The Yin and Yang of Microglia

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Abstract

Microglia, the resident immune cells of the mammalian central nervous system (CNS), play a pivotal role in both physiological and pathological conditions such as the restoration of CNS integrity and the progression of neurodegenerative disorders. Extensive data have been published that describe neuroinflammation by microglial activation to have detrimental consequences on the developing and mature brain. On the other hand, a properly directed and limited inflammatory response is known to be a natural healing process after an insult in several other tissues. Thus, it is not surprising that research results illustrating benefits of neuroinflammation have been emerging over the past decade. Inflammation-mediated benefits for CNS outcomes include mechanisms such as neuroprotection, mobilization of neural precursors for repair, remyelination and axonal regeneration. Here, we review data that highlight the dual aspects of microglia with a focus on the developing brain, i.e. as aggressors potentiating damage and as helpers in the recovery process following CNS damage.

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Introduction

Microglia are the main cellular regulators of the brain's innate immune response to both physiological and pathological conditions. Their phenotypic diversity was recognized already in the early 20th century when Río Hortega demonstrated the variety in microglial phenotypes in the healthy and the diseased brain. Although their physiological functions are only partially understood, their central role in the pathomechanisms of several neurological disorders – including acute and chronic neurodegenerative disorders of the immature and mature central nervous system (CNS) – are well established [1–9]. Clinical, epidemiological and experimental studies have shown that damage to the developing brain is caused by multiple factors and mechanisms, including inflammation, excitotoxicity and oxidative stress (see our recent review [1]). Depending on the injury as well as on the activating or inhibiting and microenvironmental conditions, microglia can aggravate an injury and subsequent neurodegeneration, but they can also play an important role in the protective mechanisms underlying tissue repair and regeneration. Thus, microglia are also a prime target for future therapeutic interventions in a wide variety of CNS disease conditions [10, 11]. In this review, we summarize current results (without any claim of being exhaustive) concerning the 'yin-and-yang' function of microglia in physiological conditions and different neurological disorders with a focus on the developing brain.

Fig. 1. Microglia in the developing brain. The physiological role of microglia in brain development is still largely uncharacterized. During development, microglia have been reported to be capable of phagocytosis and implemented in the regulation of apoptosis, cell proliferation, neuronal differentiation and angiogenesis. They also carry a dual function as mediators of inflammation potentially aggravating or causing damage, and as helpers in the recovery process following CNS damage.

The Origin and Biology of Microglia

Microglia, the resident macrophages of the CNS, represent approximately 5–10% of the adult brain cell population [12]. Although first described almost a century ago, the developmental origin of microglia is still under debate [13–17]. Several reports have delineated the existence of various types of microglia of different origins, especially under pathological conditions [12, 18]. Resident parenchymal microglia originate from pial macrophages and mesenchymal progenitors as amoeboid microglia. They invade the brain in two waves during embryonic development and early postnatal life, first through the meninges, choroid plexus and ventricle, and later through the blood vessel walls [12, 15–17, 19, 20]. Ultimately, these amoeboid microglia transform into ‘surveying microglia’ and concomitantly upregulate macrophage surface mark-

ers [21, 22]. In the human brain, this event occurs in the first two trimesters of pregnancy [16, 17, 23], and in rodents shortly before and at the time of birth [23]. Surveying microglia – originally referred to as ‘resting microglia’ – are characterized by a small cell body with fine, long and ramified (branched) processes and a sparse expression of surface molecules associated with the monocyte-macrophage lineage [24]. These surveying microglia constantly screen the CNS and can be rapidly activated by various environmental changes [21].

These early microglial cell populations are not the only ones capable of colonizing the developing CNS. Indeed, bone marrow-derived myeloid cells have recently been shown to enter the immature and mature CNS and to differentiate into microglial cells [16, 25–28]. This infiltration seems to play a central role in disease modulation in the adult brain affected by neurodegeneration or neurological insults [12] and is favored but not exclusively possible when the blood-brain barrier is compromised [12, 13, 29]. The immunological characteristics of microglia as the main immune cells of the CNS appear to differ between two major microglia subtypes of different origin [12]: parenchymal microglia express low levels of major histocompatibility complex (MHC) class II and demonstrate poor antigen-presenting cell function [12]. In contrast, bone marrow-derived microglia express MHC II at higher levels and show better antigen-presenting cell function [12].

Microglia in the Developing Brain

The physiological role of microglia in brain development and the physiological function in the mature brain are still largely uncharacterized (fig. 1). Amoeboid microglia constitute specific clusters after they have penetrated the parenchyma [30]. These specific clusters at the junctions of the internal capsule with the thalamus, with the external capsule and with the cerebral peduncle, as well as at the junctions of the cerebral peduncle with the optic tract, the medial septum, the periventricular hypothalamic area and the corpus callosum, are transient in the developing brain [30]. In the cortical layers and white matter, microglial cells migrate from the ventricular zone to the deep cortical plate by radial and tangential migration [30, 31]. At this time point at about 16–22 weeks of gestation, both the expression of monocyte chemoattractant protein 1 and chemokine macrophage inflammatory protein 1 α can be detected in the upper layer of the human cerebral cortex [20, 32]. At 19–30 weeks of gestation,

microglia proliferate and accumulate in the semioval center [20, 30]. In the mature brain, differences in microglial cell density still exist between different brain regions, with high densities being found in the telencephalon, especially in myelinated regions. This difference in microglial cell localization has been suggested to be associated with a functional difference, and phenotypic heterogeneity including receptor expression patterns has been observed within one anatomical region [33]. The mechanism underlying this phenotype diversity and its consequences are still a matter of speculation.

Microglial cells are capable of phagocytosis during development [34]. During this period, microglia not only have key functions such as the clearance of dying or dead cells. Several studies are emerging that demonstrate a role in developmental processes such as apoptosis, elimination of excess axons, promotion of neuroaxonal growth, axonal guidance, neuronal differentiation, regulation of embryonic cortical precursor cell development, astrocyte proliferation and angiogenesis [20, 30, 34–45]. Especially the role of microglia in neurogenesis is intriguing as, within the framework of CNS inflammation, the impact of this feature on the developing brain can be enormous. Several receptors have been described on microglia, indicating extensive crosstalk with CNS cells such as neurons (see below). Microglia are also capable of secreting various factors such as those that can induce cell proliferation, e.g. brain-derived neurotrophic factor, basic fibroblast growth factor and insulin-like growth factor [46, 47]. Thus, microglia might be more extensively involved in higher-order brain functions than currently believed.

Mechanism of Microglial Activation

Microglia can be rapidly activated by various environmental changes [21]. The process of microglial activation is associated with proliferation and transformation into 'reactive' microglia with different response phenotypes [10, 48–52]. During activation, microglia change from a ramified to a hyperramified phenotype and subsequently adopt an amoeboid morphology, a process which has been suggested to help microglia invade lesions [53]. Activated microglia not only change their phenotype, but also proliferate, migrate to the site of damage and secrete pro- and anti-inflammatory cytokines and chemokines, oxidative stress-inducing factors such as nitric oxide (NO) as well as growth factors [50, 54]. In case of acute neuronal death, microglia can function as brain macrophages and phagocyte cell debris [54].

Microglia have the remarkable ability to recognize a wide range of signals that indicate a threat to the structural and functional integrity of the CNS through various receptors [50]. Injured neurons release adenosine-5'-triphosphate (ATP) and chemokine CXC motif ligand 10 (CXCL10), which attract microglia via activated purinoceptors [55, 56] and chemokine CXC motif receptor 3 (CXCR3), respectively [57]. Moreover, microglia may sense neuronal activity through neurotransmitter receptors present on the microglial membrane [58]. In this line, data from our laboratories and others demonstrate the presence of glutamate receptors on microglia as a link between inflammation and excitotoxic brain damage [20, 58, 59]. As the main cells of innate immunity of the CNS, microglia constitutively express the most important immune receptors (MHC I and II, chemokine receptors) at low levels [60]. During activation, the immunologically relevant molecules are upregulated, and the appropriate antigen is presented [54] via MHC II. Additionally, it has recently been shown that microglia are able to cross-present exogenous antigens on MHC I to CD8⁺ T cells [61]. In the course of recovery from injury, activated microglia can be eliminated by apoptosis [54, 62]. Not only neurons, but also astrocytes can be critical for microglial activation, e.g. in the course of infections [63]. Astrocytes, moreover, regulate the trafficking of lymphocytes across the brain endothelial barriers [64].

Microglial activation can be acute or chronic, and it has been suggested that this depends not only on the duration of an external cue, but also on the specific factor (stress, infection, inflammation, signals from damaged neurons) responsible for the activation process [54]. It has been shown that microglial activation during stress differs from that during infection/inflammation [65]. Chronic microglial activation can lead to microglial overactivation followed by microglial degeneration, as has been demonstrated in several *in vitro* studies [66, 67]. Because of the absence of microglial support, the degeneration of microglia will be followed by secondary neurodegeneration.

Microglial Activation in the Neonatal Period

Microglia are already widely dispersed throughout the immature white matter by 22 weeks of gestation, and have complete functionality. After stimulation with lipopolysaccharides (LPS) and proinflammatory cytokines [IFN- γ , tumor necrosis factor (TNF)- α , interleukin (IL)-1 β], they are fully capable of producing proinflammatory cy-

tokines, reactive oxygen intermediates and proteolytic enzymes, and they have phagocytic activity [1, 24, 68]. In hypoxic-ischemic neonatal brain injury, the presence of activated microglia inducing cell death in immature white matter, both in preoligodendrocytes and in astrocytes, has been widely confirmed [59, 69]. It also seems that microglia and resident mononuclear phagocytes are the primary sources of proinflammatory cytokines in brains with periventricular leukomalacia [70].

Microglial activation has often been the first – or at least a significant – cellular event detected in and around a lesion in several animal models of developing brain injuries such as those induced by mechanical trauma, infection/inflammation, excitotoxic insults and hypoxia-ischemia [59, 71–86]. Moreover, microglial activation has been demonstrated in postmortem brain specimens of premature infants with periventricular leukomalacia [87–89]. The activation of microglia by LPS induces oligodendrocyte cell death and also greatly impairs oligodendrocyte development through cytokines and modulations of growth factor secretion [90]. Oligodendrocyte-microglial communication could be one of the mechanisms underlying selective white matter damage and hypomyelination in periventricular leukomalacia. Similarly, activated microglia-macrophages are seen in abundance following both neonatal hypoxia-ischemia [91, 92] and focal stroke [93, 94], producing inflammatory cytokines, high levels of NO, complement molecules and matrix metalloproteinases (MMP). By proteolytic cleavage, the MMP control the components of the extracellular matrix proteins, such as adhesion, membrane receptors and soluble proteins. The early postinjury macrophage population comprises resident microglia rather than invading monocytes [69, 93]. The notion that microglia contribute to, rather than limit, acute ischemic injury in the immature brain comes from studies illustrating an association between the reduced extent of a lesion and reduced microglial activation/monocyte infiltration [69, 95, 96].

Microglial Activation during Aging

Abundant evidence shows that the microglial cell phenotype and function changes during the normal aging process. Several authors have shown in various species that during the physiological aging process, microglia adopt an ‘activated’ phenotype with short and plump processes [33]. These ‘primed’ or ‘sensitized’ microglia are characterized by chronic low-level inflammation and

increased microglial reactivity [97]. Microglia from aged animals showed increased expression of MHC II, CD68, CD11b, CD80, CD86 and intercellular adhesion molecule 1 [97, 98], increased secretion of proinflammatory cytokines IL-1 β , IL-6 and TNF- α , and reduced secretion of anti-inflammatory cytokines IL-10 and IL-4 [97–99]. Functional alterations included increased microglial reactivity, leading to a more rapid and pronounced response to pathological stimuli. According to this, aged mice not only have higher basal levels of these inflammatory mediators, but also show a higher stress-induced increase in these mediators [100]. Several studies have shown an increased secretion of IL-1 β or IL-6 [100–102] after stress or stimulation. Although the amount of TNF- α constitutively secreted by microglia from aged mice was greater as well, the secretion of TNF- α was less responsive to stimulation, probably because of the dramatically enhanced release under basal conditions [99]. Furthermore, microglia from aged animals showed reduced glutathione levels, suggesting that the insult from reactive oxygen species (ROS) may be greater in aged brains [99]. The decreased amount of anti-inflammatory cytokines may enhance age-related neuroinflammation [97]. Microglia from aged mice also internalize less amyloid- β peptide, suggesting a lack of amyloid elimination by parenchymal microglia in aged adults suffering from Alzheimer’s disease [99]. Gene expression profiles showed that expression of genes indicative of oxidative stress, inflammation and glial activation increases with age. In contrast, expression of genes associated with synaptic function/transport, growth factors and trophic factors decreases with age [97, 103–105]. Moreover, microglial dystrophy, i.e. the adoption of aberrant features indicating microglial senescence, has been acknowledged [33]. This may change the capability of microglia to adopt a protective phenotype with aging.

Yin and Yang of Microglia

Which intra- and/or extracellular factors are responsible for transforming microglia into aggressors potentiating damage, or then helpers in the recovery following CNS damage? Whether microglia have a beneficial or harmful function depends on several factors: the kind of stress and damage signals, the duration/timing of an impact, the microenvironment, the interaction with other cell types and, interestingly, even the age of an organism [60]. Macrophages/microglia can be classified into at least two subsets with distinct molecular phenotypes and ef-

Fig. 2. Microglial phenotypes – the yin and yang. Macrophages/microglia can be classified in a simplified manner into two subsets of phenotypes and effector functions depending on the activation pathway. Further intermediate phenotypes have been described.

effector functions depending on the activation pathway. The ‘classically activated’ proinflammatory M1 macrophages, activated by LPS and by the proinflammatory cytokine IFN- γ , express CD86 and CD16/32 and produce high amounts of oxidative metabolites (NO and superoxide), proteases and proinflammatory cytokines. They play a central role in host defense against pathogens and tumor cells, and they can also damage healthy cells such as neurons and glial cells. In contrast, M2 macrophages are ‘alternatively activated’, anti-inflammatory macrophages induced by IL-4 and IL-13, and they express CD206 and arginase 1. The latter downregulate inflammation and promote tissue remodeling/repair and angiogenesis (fig. 2). The M1/M2 classification is, of course, a simplification of matters, and for macrophages, further intermediate phenotypes have been described [106]. In a mouse model of spinal cord injury, it has been shown that the M1/M2 ratio is markedly enhanced, leading to secondary neurodegeneration, in contrast to wound healing and healing of the myocardium with a shift from M1 to M2 macrophages during the healing process. Hypothetically, this delayed phase depends on the activation of an alternative set of transcription factors [107–109]. In a model of LPS-stimulated chronic systemic inflammation, it was shown that microglia in young mice protect dopamine-producing neurons against the toxin; howev-

er, microglia in old mice promoted the death of these cells [110]. Another study also illustrated a dual role: microglia induced both axon regeneration and neurotoxicity in neurons transplanted into rat spinal cord [111]. One of the most important functions of the microglia, phagocytosis, can also be both beneficial (pathogens, brain injury) and harmful (autoimmune disease). Activation of Toll-like receptor (TLR)4, the best-analyzed TLR in microglia, which plays a central role in many bacterial infections, also can be both neuroprotective and neurodestructive [60]. It can induce neurodegeneration by release of proinflammatory molecules, but it can also promote remyelination by recruiting oligodendrocyte progenitor cells [60, 112]. Concerning cytokine production in the CNS, microglia can both produce and respond to cytokines, and these can be either neuroprotective [e.g. IL-10, tumor growth factor (TGF)- β , TNF- α] and/or neurotoxic (e.g. IL-1, TNF- α , IFN- γ) [60]. In addition, secreted factors such as one of the classical proinflammatory cytokines of neurodegeneration, TNF- α , can act both neurotoxically and neuroprotectively. Although TNF- α is neurotoxic at high levels, it may be neuroprotective at low levels, as has been demonstrated in a study using TNF receptor (TNFR)-deficient mice, for instance [113]. Among several factors, this seems to be dependent on the targeted receptor: TNFR1 activation can induce neurodegenera-

tion, whereas TNFR2 activation promotes neuroprotection [114]. MMP-3 and -9 are important mediators during stroke and are released by microglia [115]. They play an important role in neurodegeneration after stroke, as was shown by (i) a reduction of infarct size following MMP inhibition and (ii) reduced ischemic injury in mice deficient in MMP-9 or -3 [116, 117]. However, MMP also play a critical role in neurovascular remodeling after stroke [118].

The Bad Guys? Microglia and Neurodegeneration

Microglial contact can be a ‘kiss of death’, and such contact between microglia and neurons plays a pivotal role in the pathogenesis of neurodegenerative disorders [50]. The presence of activated microglia and their ability to induce cell death in the immature white matter, both in preoligodendrocytes and in astrocytes, has been confirmed by several authors [59, 69]. Also, microglia have been reported to be the primary sources of proinflammatory cytokines detected in brains with periventricular leukomalacia [70].

The exact mechanism leading to microglial overactivation is still not fully understood, but glial-neuronal crosstalk seems to be central [60]. Moreover, microglia and astrocyte interaction seems important: proinflammatory cytokines secreted by activated microglia inhibit astrocyte gap junction communication, which influences the role of astrocytes in providing neuronal support [60, 119]. Microglial activation is one of the first steps in the inflammatory processes within the CNS, and it is often followed – depending on the activating mechanisms – by an infiltration of neutrophils, T lymphocytes and reactive astrocytosis [120]. Activated microglia release several cytotoxic substances such as ROS and the proinflammatory cytokines IL-1 β [121, 122], TNF- α [123], MMP and glutamate [60]. The ROS (superoxide, hydrogen peroxide, NO) cannot only kill invading microbes, but they also induce neuronal damage and reactive gliosis [60]. NO synthase [inducible (i)NOS, NOS2] is not expressed at high levels in the healthy brain, but in microglia and some astrocytes during inflammation [60] and stroke [124]. In vitro, iNOS is induced in microglia by IFN- γ , TNF- α and IL-1 β , but not by TGF- β [125]. iNOS-deficient mice have smaller infarcts [126]. Superoxide is produced by microglia via NADPH oxidase [127]. Glucose availability can be rate limiting for NADPH production. This explains why ischemic or inflammatory injury can be exacerbated by hyperglycemia [128, 129]. It has also

been shown that mice deficient in the gp91 subunit of NADPH oxidase 2 have smaller infarcts than their wild-type littermates [130, 131]. Such a role of NADPH detected in the adult brain has been shown not to contribute significantly to perinatal brain damage [132]. Microglia can release glutamate, a neurotransmitter that is well known to trigger excitotoxic neurodegeneration and cell death of astrocytes and oligodendrocytes. Especially the glutamate release from chronically activated microglia in the postischemic period could play an important role in brain injury [124]. Other processes such as activation of the prostaglandin E₂ receptor of the prostaglandin E₂ pathway can lead to microglia-induced paracrine neurotoxicity [133].

Blocking overactivated microglia in neurodegeneration settings seems to be an attractive therapeutic strategy for various neurodegenerative disorders. The tetracycline antibiotic minocycline is a drug that has been used in adults to treat infectious diseases without major side effects, but it has not been administered to children. It effectively crosses the blood-brain barrier, targets microglia by inhibiting the production of proinflammatory cytokines and NO and reduces their migration to injured neurons [134]. An inhibition of the MMP-9 pathway was described for both minocycline and doxycycline [135, 136]. Minocycline has been shown to be neuroprotective in several adult animal models of neurological disorders [137–144]. Similarly, minocycline has been reported to be neuroprotective in developing brain damage models such as hypoxia-ischemia in neonatal or juvenile rats [145–150] and excitotoxic perinatal brain damage in mice [69]. On the other hand, minocycline worsened hypoxic-ischemic brain injury in a model of neonatal brain damage [151]. The reason for the discrepancy is not clear but may depend on dosage, application time with respect to brain damage induction, developmental age and genetic background. This finding, however, highlights that microglial inhibition may not be protective at all times.

The Good Guys? Microglia and Neuroprotection

In parallel with their negative or neurotoxic effects, microglia also play an important role in the maintenance of neuronal wellbeing [52, 152]. Based on their phagocytic function as the ‘professional’ phagocytes of the CNS, microglia can enter damaged brain regions and remove toxic byproducts, invading pathogens and cell debris. In case of pathogens, stimulation of TLR induces a proinflammatory cascade. In case of cell debris due to

brain injury, the recognition of phosphatidylserine of the apoptotic cell membrane induces an anti-inflammatory response [60]. Microglia have an important protective function in brain injury by removal of damaged cells, promoting neurogenesis, inducing the reestablishment of a functional neuronal environment by restoration of the myelin sheath, and by releasing neurotrophic factors and anti-inflammatory molecules [60, 153, 154]. Insufficient removal of myelin by microglia impairs the recruitment of oligodendrocyte precursor cells and induces an arrest of oligodendrocyte differentiation [155].

The neuroprotective role of microglia has not been well studied in models of developmental brain damage. Though in the immature and mature brain, microglia appear to have differing properties, studies performed on the adult brain may offer more insight. Neuroprotective properties of microglia have been described for adult neurological diseases such as Alzheimer's. Here, microglia promote protection via the secretion of proteolytic enzymes that degrade amyloid- β , and by the phagocytotic clearance of amyloid- β plaques [60]. Furthermore, a specific macropinocytotic mechanism, different from that known for phagocytosis, has been described both in vitro and in vivo [156]. Chemokine (C-C motif) receptor 2 seems to play an important role in the protection of microglia in Alzheimer's disease since mice deficient in chemokine (C-C motif) receptor 2 exhibited increased amyloid- β deposits and died prematurely [157]. In experimental models of Alzheimer's disease, two microglial subtypes have been suggested to play different neuroimmunomodulating roles [158]. Bone marrow-derived microglia were able to eliminate amyloid deposits by phagocytosis [159]. Microglia can also be protective via the production of cytokines: (i) IL-6 may act on astrocytes to induce brain tissue repair [160]; (ii) IL-10 can inhibit apoptosis of microglia [161], and (iii) TGF- β can be neuroprotective. Inhibition of TGF- β activity in a rodent model of prion disease induced cerebral inflammation

[162]. In a model of Alzheimer's disease, it reduced the plaque load [163].

Microglia seem to be much more integrated into neuronal function than was thought in the past, and recent findings indicate neuronal-microglial crosstalk [164]. Recent findings suggest the intriguing hypothesis that microglia can sense neuronal activity based on local neurotransmitter levels [164]. This is at least in part maintained by neurotransmitter receptors identified on microglial cells, including metabotropic and ionotropic glutamate [165–171] as well as γ -aminobutyric acid B receptors [172].

Conclusion

Apart from the well-known, defense-oriented reactions of microglia [173], there is accumulating evidence of their role in physiologic brain development and normal function of the mature and immature nervous system [50, 174]. Future studies will need to illustrate more and in detail the differences in microglial function at various stages of development as well as the protective role of microglia in the immature brain. Deciphering the factors that influence the transformation of microglia into aggressors potentiating damage or into kind helpers in recovery following CNS damage will be a challenge for the future. These 'factors' may be targets for a highly effective pharmaceutical therapy for neurodegenerative diseases such as perinatal brain damage.

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