Microglia Function in the Normal Brain

Rommy von Bernhardi, Florencia Heredia, Nicole Salgado and Paola Muñoz

Abstract The activation of microglia has been recognized for over a century by their morphological changes. Long slender microglia acquire a short sturdy ramified shape when activated. During the past 20 years, microglia have been accepted as an essential cellular component for understanding the pathogenic mechanism of many brain diseases, including neurodegenerative diseases. More recently, functional studies and imaging in mouse models indicate that microglia are active in the healthy central nervous system. It has become evident that microglia release several signal molecules that play key roles in the crosstalk among brain cells, i.e., astrocytes and oligodendrocytes with neurons, as well as with regulatory immune cells. Recent studies also reveal the heterogeneous nature of microglia diverse functions depending on development, previous exposure to stimulation events, brain region of residence, or pathological state. Subjects to approach by future research are still the unresolved questions regarding the conditions and mechanisms that render microglia protective, capable of preventing or reducing damage, or deleterious, capable of inducing or facilitating the progression of neuropathological diseases. This novel knowledge will certainly change our view on microglia as therapeutic target, shifting our goal from their general silencing to the generation of treatments able to change their activation pattern.

Keywords Central nervous system · Cytokines · Development · Glia · Neuroinflammation

Abbreviations

5-HT	Serotonin
Aβ	β-amyloid
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ATP	Adenosine triphosphate

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BDNF	Brain derived neurotrophic factor
CNS	Central nervous system
CNTF	Ciliary neurotrophic factor
DAMPs	Damage- or Danger-associated molecular patterns
EP2	Prostanoid receptor subtype 2
GABA	Gamma aminobutyric acid
GDNF	Glia derived neurotrophic factor
GM-CSF	Granulocyte/macrophage colony stimulating factor
HIV-1	Human immunodeficiency virus
IFNγ	Interferon gamma
IGF1	Insulin-like growth factor 1
IL1	Interleukin 1
iNOS	Inducible nitric oxide synthase
InsP3	Inositol trisphosphate
LPS	Lipopolysaccharides
LTP	Long time Potentiation
M-CSF	Macrophage colony-stimulating factor
MHC	Class I molecules of histocompatibility major complex
NGF	Nerve growth factor
NMDA	*N*-methyl-d-aspartate
NO	Nitric Oxide
NT	Neurotrophin
PAMPs	Pathogen-associated molecular patterns
PGE2	Prostaglandin E2
PRRs	Pattern recognition receptors
RANTES	Regulated on activation, normal T cell expressed and secreted—chemokine CCL5
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
Rs	Receptors
SDF-1α	Stromal cell-derived factor
SIRPα	Signal regulatory protein α
SRs	Scavenger receptors
TGFβ	Transforming growth factor-β
TLRs	Toll-like receptors
TNFα	Tumor necrosis factor α
TSPs	Thrombospondins

Introduction

Microglia are the resident immune cells of the central nervous system (CNS), accounting for approximately 10 % of the total cell number in the healthy mammalian brain (Prinz and Priller 2014). They derive from myeloid progenitors, being related to peripheral monocyte-macrophages (Ginhoux et al. 2010). Microglial cell progenitors originating in the yolk sac migrate and colonize the CNS during embryonic development, before the blood–brain barrier is established, differentiating and becoming confined into the CNS. Throughout the life, microglia appear to be capable of local self-renewal. Adult healthy animals show very little exchange between blood and brain parenchyma (Mildner et al. 2007). Thus, maintenance of their population normally does not depend on recruitment of circulating progenitors. However, monocytes invading the brain have been observed under pathological conditions, such as blood–brain barrier damage by trauma or severe inflammation and ischemic vascular damage (Ajami et al. 2007; Casano and Peri 2015; Kierdorf et al. 2013), where they transform into microglia with a ramified phenotype (Mildner et al. 2007). The environment provided by the brain parenchyma appears to be key for microglia phenotype. Astrocytes-conditioned medium induces morphological and functional changes of microglia and blood monocytes in culture (Sievers et al. 1994; Ramirez et al. 2005; Tichauer et al. 2007; von Bernhardi and Ramírez 2001; Orellana et al. 2013), an effect that is at least partly mimicked by adenosine triphosphate (ATP) or adenosine. Other mediators capable of modifying microglia activation are cytokines released from astrocytes, including transforming growth factor β (TGFβ), macrophage colony-stimulating factor (M-CSF), and granulocyte/macrophage colony stimulating factor (GM-CSF) (Schilling et al. 2001; Alarcón et al. 2005; Flores and von Bernhardi 2012; Herrera-Molina et al. 2012; Tichauer et al. 2014; Tichauer and von Bernhardi 2012).

Microglia, as member of the monocyte-macrophage family, function as mononuclear phagocytes, recognizing and scavenging dead cells, pathogens and several endogenous, and exogenous compounds. As mentioned in Chapter "Glial Cells and Integrity of the Nervous System," under physiological conditions and in the absence of inflammatory stimuli, microglia are found in a "surveillance state," morphologically defined by having a small soma with long fine-ramified processes. Surveillance microglia are highly dynamic, retracting and extending their processes in response to environmental cues, interacting with blood vessels, neurons, ependymal cells, and other glial cells (Nimmerjahn et al. 2005; Ramirez et al. 2005; Chen and Trapp 2015; Heneka et al. 2015). They express constitutive markers like Iba-1, and several other markers, such as MHC-I, MHC-II, FcR, CD68, depending on the environmental cues they sense (Fig. 1), being involved in antigen presentation, cytotoxic activation, phagocytosis, antibody-associated phagocytosis, etc. An astrocyte labeled with antibody against glial fibrillary acidic protein (GFAP) is also included to compare their morphologies. Microglial cell surveillance is highly relevant for CNS development and function throughout life.

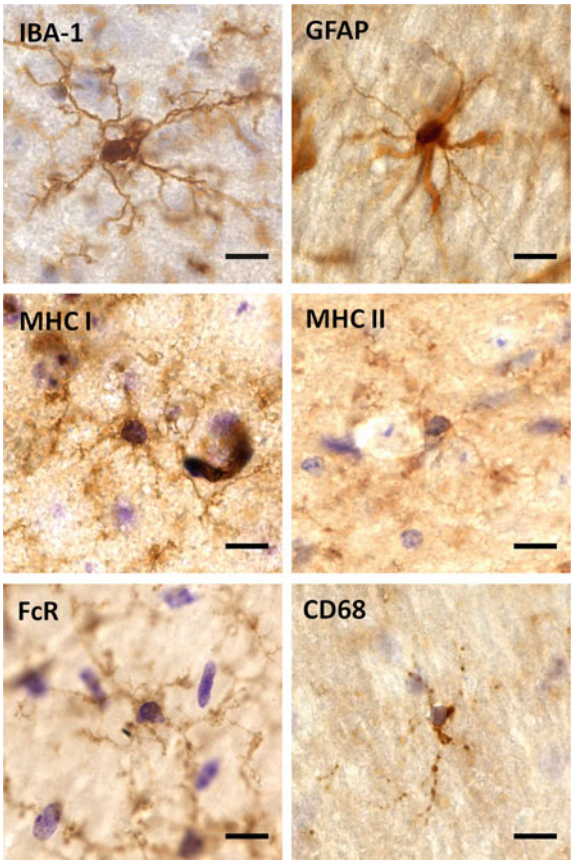

Fig. 1 Labeling of glia by activation markers. Immunohistochemical detection of glia activation markers in hipocampal cryosections obtained from unstimulated adult mice counterstaining with Harris Haematoxylin. Iba-1 and GFAP antibodies identified microglia and activated astrocytes, respectively. MHC-I, MHC-II, FcR, and CD68 identify microglia populations that are functionally different, showing differences in their morphology as well as in the labeling pattern. Scale bar = 10 μm

Microglia Motility and Migration

Microglia exhibit two types of motility: the active movement of their processes, sensing the environment, and their translocation in the brain parenchyma. Migration is frequently observed during development, when invading cells migrate into the CNS, and when recruited after an insult and migrate to the site of injury/stimulation. As discussed in Chapters "Glial Cells and Integrity of the Nervous System and Purine Signaling and Microglial Wrapping," many molecules appear to signal for microglia migration, including ATP, cannabinoids, chemokines, lysophosphatidic acid, bradykinin, ion channels, and transporters (Davalos et al. 2005; Walter et al. 2003; Schwab 2001; Rappert et al. 2002; Schilling et al. 2004; Ifuku et al. 2007).

Although under nonstimulated conditions they do not migrate, real-time imaging reveals that microglial processes are constantly moving (Davalos et al. 2005; Nimmerjahn et al. 2005). Processes move rapidly toward an injury. Time-lapse microscopy of brain slices from adult mice shows extensive migration of microglia 24 h after an injury (Carbonell et al. 2005).

Recruitment of microglia to a lesion involves several factors including chemokines released from both neurons and glial cells, among others. Most of the chemokines are released as soluble factors that form chemotactic gradients for cell migration, although CX3CL1 (fractalkine) occurs also as a surface-bound molecule. Microglial activation following neuropathological challenges affects the expression of chemokine receptors (Kremlev et al. 2004), acting as a source and a target of chemokines in an auto/paracrine fashion. Activation of CXCR3 receptor by chemokine CCL21 is linked to microglial migration (Rappert et al. 2002), and the CCL2/CCR2 system appears to be crucial for the recruitment of peripheral monocytes to the CNS, where they become microglia (Davoust et al. 2008; Mildner et al. 2007; Prinz and Priller 2010). Expression of CCR, receptor for CCL2 ligands, identifies functional subsets of microglia. The CX3CR1, the receptor for fractalkine, is also a key molecule for the CNS-relevant macrophage subclassification (Prinz and Priller 2010).

It is especially interesting that chemokines including CCL2, CCL21, or CX3CL1 also appear to serve as signals from endangered neurons to microglia (Biber et al. 2008). It has been suggested that CX3CL1 expressed by neurons could provide a constitutive calming influence on CX3CR1-expressing microglia, thus representing a neuron-to-microglia signaling system similar to those described for CD200/CD200R or CD47/SIRP-1α. Interruption of this regulatory mechanism could facilitate enhanced responses to activating signals. In fact, deficiency in fractalkine signaling results in enhanced severity of CNS damage in several disease models (Cardona et al. 2006; Prinz and Priller 2010). Similarly, activation of CCR5 by the chemokine CCL5 "regulated on activation, normal T cell expressed and secreted" (RANTES), supresses lipopolysaccharide (LPS)-induced expression of inflammatory cytokines, such as interleukin (IL)1β, IL6 and tumor necrosis factor (TNF)α, and inducible nitric oxide synthase (iNOS) in microglia. In contrast, motor neuron death after nerve injury is accelerated in CCR5 knock-out animals, suggesting that CCR5-mediated suppression of microglia toxicity protects neurons (Gamo et al. 2008).

Microglia-Mediated Phagocytosis

Microglia are the professional phagocytes of the CNS. Phagocytosis is a key function during development as well as in the normal and pathological adult brain (Neumann et al. 2009). During development, microglia remove apoptotic cells, mediated by an "eat me" signal produced by apoptotic cells to microglia (Marin-Teva et al. 2004). They are also involved in synapse removal (Stevens et al. 2007) and in pruning synapses in the developing and postnatal brain (see Chapter "Purine Signaling and Microglial Wrapping" for a complete description on microglial wrapping).

Phagocytosis depends on different mechanisms (Table 1). Pathogens are recognized by Toll-like receptors (TLRs), and apoptotic neurons are recognized by various receptor systems, including asialoglycoprotein-like-, vitronectin-, and

phosphatidylserine receptors (Witting et al. 2000). Multiple factors regulate phagocytosis, including ATP, through the metabotropic P2Y6 receptor (Inoue et al. 2009). The P2Y6 receptor is upregulated when neurons are damaged and could be a trigger for phagocytosis (Koizumi et al. 2007). In contrast, activation of P2X7 receptors suppresses phagocytosis, whereas inhibition of P2X7 expression by shRNA or oxATP/BBG restores phagocytosis (Fang et al. 2009). The ciliary neurotrophic factor (CNTF), glia derived neurotrophic factor (GDNF), and M-CSF potentiates phagocytic by microglia (Chang et al. 2006; Lee et al. 2009; Mitrasinovic and Murphy 2003). Substrate-bound complement component C1q enhance both FcR and CR1-mediated phagocytosis (Webster et al. 2000), whereas the prostanoid receptor subtype 2 (EP2), downregulates phagocytosis (Liang et al. 2005; Shie et al. 2005).

Table 1 Receptors and regulatory molecules associated with microglial cell functions

Function		Microglial receptors	Regulatory molecules	References
Phagocytosis	Apoptotic cells	Asialoglycoprotein-like-,vutronectin- & phophatidyiserine Rs		Witting et al. (2000)
		Metabotropic P1 adenosine Rs, metabotropic P2Y & ionotropic P2X purinoRS	ATP	Inoue et al. (2009); Koizumi et al. (2007); Fang et al. (2009); Kirischuk et al. (1995); Lalo et al. (2008)
		GDNF Rs	GDNF, NO	Chang et al. (2006)
		CNTFRα	CNTF	Lee et al. (2009)
	Pathogens	TLRs	Inflammatory cytokines and chemokines	Olson and Miller (2004)
Development	Neurogenesis (genesis, differentiation & migration)	TLRs	IL-1β, IL-6, IFNγ	Shigemoto-Mogami et al. (2014); Aarum et al. (2003); Walton et al. (2006); Nakanishi et al. (2007); Cepko et al. (1996)
	Programmed cell death (phagocytosis)	TNFα Rs1 (TNFR1)	NGF, superoxide ions, TNFα	Frade and Barde (1998); Marin-Teva et al. (2004); Sedel et al. (2004)
	Synaptogenesis	IL-10 receptors	TSPs, anti-inflammatory cytokine IL-10	Chamak et al. (1995); Moller et al. (1996); Lim et al. (2013)
	Synaptic maturation	KARAP\DAP12		Roumier et al. (2004)
	Synapse removal (synaptic pruning)	Fractalkine receptor (CX3CR1)	CX3CL1	Paolicelli et al. (2011)
		Complement Rs3 (CR3)	MHC1, complement components (C3, C1q)	Corriveau et al. (1998); Goddard et al. (2007); Schafer et al. (2012); Stevens et al. (2007)

(continued)

Table 1 (continued)

Function		Microglial receptors	Regulatory molecules	References
Adult life	Modulation of neuronal activity	Rs fir beurotransmitters, neuropeptides & neuromodulators	Cytokines & RNs (TGFβ-1, NO)	Li et al. (2012); Herrera-Molina and von Bernhardi (2005); Tichauer et al. (2007)
	Neuronal surveillance	Fractalkine Rs (CX3CR1), purinergic Rs P2Y12	ATP & gap junction proteins	Davalos et al. (2005); Liang et al. (2009); Haynes et al. (2006)
	Synaptic plasticity (involved in learning & behavior)	Fractalkine receptor (CX3CR1)	CX3CL1	Paolicelli et al. (2011); Rogers et al. (2011)
			NT, inflammatory cytokines (IL-1β, TNFα)	Schmid et al. (2009); Goshen et al. (2007); Beattie and Malenka (2002); Loscher et al. (2003); Avital et al. (2003); Labrousse et al. (2009)
	Neurogenesis in adult brain	Neurotransmitter Rs	NT & regulatory cytokines (IGF1, BDNF, IL4)	Butovsky et al. (2006); Parkhurst et al. (2013); Ribeiro Xavier et al. (2015)
			Inflammatory cytokines (IL1-β, IL-6 TNFα) (inhibition)	Ribeiro Xavier et al. (2015); Ben-Hur et al. (2003); Monje et al. (2003); Koo and Duman (2008)
		TLRs (TLR2, TLR4)		Rolls et al. (2007)
	Synaptic stripping	MHC class F receptors	NGF, NT-4/5, TGFβ1, GDNF, FGF, IL-3	Nakajima et al. (2007); Trapp et al. (2007); Oliveira et al. (2004); Huh et al. (2000)
			TNFα, IL-6, NO	Nakajima et al. (2005)
Pathophysiological conditions	Neurodegeneration (phagocytosis, production factors with inflammatory and immunoregulatory effect)	SRs	Chemokines (CCL2, CCL21, CX3CL1, CXCL10, CXCL12)	Rappert et al. (2004); Koenigsknecht and Landret (2004); Alarcón et al. (2005); Murgas et al. (2012); Bezzi et al. (2001); Stewart et al. (2010); van Weering et al. (2011)
		TLRs (TLR2, TLR4,TLR9)	Inflammatory cytokines (IL1-, IL-6, TNFα, IFNγ)	Murgas et al. (2012); Bezzi et al. (2001); Mount et al. (2007); Chakrabarty et al. (2010)

(continued)

Table 1 (continued)

Function		Microglial receptors	Regulatory molecules	References
	Hypoxia, cerebral ischemia, autoimunity	Chemokine Rs (CXCR3, CCR3, CCR5, CXCR4)	ROS	Block et al. (2006)
		Cytokine Rs	RNS (NO)	Murgas et al. (2012)
		M-CSFR		Mitrasinovic and Murphy (2002)
		TLRs		Stewart et al. (2010); Lotz et al. (2005); Tahara et al. (2006)

As the resident immune cells of the CNS, microglia are the first line of defense against exogenous threats. The pattern recognition receptors (PRRs), abundantly expressed in microglia, detect infectious agents and assist in the control of the adaptive immunity and the cooperative activities of effector cells (Beurel et al. 2010; Hanisch et al. 2008; Padovan et al. 2007). In addition to pathogen detection by pathogen-associated molecular patterns (PAMPs), several PRRs, including TLRs, also bind endogenous molecules that are generated or modified upon tissue injury. These molecules are classified as damage- or danger-associated molecular patterns (DAMPs) (Bianchi 2007; Kono and Rock 2008; Matzinger 2007). The TLRs 1–9 and co-receptors, like CD14 are widely expressed in cells of the innate as well as adaptive immune system, but also in nonimmune cells (Schaffler et al. 2007). In the brain, TLRs are mainly expressed in glia, although some has been detected in neurons (Aravalli et al. 2007b; Carpentier et al. 2008; Hanisch et al. 2008; Okun et al. 2009; Konat et al. 2006).

The stimulation of TLRs triggers various programs of microglial activation and activates secretion of cytokines and chemokines (Aravalli et al. 2007b; Okun et al. 2009). Several reports indicate the importance of TLRs in various CNS diseases including infection, trauma, stroke, neurodegeneration, and autoimmunity (Babcock et al. 2006; Caso et al. 2007; Lehnardt et al. 2002; Nau and Bruck 2002; Nguyen et al. 2004).

Participation of Microglia in Development

Microglia are intimately involved in the development of the nervous system (Table 1). They have roles both in neurogenesis and neuronal death. Microglia appears to have both detrimental and supportive effects on neurogenesis (Ekdahl et al. 2009), which could depend in the activation state of microglia (Schwartz et al. 2006).

Differentiation of neural precursors in culture requires the presence of soluble factors secreted by microglia (Nakanishi et al. 2007; Walton et al. 2006). Those factors are also involved in directing migration of newly generated neural cells (Aarum et al. 2003).

The role of microglia for neuronal loss by programmed cell death during development has been described in several brain regions, including the retina, where the pro-apoptotic action of microglia is mediated through nerve growth factor (NGF) (Frade and Barde 1998). Similarly, microglia induce apoptotic death of Purkinje neurons by releasing superoxide ions (Marin-Teva et al. 2004), and motoneurons apoptosis via secretion of TNFα in the embryo (Sedel et al. 2004).

In early postnatal development, elimination of excess synapses—known as synaptic pruning—appears also to be a microglia-mediated mechanism. Mice lacking fractalkine receptor (CX3CR1), have reduced numbers of brain microglia, and show impairment of synaptic pruning, resulting in an abnormally high number of synaptic spines (Paolicelli et al. 2011).

On the other hand, microglia are also involved in the formation of new synapses, especially in the early postnatal brain. Microglia stimulate synaptogenesis by secreting the extracellular matrix proteins thrombospondins (TSPs) (Moller et al. 1996), which are also produced by astrocytes (Christopherson et al. 2005). TSP1 interacts with the integrin-associated protein CD47, which is regulated by signal regulatory protein (SIRP)α, a transmembrane protein expressed by neurons and macrophages (Matozaki et al. 2009). The SIRPα-CD47 complex is involved in the regulation of migration and phagocytosis, immune homeostasis, and neuronal networks, playing homeostatic roles in the immune system, and participating in synaptic patterning (Umemori and Sanes 2008). Microglia also serve roles on the functional maturation of synapses (Paolicelli and Gross 2011). Behavioral abnormalities, including impairment of social interaction and autistic-like behavior (Tang et al. 2014; Zhan et al. 2014) have been reported on several models of microglial cell dysfunction.

Participation of Microglia in Adult Life

As the name implies, surveillance microglia actively survey the parenchyma, to rapidly activate upon appearance of a threat to the CNS. Microglial activation in response to various stimuli correlates with conspicuous morphological changes. Microglia reduce the complexity and shortens their branched processes (Fig. 2). Several stages can be identified, including process withdrawal, and formation of new processes allowing mobility in the tissue (Lynch 2009; Stence et al. 2001; Streit et al. 2005).

Microglia is a nonhomogeneous population, their activation being a highly regulated process. Thus, activated microglia can acquire distinct functional states (Hanisch and Kettenmann 2007; Perry et al. 2007; Perry and Holmes 2014; Schwartz et al. 2006). Activation is not an all-or-none process, but varies depending

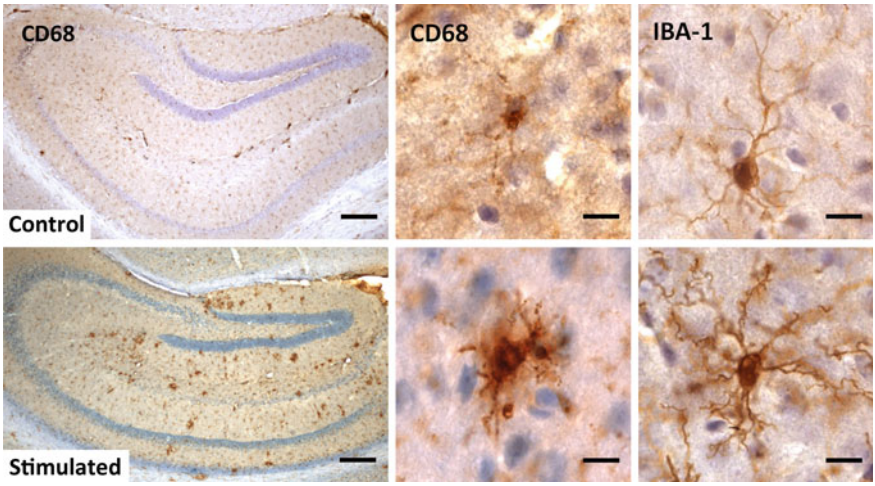

Fig. 2 Inflammatory activation-dependent morphological changes of microglia. Immunohistochemical labeling of the constitutive identity marker Iba-1 and the phagocytic activation-specific marker CD68, and counterstaining with Harris Haematoxylin, of hipocampal cryosections obtained from inflammatory unstimulated and stimulated young mice. Low (4×) magnification microphotographs of hippocampal section labeled with CD68 show slender-shaped microglia evenly distributed. In contrast, the distribution of microglia in the hippocampus becomes more cluster-like. At high magnification, activated microglia shows shorter sturdier processes. CD68-labeled microglia show an amoeba-like shape with a big cell body and very short processes, whereas Iba-1 shows many cells with long, although studier processes than those observed in unstimulated animales. Scale bar = 100 μm in the right panel and 10 μm in the higher magnification microphotographs at the left

on the stimulation context (Hanisch and Kettenmann 2007; von Bernhardi et al. 2015b; Areschoug and Gordon 2009). Multiple signals converge to maintain or change their functional state and to regulate their specific functional repertoire (Table 1). Activation is triggered when microglia detect the appearance, abnormal concentration, or altered format of molecules that serve as signals (Block and Hong 2005; Block et al. 2007; Hanisch and Kettenmann 2007). The involvement of two signaling systems has been proposed, an "on" receptor-mediated signaling corresponding to a novel molecule that is recognized by microglia triggering activation; and an "off" receptor-mediated signaling that persistently signals to maintain microglia in a certain default activation state (Biber et al. 2007; Hanisch and Kettenmann 2007; Kettenmann et al. 2011).

"On" signals include structures associated with bacterial cell walls, viral envelopes, or their DNAs and RNAs, typically identified as signs of infection. Pathogen structures are sensed through PRRs, such as TLRs (Hanisch et al. 2008) and Scavenger Receptors (SRs) (Ozeki et al. 2006; Godoy et al. 2012; Murgas et al. 2014). Molecules released after tissue damage are also signals, and they induce especially robust microglial responses (Nimmerjahn et al. 2005; Lu et al. 2010; Napoli and Neumann 2009). Intracellular proteins or serum factors can activate

microglia when they are induced upon stress, appear in new compartments or suffer biochemical modifications (Hanisch et al. 2008; Lehnardt et al. 2008; Rubartelli and Lotze 2007), as well as some neurotransmitters indicating impaired neuronal activity (Boucsein et al. 2003; Haynes et al. 2006). This, both pathogen- and damage-associated molecular patterns (PAMPs/DAMPs, respectively), activate microglia.

The "off" receptor-mediated signaling is due to the loss of constitutive control signaling in the normal CNS, as observed with ligand-receptor systems CD200-CD200R, CX3CL1- CX3CR1, and CD172a-CD47 (Barclay et al. 2002; Brooke et al. 2004; Cardona et al. 2006; Hoek et al. 2000). Thus, the "on signals" are identified as a sign of threat to the CNS homeostasis. Whereas in the "off signal," the loss of regulation is the signal.

The CNS show regional variations in glial and neuronal cell populations as well as in their environment. For example, the different vulnerability of CA1 versus CA3 neurons depends on the regional microglia response upon stimulation (Hanisch and Kettenmann 2007), with hippocampal neuronal cell death and glial activation depending on the chemokine/receptor system CXCL10/CXCR3 (van Weering et al. 2011).

As discussed in Chapter "Glial Cells and Integrity of the Nervous System," acute self-limited activation of microglia should be deemed as protective, given microglia primarily support and protect the structural and functional integrity of the CNS. Although research has mostly focused on the detrimental consequences of microglia-mediated neuroinflammation, and their potentiation of neuronal damage, it is now accepted that microglia activation is important for protection and repair of the diseased and injured brain. However, the final outcome will depend on the environmental context and timeframe of action (Hellwig et al. 2013; Kierdorf and Prinz 2013; von Bernhardi et al. 2015b). When encountering a mild injury or impairment, microglia could act immediately to repair and offer trophic support, and even reduce activating synaptic input by remodeling synapses (Trapp et al. 2007; Wake et al. 2009). However, the everyday activity of microglia is very difficult to assess (Hanisch and Kettenmann 2007). Thus, in general there is much more evidence on the failure and harmful contributions of microglia than on their physiological roles.

Microglia serve several functional roles, modulating neuronal activity and viability in culture and in the adult brain through direct contact with neurons (Li et al. 2012; Kohman et al. 2013) and through their release of soluble mediators, including cytokines and reactive species (Herrera-Molina and von Bernhardi 2005; Ramírez et al. 2008; Ramirez et al. 2005; Tichauer et al. 2007; von Bernhardi and Eugenin 2004; Glass et al. 2010; Di Filippo et al. 2010; von Bernhardi and Eugenin 2012).

Microglia play an active role in the functional integrity of the CNS and its normal physiological performance even affecting learning and behavior (Ziv et al. 2006; Ziv and Schwartz 2008), through their effect, together with T cells, at various levels. Both synaptic contacts and neuron trophism could depend on factors produced by activated microglia. Microglia express several neurotrophins (Elkabes et al. 1996; Kim and de Vellis 2005; Ferrini and De Koninck 2013), releasing many

factors with powerful neurotrophic actions (Morgan et al. 2004). A number of cytokines appear to have roles in the maturating CNS. In the adult CNS, IL1 drives astrocytes proliferation in response to injury (Giulian et al. 1988).

Microglia also contribute to the plasticity of the CNS through support of neurogenesis in adult individuals (Butovsky et al. 2006; Ziv et al. 2006; McPherson et al. 2011; Ekdahl et al. 2003), which appears to depend on certain subpopulations of microglia (Ribeiro Xavier et al. 2015). Microglia have neurotransmitter receptors and are responsive to serotonin (5-HT) (Pocock and Kettenmann 2007) and cytokine levels, and can influence precursor cells, showing a positive regulation of neurogenesis by 5-HT and a negative regulation by stress and elevated glucocorticoids (Kempermann 2002; Kempermann and Kronenberg 2003). Thus, under certain conditions, microglia can adopt a pro-neurogenic phenotype, which involves the expression of neurotrophins and regulatory cytokines, such as insulin-like growth factor 1 (IGF1), BDNF, and IL4 (Parkhurst et al. 2013; Chen and Trapp 2015; Ribeiro Xavier et al. 2015). However, in inflammatory activation states, microglia consistently appears to inhibit neurogenesis (Monje et al. 2003; Nakanishi et al. 2007).

Similar to the synaptic pruning observed during development, microglia keep a structural role in circuit refinement throughout life. The role of microglia in removing synapses, is known as "synaptic stripping." It is also observed in response to focal inflammation (Trapp et al. 2007). The "stripping" predominantly removes excitatory glutamatergic synapses, thus limiting neuronal excitability and glutamate excitotoxicity (Linda et al. 2000). Microglia scan synapses, establishing contacts with them that last a few minutes. In ischemia, contacts become longer, lasting for around an hour (Wake et al. 2009). These long lasting interactions often result in the disappearance of that synaptic contact. Any abnormalities in synaptic performance could activate microglia. However, the signal for microglia to remove a synapsis is poorly understood. The specificity of this action is associated with major histocompatibility complex (MHC) class F receptors, which are present in both neurons and microglia (Cullheim and Thams 2007) (see Chapter "Purine Signaling and Microglial Wrapping" for further reading on synaptic stripping).

Participation of Microglia in Pathophysiological Conditions

Both the absence of protective functions served by microglia, or their abnormal or excessive activation (von Bernhardi 2007; von Bernhardi et al. 2015b), could led to functional impairment and eventually to development of a disease of the CNS. The relevance of microglia activation and subsequent proliferation in aging, in which condition they adopt an "activated-like" morphology (Fig. 3; see Chapter "Age-dependent Changes in the Activation and Regulation of Microglia" for further reading on aging) (Conde and Streit 2006; Gavilan et al. 2007; von Bernhardi 2007; von Bernhardi et al. 2015b) as well as in many pathological contexts have been discussed over the past years (von Bernhardi et al. 2010; Heneka et al. 2014; Perry

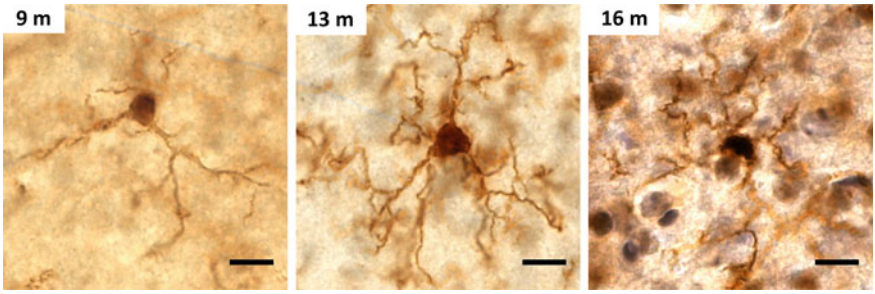

Fig. 3 Activation of hippocampal microglia with aging. Hippocampal cross section obtained from 9-, 13-, and 16-month old mice were labeled for Iba-1 and counterstaining with Harris Haematoxylin, a monocyte-macrophage identity marker that labels constitutively microglia, to compare the morphological features as the animal ages. At 9-months-old animals, microglia have long and ramified processes, which persisted at 13 months of age. In contrast, microglia from 16-month-old mice begins to shorten their processes, which become sturdier and the cell body increases in size. Scale bar = 10 μm

and Holmes 2014; Heneka et al. 2015; Hu et al. 2015; von Bernhardi et al. 2015a; Yirmiya et al. 2015).

Any disturbance on brain homeostasis, as observed in infection, trauma, ischemia, altered neuronal activity, and both acute and chronic neurological injuries and diseases, induces profound changes in microglial cell shape, gene expression and functional behavior in which is defined as microglial cell activation (Hanisch and Kettenmann 2007; Block et al. 2007; Colton and Wilcock 2010; Colton 2009; Davoust et al. 2008; Graeber and Streit 2010; Streit et al. 2005; van Rossum and Hanisch 2004). Activated microglia show enlarged cell bodies and short and sturdy processes (Fig. 2). They can become motile and be actively recruited to the injury site following chemotactic gradients, and can also increase their proliferation. This phenotype is also correlated with functional changes occurring in complex and broad spectrum responses (Table 1). The range of microglial cell activities covers induction and release of multiple factors with inflammatory and immunoregulatory effects, phagocytotic activities to clear debris, damaged cells, or pathogens, production of neurotrophins and interaction with damaged neurons. Inflammatory response goes from responses centered around the production and release of inflammatory cytokines, such as TNFα, IL1β, and IL6 to release of factors with an anti-inflammatory effect (Casano and Peri 2015; Hu et al. 2015; Chen and Trapp 2015). Although some authors consider inflammatory microglia as detrimental, and anti-inflammatory regulatory microglia as neuroprotective, this rigid classification fails to recognize the complexity of microglial cell function and regulation (Fenn et al. 2014). Furthermore, regulatory microglia do not show always neuroprotective effects (Cherry et al. 2014).

The role of microglia-mediated phagocytosis in neurodegeneration has been established by several experimental approaches. Microglia are needed for removal of the dendritic trees of interneurons in the dentate gyrus after entorhinal cortex

lesions (Rappert et al. 2004). In response to the lesion, microglia accumulate at the molecular layer in the dentate gyrus, mediated by signaling through the chemokine receptor CXCR3. Deletion of CXCR3 results in the failure of microglia recruitment, and the dendritic trees of interneurons are preserved.

Microglia also phagocytose molecules and debris such as myelin or amyloid deposits. Several studies report that Aβ is taken up by microglia in culture through mechanisms depending on Scavenger Receptors (Koenigsknecht and Landreth 2004; Alarcón et al. 2005; Cornejo and von Bernhardi 2013; Murgas et al. 2012), among others.

As discussed in Chapter "Age-dependent Changes in the Activation and Regulation of Microglia," there is increasing evidence for altered chemokine signaling in diverse CNS diseases such as Alzheimer's disease (AD) or multiple sclerosis (Gebicke-Haerter et al. 2001; Trebst et al. 2008) which may involve microglia activation (Stewart et al. 2010). Microglial cells from AD brains may have elevated levels of CCR3 and CCR5 receptors (Gebicke-Haerter et al. 2001). CXCL10 and its receptor CXCR3 have been linked to various CNS pathologies (van Weering et al. 2011). Studying the mechanisms by which this system mediates *N*-methyl-d-aspartate (NMDA)-induced neuronal toxicity in the hippocampus, the authors demonstrated that astrocytes and microglia cooperate to deliver the effect and that the deficiency in either the ligand or the receptor diminished or enhanced cell death depending on the tissue subregion and that microglia was the responsible cellular element by which this difference in neuronal vulnerability is organized.

A mechanism involving microglia, astrocytes, and chemokines has been proposed for glutamate toxicity (Bezzi et al. 2001). Binding of CXCL12 (stromal cell-derived factor, SDF-1α) to its receptor CXCR4 in astrocytes, results in Inositol trisphosphate (InsP3) production, $[Ca^{2+}]i$ increase, and release of TNFα. The binding of TNFα to its receptor triggers signaling, through autocrine a paracrine mechanism that causes prostaglandin E2 (PGE2) production. The PGE2, in turn, induces the release of glutamate, which can participate in glia-glia or glia-neuron communication, but can also initiate neurotoxicity. In the latter situation, SDF-1α would also act on microglia, thus driving enhanced TNFα release from both glial populations and ultimately causing massive glutamate release.

AD is associated with a significant elevation of TLR expression in the brain (Letiembre et al. 2009; Walter et al. 2007). Treatment with Aβ potentiated TLR2 and TLR4-mediated responses, while inhibiting TLR9 in mouse microglia cultures, (Lotz et al. 2005). At the same time, all three receptors (TLR2, TLR4, and TLR9) stimulated the uptake of Aβ by microglia (Tahara et al. 2006). The levels of TLRs in CNS are generally upregulated in many neurodegenerative diseases, including multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (Okun et al. 2009).

Microglia activation, in turn, upregulates the synthesis of TLRs (Kielian et al. 2005; McKimmie and Fazakerley 2005). Similarly, the levels of TLRs in microglia are increased following hypoxia (Ock et al. 2007) and cerebral ischemia (Ziegler et al. 2007) and by inflammatory processes; for example, TNFα stimulates expression of TLR2 in cultured mouse microglia (Syed et al. 2007).

TLRs also regulate microglial death following pathological activation. TLR4 triggers microglial apoptosis via autocrine production of interferon gamma (IFNγ), whereas TLR2 is coupled to caspase-8-dependent apoptotic pathways (Lehnardt et al. 2007). Similarly, TLR2 participate in microglial apoptosis following human immunodeficiency virus (HIV-1) infection (Aravalli et al. 2007a, 2008).

A link of neurodegenerative processes in AD to microglial TLR4 is suggested because Aβ fibers bind to CD14, the co-receptor for LPS signaling via TLR4 (Fassbender et al. 2004). CD14 and TLR-dependent mechanisms appear to promote Aβ clearance and participate in inflammatory responses of microglia (Fassbender et al. 2004; Landreth and Reed-Geaghan 2009; Reed-Geaghan et al. 2009; Tahara et al. 2006). Pronounced CD14 immunoreactivity is observed in microglia close to AD lesion sites in AD brains (Liu et al. 2005). Importantly, a microglial CD36-TLR4-TLR6 complex appears to promote inflammation in response to Aβ (Stewart et al. 2010).

However, TLR signaling can also be neuroprotective, by both driving clearance of infectious agents, and by organizing CNS-intrinsic as well as immune system-mediated support of neural cell survival, tissue preservation, and CNS functioning (Glezer et al. 2007; Hanisch et al. 2008). Thus, a critical issue is to understand the mechanisms by which TLRs could engage in detrimental or in beneficial programs.

Concluding Remarks

Microglia affects the development, structure, and function of neuronal networks. They constantly monitor the status of synaptic contacts and receive information from neuronal activity. Multiple activation states of microglia may allow for the existence of microglia with different functions, which dynamically interact with neurons and potentiate their plastic capabilities. Furthermore, they appear to be also able to remodel neuronal connectivity and thus participate in physiological processes.

Commitment to distinct reactive phenotypes depending on their activation profile would then have a variable effect on neurons. It will be important to identify the nature of such instructing signals as they govern functional orientations of microglia. Little is also known about the heterogeneity of microglia, i.e., the differences in functional capacities of individual microglial populations within different CNS regions. Finally, in pathological situations with blood-derived monocytes/macrophages infiltrating the CNS, features and functions of resident microglia and the newly invading cells may complement each other, with both detrimental and beneficial consequences (Shechter et al. 2009; Simard et al. 2006). Understanding this various issues will be especially interesting to develop migroglia-based strategies for the management of several impairments of the nervous system.

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