microglia are involved in first line innate immunity of the CNS. Proper antigen presentation is critical in the generation of specific, durable responses by the adaptive immune system, and requires interaction between the T cell receptor and processed antigen peptide presented on major histocompatibility complex (MHC) molecules by the antigen presenting cells. Microglia also have a large regulatory role in CNS immunity. Histopathologic studies of glioma tissue have consistently shown high levels of infiltrating microglia. Microglia are also localized diffusely throughout the tumor, rather than to the areas of necrosis, and phagocytosis of glioma cells or debris by microglia is not observed. Recent evidence indicates that glioma-infiltrating microglia/macrophages might be promoting tumor growth by facilitating immunosuppression of the tumor microenvironment. When activated, microglia can be potent immune effector cells, able to perform a broad range of functions, and they mediate both innate and adaptive responses during CNS injury and disease while remaining quiescent in the steady state. Their versatility in bridging the gap between the immune-privileged CNS and the peripheral immune system, in addition to their significant numbers in gliomas, makes them an attractive candidate in immunotherapy for gliomas. An enhanced understanding of microglia–glioma interaction can provide better methods to manipulate the glioma microenvironment to allow the generation of a specific and durable anti-glioma immunity. The role of microglia in CNS immunity is discussed, with a focus on key advances made in glioma immunology.

Keywords

Antigen presenting cells; Gliomas; Immunology; Immunotherapy; Innate immunity; Microglia; Specific immunity

1. Introduction

The central nervous system (CNS) historically has been considered an immune-privileged organ, lacking a lymphatic system and shielded from the circulatory system by the blood-

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brain barrier. Thus, the CNS is isolated from entry of most peripheral immune cells, soluble factors and plasma proteins. However, the infiltration of T lymphocytes and antigen presenting cells (APC) during a variety of CNS pathologies, such as multiple sclerosis and glioma [1, 2], is evidence for an adapted system of immunosurveillance with coordination with the systemic immune system. As resident APCs and macrophages, microglia are in the key position for coordinating this system of active surveillance.

Through intimate relationships with the surrounding microenvironment, microglia maintain a quiescent phenotype in the normal CNS, expressing low levels of major histocompatibility complex (MHC) class I and class II molecules as well as costimulatory molecules such as CD86 and CD40 [3–7]. In the context of CNS insult or injury, microglia convert to an active phenotype, with increased proliferation [8], motility [9], and phagocytic activity [10, 11], and release cytokines and reactive oxygen species [12]. As activated APCs, microglia have similar roles to macrophages in peripheral tissues, serving as essential components of both the innate and adaptive immune responses. Upon activation, microglia upregulate both MHC and costimulatory molecules, and contribute to both CD4-specific and CD8-specific T cell responses [13–15]. Microglia, in addition to lymphocytes, have also been found in CNS disease processes, including tumors of the CNS [16]. In this review, we focus on the recent and key advances in understanding the role of microglia in CNS immunity and glioma immunology.

2. Origin of Microglia

Microglia are an abundant portion of the CNS cell population, comprising 5% to 20% of the total glial cell population, and are as numerous as neurons [17–19]. Nissl first described microglia, naming them “Staebchenzellen” or rod cells based on the shape of nuclei. He considered microglia as reactive neuroglia, hinting at their capacity for migration and phagocytosis. They were subsequently characterized by Santiago Ramon y Cajal in 1913 as part of three elements of the CNS and by del Rio Hortega, who recognized microglia as a cell type distinct from other glial cell populations. By studying the results of stab wounds made in animal brains, Hortega observed and accurately described that microglia cells can transform from a resting ramified form into amoeboid phagocytic macrophages [20]. From these findings, he proposed that microglia originated from peripheral mononuclear cells [20].

After a long debate over the role and origin of microglia, they have been established as a developmentally and functionally distinct population of glial cells that are of myelomonocytic origin [21]. Circulating microglia precursors derived from mesodermal hematopoietic cells enter the developing brain during perinatal stages and transform into microglia cells. Mature microglia express a variety of macrophage-specific markers including Toll-like receptors (TLR) [22, 23], the integrin CD11b [24], and the glycoprotein of unknown function, F4/80. However, they have lower levels of leukocyte common antigen, CD45, when compared to macrophages [25, 26]. Thus, microglia are closely related to peripheral monocytes in regard to their origins, phagocytic activity, and surface markers.

Microglia are classified according their morphology into three types: resting ramified, activated, and amoeboid phagocytic [21]. In the perinatal brain, the amoeboid phagocytic microglia are the predominant form [27]. During postnatal maturation, amoeboid microglia transform into ramified resting microglia, and these cells remain a semi-permanent population with relatively slow turnover rates when compared to peripheral macrophages [27, 28]. As resting ramified microglia, they monitor their microenvironment and adapt their morphology and expressed cell surface markers accordingly [18, 19]. They remain quiescent

until stimuli from injury, infection or neurodegenerative process activate their transformation into amoeboid phagocytic cells [10, 11].

3. Active Surveillance of the Central Nervous System

As routine surveillance of the CNS, microglia, even in their quiescent form, continually monitor their microenvironment through pinocytosis and interaction with neurons [29]. A complex set of interactions exist between local stimulatory and inhibitory signals in shaping microglial responses: while some neurotransmitters like substance P enhance the active phenotype of microglia [30], electrically active neurons inhibit the increase in expression of MHC class II molecules on microglia in response to Th1 cytokine interferon-gamma (IFN-γ) [31]. In addition, Hoek and colleagues have implicated a membrane-bound glycoprotein, OX2 or CD200, expressed on neurons as a key regulator of microglia [32, 33]. The authors showed that microglia in OX2-deficient mice exhibit a constitutively active phenotype with increased subset with amoeboid phagocytic morphology, and elevated levels of expression of CD45 and complement type-3 receptor (CR3) [32]. OX2-deficient mice also show an accelerated reactive response to CNS injury.

Moreover, soluble factors in the microenvironment influence the functional and morphological plasticity and activity of microglia as well. Granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage-CSF (M-CSF) have crucial roles in the terminal differentiation of tissue macrophages. In Alzheimer's disease and multiple sclerosis, levels of GM-CSF are elevated in addition to upregulation in M-CSF receptors [34]. Fischer and Reichmann have demonstrated that *in vitro* incubation of purified microglia with GM-CSF increases microglia cell size and induces a heterogeneous population that contains cells resembling other tissue macrophages [35]. These populations of microglial cells take on APC activity by expression of MHC class II molecules [25].

These findings in combination provide strong support for microenvironmental regulation of microglia function, through soluble factors, such as GM-CSF and M-CSF, and cell–cell interactions, particularly with neurons, which have key roles in delivery of regulatory signals, in part through the glycoprotein OX-2.

4. Microglia as Mediators of Inflammation

A crucial functional similarity of microglia to peripheral macrophages is the ability to generate significant innate and adaptive immune responses. The resting ramified microglia cells are activated by a variety of CNS pathologies, such as infection, injury, and neurodegenerative disease, by detecting lipopolysaccharide (LPS), beta-amyloid (Aβ), thrombin, IFN-γ, and other proinflammatory cytokines [36]. For example, microglia express TLR [22] and initiate innate responses with the production of cytokines, chemokines and nitric oxide (NO) [37, 38]. Specifically, cytokines released by activated microglia include interleukin (IL)-1 [39], IL-6 [40] and tumor necrosis factor-alpha (TNF-α) [41], as well as monocyte chemoattractant protein-1 (MCP-1) [42], macrophage inflammatory protein-1 [43, 44] and RANTES [45], and chemokines for lymphocyte recruitment. These results show that microglia are involved in first line innate immunity of the CNS. Once the microenvironment of the CNS becomes activated, local cells also produce proinflammatory cytokines, chemokines and upregulate immunomodulatory surface markers. These changes in turn decrease the stringency of the blood-brain barrier, allowing entry of soluble factors and peripheral immune cells [46], including macrophages, natural killer cells and lymphocytes [47, 48]. The specific sequence of events demonstrating that microglia activation precedes peripheral cell infiltration has been demonstrated in bone marrow chimeric mice in an elegant study by Schilling and colleagues [49].

Phagocytic and cytotoxic functions of microglia are also triggered during CNS injury. Upon activation, microglia upregulate opsonic receptors including complement receptors (CR1, CR3, CR4) and Fc gamma receptors (I, II, III), which enhance phagocytic activity by binding to complement components and immunoglobulin fragments respectively [50, 51]. Microglia also show transitory phagocytosis during CNS ontogeny to clear apoptotic neuronal cell bodies [52]. A similar phenomenon is seen in animal models of multiple sclerosis – T cell debris undergoes phagocytosis by microglia [53]. Contents that undergo phagocytosis by microglia are degraded by the immediate induction to produce reactive radicals. In addition, the cytotoxic functions of microglia are carried out by release of superoxide radicals and NO into the microenvironment in response to pathogens and cytokine stimulation [54].

Proper antigen presentation is critical in the generation-specific durable responses by the adaptive immune system, and requires interaction between the T cell receptor and processed antigen peptide presented on MHC molecules by the APCs. The presentation is augmented by interaction between costimulatory molecules such as B7.1, CD40, CD80, and CD86 expressed on the surface of APC and specific counter-receptors on T cells [55, 56]. Within the CNS under resting states, MHC class I and II expression is generally absent or minimally present [3, 57]. MHC molecules are generally restricted to microglia in low levels [6, 57, 58]. Resting microglia serve as poor APC [59]; however, activating stimuli induce microglia to robustly increase their expression of MHC [60] and costimulatory molecules [61]. Costimulatory molecules CD80 and CD86 on microglia in turn bind to CD28 expressed on T cells to induce cytokine secretion and proliferation by T cells [55]. CD40L on T cells in turn interact with CD40 of microglia and increase the expression of CD80 and CD86 MHC class II molecules [56]. The CD40–CD40L interaction also induces microglia to increase the release of nitric synthase [56]. Additionally, *in vivo* and *in vitro* studies have demonstrated that IFN-γ induces and maintains expression of MHC class II and adhesion/costimulatory molecules on microglia to maintain T cell stimulation [62]. This cooperative enhancement of costimulation between microglia and T cells has been demonstrated in animal models of multiple sclerosis [34].

Microglia also have a large regulatory role in CNS immunity. In the absence of sufficient costimulatory molecules, the interaction of Fas ligand (FASL) on microglia and Fas receptor on the T cell leads to activation-induced T cell apoptosis [63]. The FASL expression on microglia has been described *in vitro* [64, 65] and in mouse models of multiple sclerosis [66]. Microglia in turn also express FAS molecules which, upon binding FASL, leads to their own apoptosis [66]. In addition, cytotoxic molecules like NO produced by microglia can also contribute to the death of immune effector responses. Hence, microglia activation can be self-limiting and microglia have regulatory functions in silencing other immune effector cells.

5. Microglia in Glioma Immunology

In 1925, Wilder Penfield, employing the same silver staining method used by Rio-Hortega, provided the first detailed descriptions of microglia in glioma tissue [20]. Subsequently, gliomas have been shown to accumulate many microglia along with a small population of lymphocytes [16]. Initially, the observation that malignant gliomas contain particularly high levels of microglia infiltrates led to the hypothesis that microglia may contain anti-tumor activity and have a role in tumor necrosis. However, recent evidence strongly supports that microglia contribute to the immunosuppressive environment of gliomas and may promote tumor proliferation and progression [16, 67–70].

5.1. Microglia chemoattraction and proliferation

Histopathologic studies of glioma tissue have consistently shown high levels of infiltrating microglia [2, 71–74]. Flow cytometry studies by Badie and colleagues demonstrated that as many as one-third of cells of glioma tissues express resident microglia markers, consisting of the largest population of immune cells [2]. Current evidence supports that the accumulation of microglia in glioma is due to local production chemoattractants and growth factors by glioma cells. MCP-1 is produced by glioma cells, and microglia express a specific MCP-1 receptor, CCR2 [75, 76]. Furthermore, growth factors known to induce macrophage/microglia proliferation, such as CSF-1, G-CSF and hepatocyte growth factor/scatter factor (HGF/SF) are also secreted by various gliomas [77–79].

5.2. Microglia and glioma progression

Historically, the recruitment of microglia in gliomas was postulated as evidence of the attempt by CNS to fend off dividing neoplastic cells [80]. However, the paradox of continuing aggressive tumor growth despite high levels of microglia infiltrates offered little support for anti-glioma activity of these microglia. Microglia are also localized diffusely throughout the tumor, and not to the areas of necrosis, and phagocytosis of glioma cells or debris by microglia is not observed [1]. Recent evidence indicates that glioma-infiltrating microglia/macrophages might be promoting tumor growth by facilitating immunosuppression of the tumor microenvironment [16].

Microglia are a cellular source of matrix metalloproteases-2, extracellular matrix-degrading enzymes. Their release into the tumor environment can help increase the spread of tumors by paving the road for proliferation of tumor cells [81]. Microglia also secrete tumor proliferation promoting factors including epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) [82, 83]. These studies in combination suggest that microglia have an integrative role in the tumor progression by supporting migration (MMP-9), angiogenesis (VEGF), and proliferation (EGF) of glioma cells.

5.3. Inhibited microglia function in glioma

Co-culture of human peripheral blood mononuclear cells with human glioma lines caused glioma-conditioned monocytes to reduce phagocytic activity [84]. The glioma–monocyte co-culture, but not monocyte in isolation, also induced apoptosis of activated lymphocytes [84]. Although MHC molecule expression is seen on microglia within glioma tissues [85, 86], they appear deficient in proper antigen presentation [87] for cytotoxic and helper T cell activation. The number of microglia cells expressing MHC class II antigen is reduced even further in high grade gliomas despite the high abundance of microglia present. Schartner and colleagues demonstrated that glioma infiltrating microglia isolated from mice do not show MHC class II upregulation following stimulation [67]. In contrast, the expressions of MHC class II and costimulatory B7 molecules were significantly increased when freshly isolated microglia were cultured in the absence of glioma cells [88].

Kostianovsky and colleagues demonstrated *in vitro* that glioblastoma cells down regulated the production of the proinflammatory cytokine TNF-α by microglia when stimulated with LPS or β-amyloid [70]. Instead, the stimulation resulted in the secretion of IL-10 an anti-inflammatory cytokine by the microglia [70]. IL-10 in turn inhibits cytotoxic T cell function, further contributing to the immunoresistant phenotype of glioma cells [89]. IL-10 also suppresses function of microglia: *in vitro* studies demonstrated that IL-10 suppresses IFN-γ induced MHC class II expression [90]. These studies together suggest that phagocytosis, antigen presentation, and secretion of proinflammatory cytokines are strongly suppressed by glioma cells.

5.4. Microglia and local immune suppression by glioma

Glioma cells produce anti-inflammatory cytokines such as IL-6 and TGF-β2 and PGE2 along with producing tumor growth promoting cytokines such as IL-1 and bFGF [1, 91]. In particular, TGF-β2 inhibits proliferation and secretion of proinflammatory cytokines by microglia and lymphocytes [92]. In normal brain, microglia express B7-H1, a potent immunosuppressive molecule that induces T cell apoptosis [93, 94]. In addition to increased expression of B7-H1 in a subset of gliomas with immunoresistant phenotypes, the expression of B7-H1 is upregulated in microglia found in glioma [93–95]. FASL is another inhibitory molecule expressed on tumor-associated microglia that might be crucial in limiting the ability of T cells to recognize and respond to tumor cells. FASL also induces T cell apoptosis, particularly of CD8+ cytotoxic T cells. Microglia in intracranial tumors express FASL and inhibition of FASL leads to a dramatic increase in the number of peripheral immune effector cells seen within tumors [69, 96].

5.5. Therapeutic potential of microglia in glioma

When activated, microglia are potent immune effector cells, able to perform a broad range of functions, and they mediate both innate and adaptive responses during CNS injury and disease while remaining quiescent in the steady state. Their versatility in bridging the gap between the immune-privileged CNS and the peripheral immune system in addition to their significant numbers in gliomas makes them an attractive candidate in immunotherapy for gliomas. Unfortunately, microglia associated with malignant gliomas appear incapable of inducing an effective anti-tumor T cell response. If glioma-induced immunosuppression of microglia function could be overcome, CNS immunity against tumors can be significantly enhanced. For example, Carpentier and colleagues demonstrated long-term survival in animals with glioma using single intratumoral injection of CpG oligodeoxynucleotide, an immuno-stimulatory sequence that signals through TLR9 to induce the production of IFN-α, IFN-β, IL-12, and TNF-α [97, 98]. However, animals depleted of macrophage/microglia were unable to reject the tumor after CpG treatment, showing that microglia/macrophages are critical components of an anti-tumor response [99]. Although CpG is relatively safe in humans, an enhanced understanding of the microglia–glioma interaction can provide better methods to manipulate the glioma microenvironment to allow the generation of a specific and durable anti-glioma immunity.

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