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Microglia—friend or foe

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1. ABSTRACT

Microglia, as the immune effectors in the central nervous system, respond to pathological conditions and participate in the initiation and progression of neurological disorders such as inflammation and brain tumor by releasing potential neurotrophic or cytotoxic molecules, presenting the antigen to T cell and interacting with brain tumor. Evidences also suggest that microglia are capable of promoting or inhibiting the proliferation and differentiation of neural stem cells by secreting series of biologically active molecules. In this review, we focus on three aspects—inflammation, neurogensis and brain tumor to illustrate the multi-faceted activities of microglia in the normal and pathologic brain.

2. INTRODUCTION

In recent years, the glial cells, especial microglial functional phenotype causes great interest. Microglia comprise 10-20% of all glial cells in the central nervous system (CNS) and make up the main cellular component of CNS (1). Although the origin of microglia has been debated for many years, current data indicate that they are of mesenchymal origin and invade the brain during development. So, microglia have the functions similar to those of other tissue macrophages, including phagocytosis, production of a plethora of bioactive molecules and antigen presentation (2).

In the physiological conditions, microglia display a “quiescent” phenotype, also called “surveying” state. On

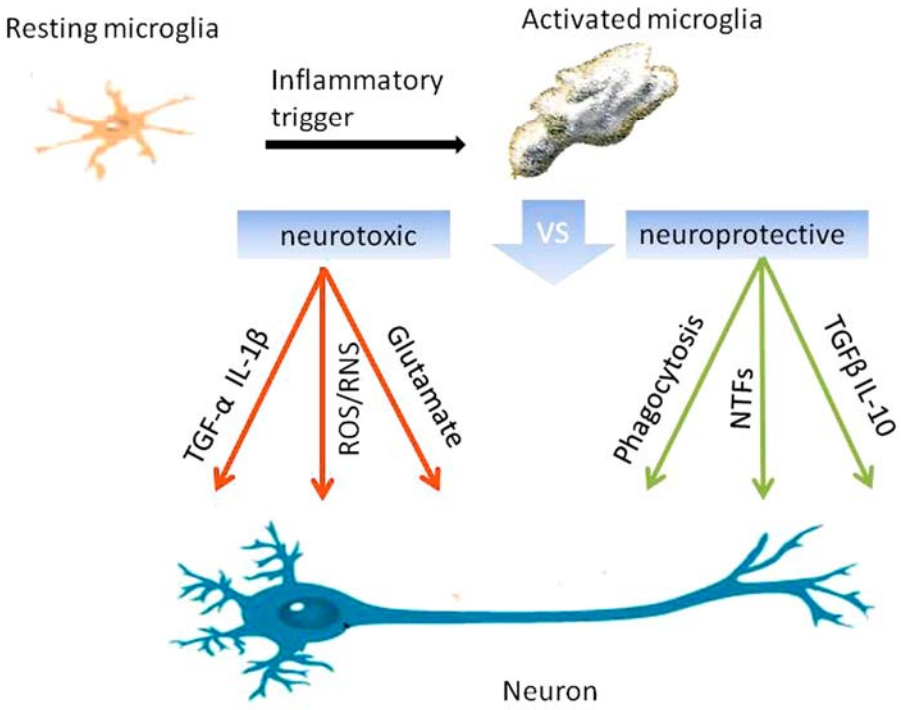

Figure 1. Microglia play important roles in the neuroinflammation. On one hand, microglia are neuroprotective by secreting neurotrophic and anti-inflammatory molecules and the clearance of toxic products or invading pathogens; On the other hand, overactivated microglia can be neurotoxic by releasing pro-inflammatory factors, and several cytotoxic substances including reactive oxygen and nitrogen species and glutamate .

insult to brain, microglia become markedly activated and produce a great deal of molecules. It was reported that activated microglia can release series of inflammatory chemical substances such as interleukin-1(IL-1), interleukin-6(IL-6), tumor necrosis factor-α□(TNF-α), and Nitric-Oxide Synthase (NOS) (3), which enhance the inflammatory response in and around the injuried sites, promote the neuronal death and inhibit the neuronal maturation and differentiation. Besides, activated microglia produce many kinds of neurotrophic factors, growth factors and anti-inflammatory factors such as brain-derived neurotrophic factor(BDNF), glial cell-derived neurotrophic factor (GDNF), and transforming growth factor-β(TGF-β)(4-5). And the factors can downregulate the inflammatory response, protect the neuron from injury and promote the neurogenesis. In addition, microglia also can modulate the migration, survival, and proliferation of brain tumor cells via different mechanisms by secreting lots of relative molecules (6). The findings above suggest that the activated microglia may function as a double edged sword in the CNS. In this review, we focus on the dual action of microglia in CNS inflammation, neurogenesis and brain tumor in the intact and injured brain.

3. MULTI-FACETED FUNCTIONS OF ACTIVATED MICROGLIA IN CNS INFLAMMATION, NEUROGENESIS AND BRAIN TUMOR

3.1 Microglia in neuroinflammation

Any injury or insult to the brain including ischemia, stroke, trauma and neurodegenetive diseases will elicit an obviuos neuroinflammatory response in the CNS, and the neuroinflammatory diseases are calling for more attentions beause of the high morbidity nowsdays. With an enhanced understanding about the pathological process, it was reported that microglia, as the resident immune cells in the CNS, play a critical role in the inflammation of CNS. Their engagement can become either neuroprotective or neurotoxic, leading to amelioration or aggravation of disease progression. For one thing, activation enables microglia to maintain and support neuronal survival (7-8) by releasing neurotrophic factors, anti-inflammatory molecules and clearing toxic products or invading pathogens. For another, overactivated microglia can be neurotoxic by releasing pro-inflammatory factors(9), cytotoxic substances such as reactive oxygen and nitrogen species (10) and glutamate(Figure 1).

3.1.1 .Neuroprotective microglia

Activated microglia can involve in neuron protection by blocking proinflammatory response and producing high levels of neurotrophic factors (NTFs) and anti-inflammatory cytokines together with enhanced phagocytic activity.

3.1.1.1. Neurotrophic factors

Microglia can produce NTFs to support neuronal survival and growth (11-12) . NTFs, such as nerve growth factor (NGF), BDNF, GDNF and insulin-like growth factor-1(IGF-1), play important roles in functional

maintenance, axons growth, synaptic transmission and plasticity (13) and neuronal survival (14) in the pathological state. Besides their classical effects, NTFs can also inhibit the inflammation (15-16). Based on their effects, NTFs are protective in neuroinflammatory diseases. For example, NGF can attenuate deterioration of AD by reducing oxidant-induced beta-amyloid neurotoxicity in sporadic Alzheimer's disease cybrids (17) and inhibiting the amyloidogenic processing of amyloid precursor protein (APP), which is among the first hypothesized primary trigger of AD pathogenesis.(18). BDNF has been demonstrated to be positive in AD (19), stoke(20) and others. GDNF is also beneficial for the survival of dopaminergic neurons (21). Additionally, IGF-I can promote neuronal survival by blocking apoptosis, even play an essential role in Purkinje neuron survival at birth (22). What's more, IGF-1 protect the developing oligodendrocytes from glutamate toxicity In vitro (23) and IGF-1 treatment attenuated the damage to oligodendrocyte progenitors in hypoxic-ischemic injury in neonatal rats (24).

3.1.1.2. Anti-inflammatory factor

Activated microglia can protect neurons by producing antiinflammatory cytokines . Here, interleukin-10(IL-10) and TGFβ1 will be discussed. Microglia can both produce and respond to IL-10(25) . Studies show that IL-10 plays an essential role in mediating the inflammatory processes and cell survival in brain by inhibiting the production of proinflammatory cytokines (26). In addition, it was reported that in many models of CNS injury, administration of IL-10 can also suppress the morphological alterations associated with glial activation (26-27), enzymes involved in the generation of inflammatory mediators and oxygen-free radicals (28-29), leukocyte infiltration (30) and the production of A chemokines (31). Further more, IL-10 can directly increase the survival of neurons (32 33), astrocytes (34), oligodendrocytes (28) and microglia (35). TGF-β1, which is highly expressed in several models of CNS pathology, has multiple roles including modulating inflammation and neuronal survival□36-37). It has been shown that TGF-β1 knockout mice develop spontaneous neurodegeneration□38-39). TGF-β1 can directly downregulate the expression of other proinflammatory cytokines and is involved in the resolution of inflammation (40) in diseases such as periventricular white matter damage(41-42). In the AD model, neuroprotective effects of TGF-β1 may contribute to both directly promoting the neuronal survival and enhancing the Aβ uptaking (43). TGFβ1 can elicits the expression of Fas-associated death domainlike interleukin 1β-converting enzyme(FLICE)-inhibitor protein in microglia through a MAPK kinase-dependent pathway and inhibits Fas-mediated apoptosis of microglia (44).

3.1.1.3. Microglial motility and phagocytosis

In the neuroinflammatory diseases, microglia are obviously activated, rapidly extend their processes and migrate to the lesion sites or toward damaged neurons to act more locally in the killing of microbes or clearing the debris (45). Chemokine receptors and Integrin-associated receptor complexes play important roles in the process. Chemokine receptors are the major class of receptors for triggering directed migration of microglia, including CXCR3(46), CX3CR1(47), CCR2 and others. Integrin-associated receptor complexes, containing the macrophage antigen complex-1 (Mac-1), receptor CD11a/CD18, leukocyte common antigen 1 (LFA-1)(48) and all β2-integrin receptor complexes and others also function importantly in guiding the migration of microglia to the destination. Microglial phagocytosis could be divided into two distinct responses: a pro-inflammatory cascade which is induced by phagocytosis of pathogens and stimulation of toll-like receptors (TLRs); anti-inflammatory response which is induced by clearance of apoptotic cell membranes and recognition of phosphatidylserine (PtdSer) residues(49). Microglia express distinct types of receptors such as scavenger receptors and complement binding receptors, which take part in the phagocytosis of apoptotic neurons, uptaking of denatured or modified proteins and lipoproteins (50) or the clearance of neuronal structures predetermined to die.

The protective role of phagocytosis are proved in many inflammatory diseases. In AD, microglia play critical roles in the uptake and proteolytic clearance of both soluble and fibrillary forms of amyloid-beta protein (51). In ischemia/reperfusion (I/R) models, microglia may appear at the time of apoptotic neuronal death, and participate in phagocytic action in the CA1 region(52).

3.1.2. Neurotoxic microglia

Besides the protective effects, microglia have been shown to attack damaged neurons by secreting a variety of neurotoxic factors including inflammatory cytokines, reactive oxygen species, NO and glutamate, thus complicate the pathogenesis of neuroinflammatory diseases.

3.1.2.1. Pro-inflammatory cytokines

Over or prolonged production of cytokines by microglia may lead to more neurotoxicity. During a disruption of CNS homeostasis, microglia can produce as well as respond to a multitude of inflammatory cytokines such as TNF-a, IL-1, IL-6, IL-2 and interferon-γ (IFN-γ) (53).

The knockout mice showed significant reductions in the number of dying hippocampal neurons after ischemia because of lacking TNF-a and IL-1 (54). TNF-α is complicated in the pathogenesis of CNS inflammatory diseases. Although TNF-α at lower levels is associated with a neuroprotective effect, this cytokine appears to induce neurodegeneration at high level. The actions of TNF-a are mediated through two membrane receptors, TNF-receptor-1 (TNF-R1) and TNF-R2(55). The activation of TNF-R1 leads to cell apoptosis (56) whereas TNF-R2 promotes cell growth and proliferation (57). Aberrant TNF-a/TNF-R1 signaling can have a potentially major role in the CNS pathologies such as in hypoxic rats and the pathology can cause oligodendrocyte death and demyelination(58). IL-1 appears to be involved in the processes of leading to neuronal death, and inhibition of

this cytokine block the effects (59). The actions of IL-1β (the major soluble form of IL-1) are accomplished via the type I receptor (60). A significant increase in IL-1β production by microglial cells and expression of IL-1R1 on oligodendrocytes in PWM of neonatal brain was observed following hypoxic injury (61). IL-1β can delay the white matter development and recovery in hypoxic conditions via block oligodendrocyte proliferation at the late progenitor/pro-oligodendrocyte stage (52,62) and involved in transcriptional activation of iNOS gene and NO generation (55).

3.1.2.2. Reactive oxygen and nitrogen species

Reactive oxygen and nitrogen species are significant factors in microglial-driven inflammation□63). Excess production of ROS and reactive nitrogen species (RNS) has been described to damage immature oligodendrocytes (64). Of these reactive oxygen and nitrogen species, nitric oxide (NO) is most studied . NO is synthesized by the enzyme nitric oxide synthase (NOS) from Larginine (52). Three isoforms of NOS are known to exist: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). In the damaged brain iNOS is induced mainly in microglia and astrocytes by pathogens, damage or hypoxia (65-67). Although low concentrations inhibit apoptosis, excessive production of NO can lead to neuronal damage and toxicity to the immature oligodendrocytes resulting in their death and delayed myelination in hypoxic injury (67). High levels of NO induce RONS, which cause oxidative/nitrosative stress to cells, in turn activating the mitochondrial pathway of apoptosis.

3.1.2.3. Glutamate

Glutamate, a major excitatory transmitter in the CNS, can turn excitotoxicity under various neurological disorders, including inflammation, ischemia and neurodegenerative diseases (68-69). Previous studies have demonstrated that activated microglia release a large amount of glutamate leading to neuronal damage (70-72), and then the released glutamate activates microglia in an autocrine/paracrine manner(11). In fact, activated microglia act as an executioner to determine neuronal and glial survival. Glutamate not only can directly induce neuronal death through NMDA receptor signaling(72), but also can affect the neuronal apoptosis directly by altering the release of proinflammatory cytokines, neurotrophic factors and growth factors such as TNF-a, IL-1β and IGF-1 produced by microglia under hypoxic conditions (24).

Efficient reuptake of released glutamate is essential for preventing glutamate receptor overstimulation and neuronal and glial death. High-affinity Na+-dependent glutamate transporters, also called excitatory amino acid transporters (EAATs), are responsible for this(73-74). Five different types of glutamate transporters are distributed in neuron and glia in the mature CNS (74-75). Although microglia may serve as a back-up system by expressing glutamate receptors and transporters, they did not prevent excito-neurotoxicity with the uptake of extracellular glutamate via EAATs as astrocytes did (72). In vitro studies have also shown that activated microglia block glutamate transporters in oligodendrocytes, resulting in extracellular glutamate accumulation and the subsequent oligodendrocyte death. And AMPA/kainate mechanism may contribute to altering glutamate homeostasis during the process (76). However, whether activated microglia also downregulate or dysregulate astrocytic EAATs, then contribute to neurodegeneration in neurological diseases need to be elucidated .

3.2. Microglia in neurogenesis

Although it is well known that neural stem cells (NSCs) in adult mammal brain (77-78) can continuously produce new neurons throughout life to replace dying neurons and contribute to specific functions, the exact regulatory mechanisms are largely unknown. In addition to intrinsic properties, NSCs proliferation and differentiation are regulated by the characteristics of the microenvironment or niche in which they reside (79-80). Recently, microglia, as well as astrocytes have been regarded as the component of the CNS microenvironment and play important roles in the neurogenesis (81-82).

It was reported that in normal conditions, microglia display a quiescent phenotype and secret several neurotrophic factors, as well as some cytokines and chemokines (8), which are involved in modulating the cell behavior of NSCs (83). Under pathological circumstance, microglia, as one of the first cell types in brain to respond to injury or insult, become significantly activated and express series of bioactive factors such as proinflammatory cytokines, free radicals, chemokines, and neurotrophic factors (84-85). Generous evidence demonstrate that it was the soluble bioactive molecules produced by activated microglia that participated in modulating the behaviors of NSCs (86-87). Although initial studies show that microglia activation can be detrimental for adult neurogenesis, recent findings indicate that microglia under certain circumstances can be beneficial and support the neurogenesis. Here we summarize the current knowledge about microglia in the neurogenesis by discussing the dual action of molecules secreted from microglia (Figure 2).

3.2.1. Proinflammatory cytokines and their dual role in neurogenesis

It is well known that any injury or insult, ranging from hypoxia, ischemia, infection to neurodegenetive disease, would elicit a characteristic neuroinflammatory reaction in the CNS. Microglia, as the key player mediating this response, secret a series of pro- and anti-inflammatory molecules. Among the various molecules, we mainly discussed the following proinflammatory cytokines.

3.2.1.1. IL-6 and its dual role in neurogenesis

IL-6, as a pleiotropic inflammatory cytokine, is overexpressed by activated microglia once insult. An in vitro study showed that the neuronal differentiation of hippocampal neural progenitor cells (NPCs) expressing the IL-6 receptor significantly decreased by approximately 50% when exposed to recombinant IL-6 cytokine, while the gliogenesis (astrocytic and oligodendrocytic differentiation) was unaffected. Addition of neutralizing anti-IL-6 antibody to microglial conditioned medium fully restored the in vitro neurogenesis (86). This implies that IL-6 serves as a key

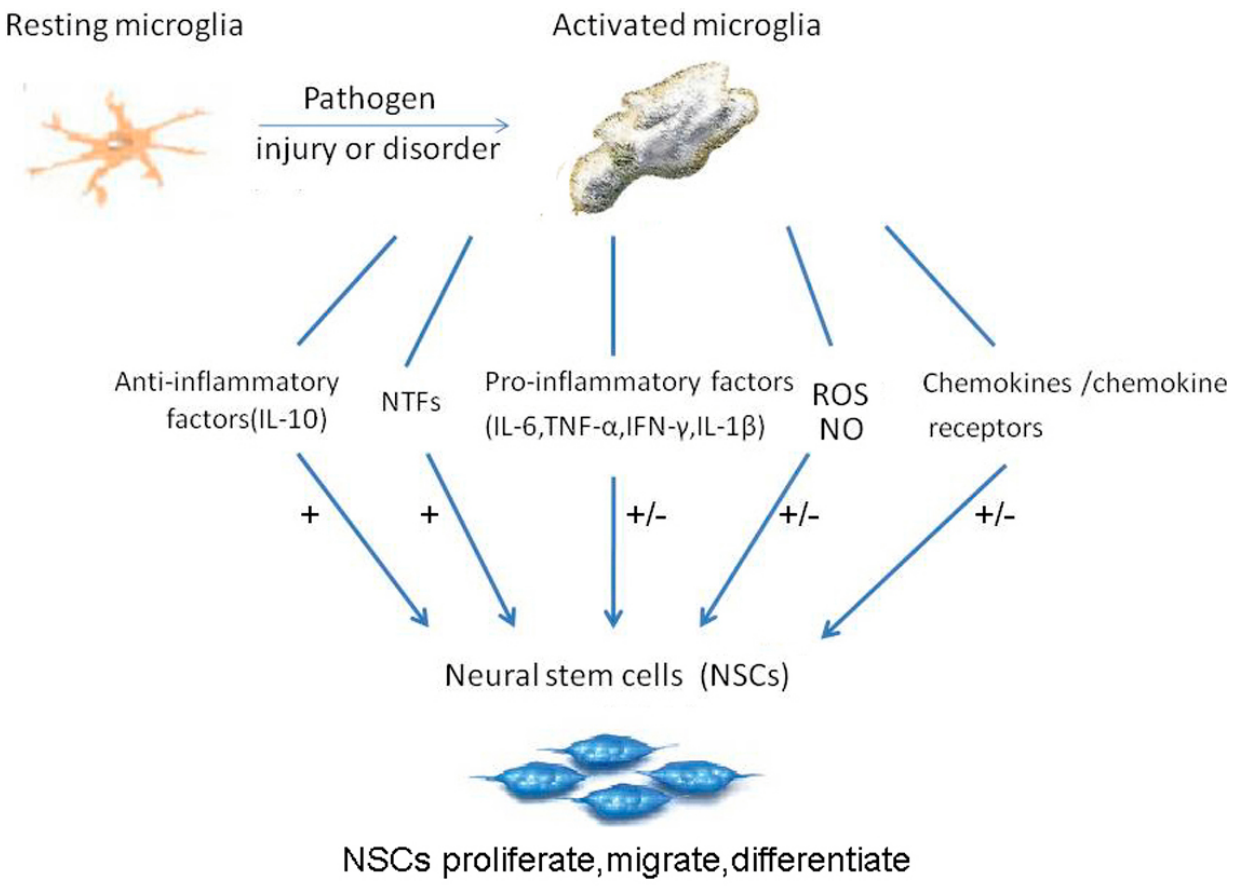

Figure 2. Microglia affect the neurogenesis by secreting bioactive molecules. Microglia, as one of the first cell types in brain to respond to injury or insult, become significantly activated and express series of bioactive factors such as proinflammatory and antiinflammatory cytokines, free radicals, chemokines, and neurotrophic factors. Studies show that microglial activation plays a dual role in the neurogenesis and microglia can be either beneficial or detrimental for the neurogenesis under certain circumstance.

inhibitor of neurogenesis (88). However, several studies showed that IL-6 released by activated microglia promote astrocytic differentiation of NSPCs via the activation of the Janus kinase / signal transducer and activation of transcription (JAK / STAT) and mitogen-activated protein kinase (MAPK) pathways (89-90). Besides, IL-6 induces the proliferation of adult spinal cord-derived neural progenitors *via* the JAK2/STAT3 pathway with EGF-induced MAPK phosphorylation (91). The data above suggest that the IL-6 plays important and complex roles in modulating the cell behaviors of NSCs via different signaling pathways.

3.2.1.2. TNF-a and its dual role in neurogenesis

TNF-a, another common proinflammatory cytokine, is up-regulated by microglia in most injuried responses and neurodegenerative diseases, and functions by interacting with its receptors, TNF-R1 or TNF-R2. It was reported that TNF-α causes the death of hippocampal NPCs in vitro and markedly reduces their proliferation in a dose-dependent manner (92). In addition, recombinant TNF-α (20ng/ml) was reported to suppress the neurogenesis of NPCs by about 50% (86). Other studies also showed the detrimental effects of TNF-α from LPS-activated microglia on the neurogenesis and cell survival (93). In contrast, several studies showed that TNF-α increased the proliferation of neurospheres from SVZ via IKK/NF-κB signaling, and in vivo findings also illustrated its mitogenic role (94-95). TNF-α also enhances stroke-induced neurogenesis, indicating a possible neuroprotective role (96). Furthermore, Iosif reported that the cell proliferation and generation of new hippocampal neurons significantly increased in both normal and status epilepticus brain of TNF-R1(-/-) and TNF-R1/R2(-/-) mice. However, these was no significant alteration in TNF-R2(-/-) mice under both normal and pathological conditions (97). This implies that TNF-α plays conflicting roles in regulating the differentiation of NSCs acting via different TNF-α receptors.

3.2.1.3. IL-1β and its dual role in neurogenesis

IL-1β, another potent proinflammatory cytokine secreted by activated microglia, its function on neurogenesis was also extensively investigated. Koo found that administration of IL-1β or activation of IL-1

receptor(IL-1R) suppressed hippocampal cell proliferation via the NF-κB signaling pathway. And specific IL-1RI inhibitor or IL-1RI null mice demonstrated the antineurogenic effect (98), which is consistent with the findings that intrahippocampal transplantation of transgenic NPCs overexpressing IL-1R antagonist blocks chronic isolation-induced impairment in neurogenesis (99). However, several studies showed that exposure of NSCs to recombinant IL-1β or neutralization of IL-1β in the conditioned medium from LPS-activated microglia does not exert significant effects on hippocampal neurogenesis (86,93). In addition, it was reported that addition of IL-1β or blocking IL-1R inhibited the astrocytic differentiation, and the effect of IL-1β on NPCs proliferation and differentiation appeared to be mediated by SAPK/JNK, but not ERK, P38MAPK nor NF-κB pathways (100). Taken together, the complex of IL-1β in function and mechanism need to be further explored.

3.2.1.4 IFN-γ and its dual role in neurogenesis

Previous studies showed that IFN-γ inhibited cell proliferation of newborn rat striatal NPCs sphere, increased cell apoptosis and promoted outward migration of cells from spheres without influencing the differentiation of NPCs in vitro (101). This indicates the detrimental effect of IFN-γ on NSPC survival and proliferation (102). In addition, Monje showed that recombinant IFN-γ cytokine did not dramatically affect the neurogenesis (86). However, recent studies have demonstrated that microglia treated with low levels of IFN-γ promote the neurogenesis (103), and IFN-γ can directly increases the neurogenesis of NSCs (104-105). Johansson further demonstrated that IFN-γ increased the neuronal yield threefold in striatal NSPC cultures and enhanced the number of oligodendrocytes twofold in hippocampal NSPC cultures (106). Moreover, several studies showed that the effects of IFN-γ promoting the neuronal differentiation of NSCs is mediated by the JNK pathway without affecting activities of ERKs 1 and 2 (107). And the proliferation and differentiation of NSC in adult dentate gyrus was markedly increased in IFN-γ transgenic mice (108). It was supposed that the neurotoxic and neuroprotective effect of IFN-γ could be due to its occurrence in high and low concentrations or to the presence of other bioactive mediators such as LPS or TNF-α (108-109).

3.2.2. Nitric oxide and its dual role in neurogenesis

NO is synthesized by the enzyme NOS in activated microglia and modulate the neurogenesis positively or negatively. It was demonstrated that NO produced by the nNOS inhibits the proliferation and differentiation of NSCs in the SVZ (110-112). And inhibition of nNOS using its selective inhibitor 7-nitroindazole (7-NI) significantly promotes the cell proliferation in the SVZ, rostral migratory stream and olfactory bulb (111). In contrast, NO secreted by iNOS in dentate gyrus and by eNOS in the SVZ promotes neurogenesis after focal ischemia (113-114). Recent finding showed that in rat hippocampus after transient ischemia induced by middle cerebral artery occlusion, the number of nNOS-IR interneurons were significantly decreased, meanwhile, iNOS-IR interneurons appeared and increased (115). In addition, Arora reported that NO inhibits neurogenesis independent of cGMP in dorsal root ganglion, while Koriyama showed that the NO-cGMP signaling promotes the axonal elongation during optic nerve regeneration in the goldfish in vitro and in vivo(116-117). Comprehensively, the effect of NO on the cell survival, proliferation and differentiation varies and different NO synthases play distinct roles in regulating the effect on neurogenesis (118-119).

3.2.3. Effect of chemokines and chemokine receptors on the neurogenesis

Chemokines are small,secreted protein by activated microglia after insult and can modulate the neurogenesis by acting through their chemokine receptors (120). Belmadani reported that in mouse embryos, chemokine receptor CXCR4 was expressed in neural crest cells migrating from the dorsal neural tube and dorsal root ganglia, while chemokines SDF-1 was expressed along the path taken by crest cells to the dorsal root ganglia, suggesting SDF-1/CXCR4 signaling participates in their migration (121). In addition, SDF-1 not only promotes the survival and quiescence of neural progenitor cells (122), but also induces the persistent production of neurons from adult brain stem cells during recovery after stroke by activating the CXCR4 receptor expressed in NSPCs (123 - 124). And in cases of CNS damages, SDF-1 can regulate the migration of NSPCs to the damaged sites acting through CXCR4 (125-126), thus promoting the neurogenesis following any insult. Besides, Tran found that human immunodeficiency virus causes direct death of the dentate granule neurons via CXCR4/CCR5 expressed on these cells, and the binding of viral protein gp120 to CXCR4 prevents SDF-1 to initiate its CXCR4-mediated signaling in NSPCs (127). However, the chemokines also recruit the resident microglia and peripheral macrophages to the injuried sites, resulting in uncontrolled inflammatory response and inhibit the neurogenesis (128).

In addition, activated microglia also produce a great deal of anti-inflammatory factors, reactive oxygen species, neurotrophic factors and growth factors such as TGF-β (5), ROS(129), BDNF, GNDF(4) and IGF-1(130). And these molecules have been already demonstrated to be involved and play important roles in modulating the neurogenesis.

It was reported that there are several subpopulations of parenchymal CNS microglia (131-132), which may explain the functional diversity of microglia in modulating the neurogenesis even if both populations were supportive (7,87). In future, the studies exploring the effects of microglia on neurogenesis should focus on the different activated states or short- and long-term influence of microglia on the cell behaviors of NSPCs and survival of new neurons, as well as its possible molecular mechanism.

3.3. Microglia in brain tumor

Besides the important roles in inflammation and neurogenesis, the presence of microglia in brain tumor has also been paid much attention. As the development of immunohistochemistry, the detailed descriptions of the

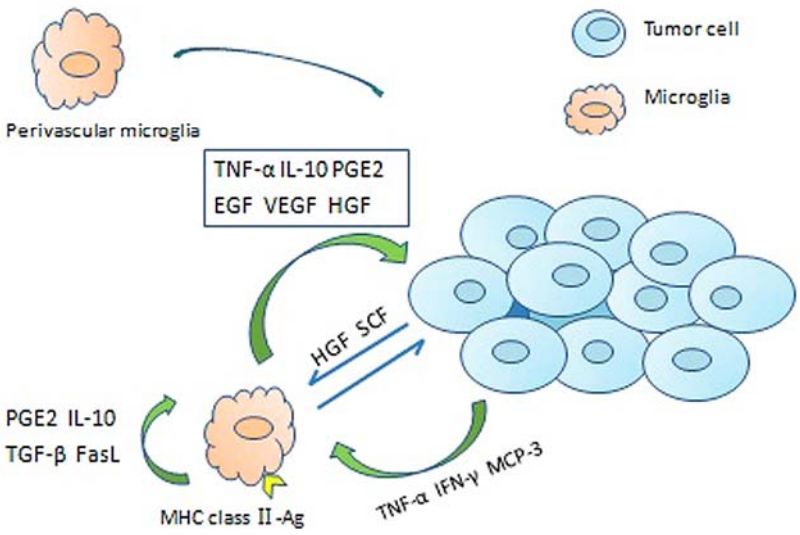

Figure 3. Microglia immune function in brain tumor. Microglia play an anti-tumor activity through MHC class □; However, bioactive substances secreted by microglia (IL-1β, PGE et al) can promote microglia migration, proliferate. There is an interaction between microglia and brain tumor cells. Brain tumor cells can express series of factors such ad TNF-α, IL-10 to recruit microglia to the injury site.

infiltrating macrophage and microglia in brain tumor were demonstrated (133-135). Previously, it was proposed that microglia may play a role in anti-tumorigenesis and induce tumor necrosis. However, recent evidences suggest that microglia suppress immune response and promote tumor progression(136-138;Figure 3).

3.3.1. Anti-tumor activity

The most effective mechanism against tumor cells is antigen-specific cytotoxicity through major histocompatability complex (MHC). Microglia, as one of antigen-presenting cells, present tumor-associated antigens through their MHC class □ molecules with the presence of costimulatory molecules (i.e., B7.1, B7.2, CD40, CD80) (6). Microglia obtained from newborn rodent can upregulate MHC class II and adhesion/costimulatory molecules, process antigen and activate T cells. In human glioma microglia express MHC class II and B7.1 and B7.2 costimulatory molecules, indicating that microglia may be capable of presenting antigen in vivo (139). However, tumor cells may aberrantly express MHC class II in the absence of the B7costimulator(139). Recently, reports supported that the antigen presentation function of microglia against glioma is limited (140). MHC molecules are generally restricted to microglia in low levels, when in high concentration ,T-cell activation and proliferation was not induced.

Another cytotoxic effector function of microglia is the generation of superoxide anions. In rat glioma microglia is more dependent on NO than ROS for exerting effector function(141). Microglia releases iNOS in astrocytoma by IL-1β production probably using p38 MAPK and NF-κB signaling pathway (142). However, cytotoxic molecules, such as NO and ROS can also induce the death of immune effector cells. STAT-1 and STAT-3 increase in NF-κB DNA binding and transcriptional activations in microglia (143). It was found that Fas and its ligand FasL was expressed in microglia and G26 glioma, respectively, and leukocyte propagation increase more than three folds when FasL is inhibited (144).This implies that microglia may induce the death of tumor cells by the Fas/FasL signaling.

3.3.2. Pro-tumor activity

Although, previous studies showed that microglia are capable of presenting antigen to T cells in vivo, several studies demonstrated that the antigen presentation function of microglia against glioma is significantly suppressed (140). Increasing studies showed that not only microglia, but glioma also secrete chemoattractants, which can promote microglial accumulation to the site of tumor (145). For example, monocyte chemoattractant protein-3 (MCP-3) produced by glioma contributes to the microglia/macrophage(MG/MP) recruitment to gliomas and spreading rapidly in glioma by binding with its specific receptor CCR2 expressed on the MG/MP (146). In addition, the transmembrane chemokine CX3CL1 and its receptor CX3CR1 are also involved in the trafficking. It was demonstrated that CX3CR1 is highly expressed in solid human astrocytomas, glioblastomas and microglia, and the binding of CX3CL1 and CX3CR1 significantly promotes the migration of cultured human glioma-infiltrating microglia/macrophages in vitro(147). Besides, other factors such as hepatocyte growth factor (HGF) and its receptor Met, stem cell factor (SCF) and its receptor c-kit also demonstrate the interaction between microglia and tumor. Furthermore, several studies showed that the activated and migrated microglia caused by glioma can secret a plethora of factors, which in turn modulate the behaviors of tumor again. For instance, HGF produced by glioma could attract the microglia to the tumor through their Met receptor, meanwhile, the HGF secreted by

microglia promotes the angiogenesis, cell motility, chemoattraction and invasion of tumor (148).

TNF-α, as an potent proinflammatory cytokine, its influence in the brain tumor is also discussed extensively. It was showed that microglia are the major source of TNF-α in glioma(149). Several in vitro studies shows that TNF-α can increase the expression of growth factor receptor including VEGFR, EGFR and HGFR in glioma cells. And generous studies have demonstrated that activated microglia can produce a great deal of growth factors such as EGF, VEGF and HGF, and the latters were demonstrated to promote the angiogenesis, glioma survival, cell proliferation and invasiveness(150;151). In addition, TNF-α has been showed that it can significantly increase the expression of MMP-9 in gliomas, while MMP-9 was proved to play a critical role in the brain tumor invasion (152).

Interleukin 10 (IL-10) is a cytokine with a broad spectrum of immunosuppressive activity, but its effect on the oncogenesis of gliomas is still unknown. Huettner once reported that the expression levels of IL-10 produced by microglia significantly increased with malignancy of the gliomas in vivo(153). In vitro study also showed that IL-10 increased glioma cell proliferation and motility significantly, and administration of IL-10 specific antibody blocked the effects (154) indicating that IL-10 participates in the progression of glioma, which is consistent with the results of Behnam (155).

Prostaglandins E(PGE), another immunosuppressant released from microglia in gliomas, was also reported to be involved in the oncogenesis of gliomas. Mandapathil reported that PGE can suppress the host immune response, weaken the immune surveillance against tumor cells and thereby promote the progress of tumor (156). The results of Badie showed that glioma-infiltrating microglia are a major source of PGE2 production through the COX-2 pathway and inhibition of cyclooxygenase-2(COX-2) decreases the blood-tumor barrier permeability, (135) suggesting that PGE may suppresses the leukocyte infiltration into tumors(6). In vitro study also demonstrated that the cytolytic activity of circulating peripheral blood leukocytes and tumor that had been activated with IL-2 was greatly decreased in the presence of PGE. Nowadays, the selective inhibition of COX-2 become the research focus and present a therapeutic potential for gliomas in clinic.

3.3.3. Therapeutic potential of microglia activation in brain tumor

Microglia are potent immune effector cells and mediate both innate and adaptive responses when they were activated in CNS injury and disease. Although in brain tumor, a high number of microglia is recruited. the microglia associated with glioma do not inducing an effective anti-tumor T cell response as they do in CNS inflammation. It was reported that factors secreted by microglia such as IL-10, TNF-α can suppress the immune response in glioma. So, Glioma-induced immunosuppression of microglia function becomes a great obstacle of anti-tumor therapy. Animal experiments showed that a single intratumoral injection of CpG oligodeoxynucleotide can keep a long term survival in animals with glioma, while animals depleted of macrophage/microglia were unable to reject the tumor after CpG treatment, indicating that microglia/macrophages are critical players in reducing the angiogenesis and tumor progression(157). It is suggested that targeting macrophages presents a potential strategy to control the tumor growth. In recent years, some studies focus on the macrophage polarization in tumor progression, which selectively tune their functions within a functional spectrum encompassing the M1 and M2 extremes. Macrophages can be phenotypically polarized by the microenvironment to mount specific M1 or M2 functional programs (158;159). M1 macrophages are generally considered potent effector cells which can produce copious amounts of pro-inflammatory cytokines and kill microorganisms and tumor cells. In contrast, M2 macrophages induced by various signaling molecules (e.g. IL-4, IL-13, glucocorticoids, IL-10, immunoglobulin complexes/TLR ligands) can tune inflammatory responses and adaptive Th2 immunity and promote the angiogenesis. This was consistent with that pharmacological skewing of tumor-associated macrophages polarization, from M2 to a full M1 phenotype, may sustain an anti-tumor activity (160). CNS microglia derived from monocyte precursor cells during embryogenesis(161) may also have similar properties to monocytes. Thus, polarized inflammation in brain tumor would be an interesting area of research. As the understanding of glioma progression, polarized inflammation induced by microglia may be a potential target of anticancer strategies.

4. CONCLUSION

Microglia are highly plastic cells and their activation states are regulated by the signals of the microenvironment. Now a bulk of experimental evidences indicate that microglia, depending on their states of activation and functional phenotype, can be either detrimental or supportive both in the intact and injured brain. Moreover, microglia are now recognized as the principal and necessary cells engaged in “CNS defense”. The disease environment is a source of stimuli of microglia activation. So monitoring of microglia activation throughout the disease would give an indication of disease progression and more special markers need to be notarized (162). In addition, modulation of microglial activation will be a therapeutic target in future.

5. ACKNOWLEDGMENTS

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