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Review

Microglia at center stage: a comprehensive review about the versatile and unique residential macrophages of the central nervous system

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ABSTRACT

Microglia cells are the unique residential macrophages of the central nervous system (CNS). They have a special origin, as they derive from the embryonic yolk sac and enter the developing CNS at a very early stage. They play an important role during CNS development and adult homeostasis. They have a major contribution to adult neurogenesis and neuroinflammation. Thus, they participate in the pathogenesis of neurodegenerative diseases and contribute to aging. They play an important role in sustaining and breaking the blood-brain barrier. As innate immune cells, they contribute substantially to the immune response against infectious agents affecting the CNS. They play also a major role in the growth of tumours of the CNS. Microglia are consequently the key cell population linking the nervous and the immune system. This review covers all different aspects of microglia biology and pathology in a comprehensive way.

INTRODUCTION

Microglia cells belong to the innate immune system and are the resident tissue macrophages of the central nervous system (CNS), including the brain, the spinal cord, the retina and the olfactory bulb. The term "microglia" was coined by Del Rio-Hortega in the first half of the 20th century [1]. More recently, the embryonic yolk sac macrophages have been identified as microglia precursors that migrate into the CNS [2]. Microglia have a multitude of functions, including support of CNS development and synaptogenesis, sustaining homeostasis and structure, contribution to an immune response against infectious agents and participation in adult neurogenesis, neuroinflammation, degenerative diseases, stroke, trauma and regeneration [3]. Resting ramified microglia build a dense steady-state network of dynamic and reactive cells throughout the nervous tissue that they monitor, scan and control [4]. They interact with all different cell types of the CNS, including neurons [5, 6] and oligodendrocytes [7]. They are important phagocytes and essential for the development of the CNS, as they eliminate apoptotic neurons, produce growth factors and contribute to function and structural organisation of the nerve tissue [8, 9]. Later in life, microglia play a major role in adult neurogenesis [10] and in remodelling of the CNS, especially by contributing to synapse structure and function [11, 12]. Various danger signals can activate microglia, including intrinsic factors derived from cellular and tissue damage, like stroke [13–15] and traumatic injury [16], as well as extrinsic inflammatory factors like cytokines or microbial products [17, 18]. Thereby, microglia responses may be very diverse with a broad range between the two opposite functions, i.e. pro-inflammatory and pro-regeneration responses [19–26]. Microglia often change shape upon activation and may even become migratory [27]. However, activated microglia are the major players in neuroinflammation with possible induction of substantial damage to CNS function and structure. In addition, microglia play an important role in various CNS diseases, including encephalitis [28], Alzheimer's [29–31] and Parkinson's disease [32], multiple sclerosis (MS) [33], amyotrophic lateral sclerosis (ALS) [34] and even in mental conditions [35]. Microglia help to sustain the

blood-brain barrier (BBB) and upon activation are often responsible for its functional and structural disruption [36, 37] with consecutive invasion of various immune cell types into the CNS [38–41], including blood monocytes [42], granulocytes [43] and lymphocytes [44]. In addition, chronically activated microglia may also be responsible for age-related cognitive and structural decline of the brain [45]. Microglia play also a major role in the immune response against infectious agents that invade the CNS, including viruses [46, 47], bacteria [48] and parasites [49]. Microglia have also a major contribution to development and growth of primary brain tumours, including glioma and glioblastoma, as well as tumour metastasis [50]. Due to the emerging importance of microglia in health and disease of the CNS, various *in silico*, *in vitro* and *in vivo* research models have been developed [51], which resulted in the generation of plenty of new recent knowledge [52] that is to be translated into various promising therapeutic approaches [53]. This review covers all the issues mentioned above, but focusing on immune, infection and inflammatory perspectives. It includes up-to date review articles for important subtopics that are not covered in detail and original research articles for emerging topics. It also emphasizes gaps of knowledge, raises important research related question and suggests areas where more research work may be required.

Origin of microglia and their role in brain development, synapsogenesis and adult neurogenesis

Microglia are the tissue macrophages of the CNS and serve initially its development and subsequently its homeostasis [54, 55]. The origin of microglia has only recently been discovered [2, 56]. Specialized precursor yolk sac macrophages [57–59] migrate at an early embryonic stage into the developing CNS within a limited time frame, once the cardiovascular development has started [60] and before the blood-brain barrier is closed [61]. Expression of transcription factor PU.1 is essential and defines the microglia lineage, which separates them from other tissue macrophages [62, 63]. Most studies have been done in mouse models, where microglia populate the developing CNS at around E8.5 to E9.5, even before astrocytes and oligodendrocytes emerge [64, 65]. More recently, also zebrafish has been used as a model to study microglia in the embryo, where colonisation takes place around 48hpf [66–70]. Much less is known about early microglia colonisation of the CNS in humans [71, 72].

Expression of the colony-stimulating factor 1 receptor (CD115, M-CSFR, c-*fms*) [73] and the corresponding ligands CSF-1 (M-CSF) and/or IL-34 [74] are essential for the maintenance and expansion of microglia [73, 75]. In addition, GM-CSF and its receptor, as well as neurotrophins sustain survival and proliferation of microglia [76–78]. Initially, neuronal cells provide these factors, before later emerging astrocytes also contribute to their production. However, little is known about spatial expression patterns and the regulation of these factors in the CNS.

Microglia have multiple functions in the developing CNS [8], as they contribute to (1) elimination of apoptotic cells and preventing oversupply of neurons, (2) support of neurogenesis, migration and differentiation of neurons, (3) axon growth and synaptogenesis, (4) generation and maturation of astrocytes and oligodendrocytes and (5) angiogenesis (Figure 1). The main mechanisms for these functions are phagocytosis and cell-to-cell communication through direct intercellular contacts or via soluble mediators, which often are still not well understood at cellular and molecular level and which require more future research.

Microglia are attracted to and accumulate in locations of cell death where they engulf apoptotic cells during neurogenesis and migration, differentiation and positioning of the newly generated neurons [66, 79, 80]. Microglia phagocytosis function will be covered in more detail further down. During the early phase of development, the density of microglia is rather low, which is compensated by their increased mobility [81]. Depending on timing and developmental processes, there is a corresponding dynamic spatial patterning of microglia [82–84]. First, they accumulate around areas with proliferation of neuronal precursor cells. Then they line up along the developing axons in the white mater. Later, when neurons have formed the relevant functional structures and have built their wiring connections, supported by astroglia and oligodendroglia, microglia density increases, migration decreases and the cells become highly ramified and remain in their preferred spatial area, whereby as described for the mouse, they are not uniformly shaped across the brain regions [85]. There is a steady-state condition with dying microglia being replaced through proliferation of remaining cells [86]. Of note, the areas covered by ramified microglia do not overlap, in comparison with the area covered by astrocytes [87]. Only little is known about the factors and molecular mechanisms controlling colonisation, migration and settling of the cells, although α5β1 integrin and fibronectins, as well as γ-secretase, seem to play an important role [88, 81]. In addition, little is known about the molecular mechanisms of the interaction between microglia and neurons. However, CX3CL1 (fractalkine) that is expressed on neurons and its receptor CX3CR1 that is expressed on microglia mediate the intercellular communication [5, 89, 90]. Of note, absence or functional deficiency of microglia or the interaction between microglia and neurons result in oversupply of newly generated neurons and accumulation of apoptotic cells in the developing brain leading to functional and structural brain deficiencies [9, 91–96].

As soon as neurons have found their appropriate location, they grow their dendrites and axon, and synaptogenesis emerges, in which microglia play an important role [9, 11, 12, 97–99]. Microglia are essential for the pruning of synapsis, synaptic maturation and

the subsequent synaptic communication [4]. In the case of glutamatergic excitatory neurons, pre- and post-synaptic structures are supported and controlled by the interaction between the neurons, astrocytes and the microglia forming a quad-partite synapse [100, 101]. Interestingly, complement factors C1 and C3, as well as the corresponding receptor CR3 (also termed CD11b), which is a β2-integrin, play an important role in microglia mediated synapse modification [102], as such that astrocyte-mediated activation of C1q, the initiator of the classical complement cascade, has been suggested to result in downstream activation of C3b, which then deposits on neurites, thus "tagging" synapse for elimination [103].

Microglia link the immune system with the nerve system, but also respond to endocrine events. In that respect, immune-related or endocrine pathologies may affect microglia functions during development, leading to subsequent functional or even mental disturbance [104, 105]. For mammals, these disturbances can happen during the foetal phase in the course of maternal inflammation or infections, or subsequently because of neonatal systemic immune activation and inflammation [106–109] or stressful social events [110, 111]. Interestingly, it has recently also been proposed that a pathological gut microbiome may somehow act on microglia and their function, resulting in certain mental diseases [112, 113]. However, more neuroimmunology research is needed to get better understanding of long-term influence of microglia deficiencies and pathologies during development on post-natal and adult mental health.

After the embryonic stage, there is a natural turnover of bone marrow derived monocytes that find their way through the blood circulation into the meninges, the perivascular space of the CNS and across the choroid plexus into the cerebral liquor space, from where these monocytes may be quickly recruited into the CNS if required [114–118]. CCR2 expressing monocytes have thereby been identified as a key population that immigrate into the CNS [119], integrate within the microglia network and may no longer be separated from the resident microglia population.

Microglia also contributes substantially to adult neurogenesis [10, 120–123], which takes place in the dentate gyrus for the hippocampus [124], the subventricular zone for the olfactory system [125, 126] and in the hypothalamus for the neuro-endocrine system [127]. Life-long adult neurogenesis is required for the function of memory, olfaction, neuroendocrine system and possibly others. As for the development of the CNS, in adult neurogenesis, enhanced or reduced generation of new neurons and their integration may substantially influence the brain function [124]. Neurogenesis is influenced by microglia [128] either by producing corresponding supporting or suppressing factors, or by eliminating new neurons [129], as well as by sustaining new neurons alive. Thereby, microglia may be influenced in their function by local [130] and systemic factors [131], including fractalkine (CX3CL1) [132], TLR9 [133] and Wnt signalling [134], LPS [135, 136], progranulin [137], allergic reactions [138], systemic inflammation [139],

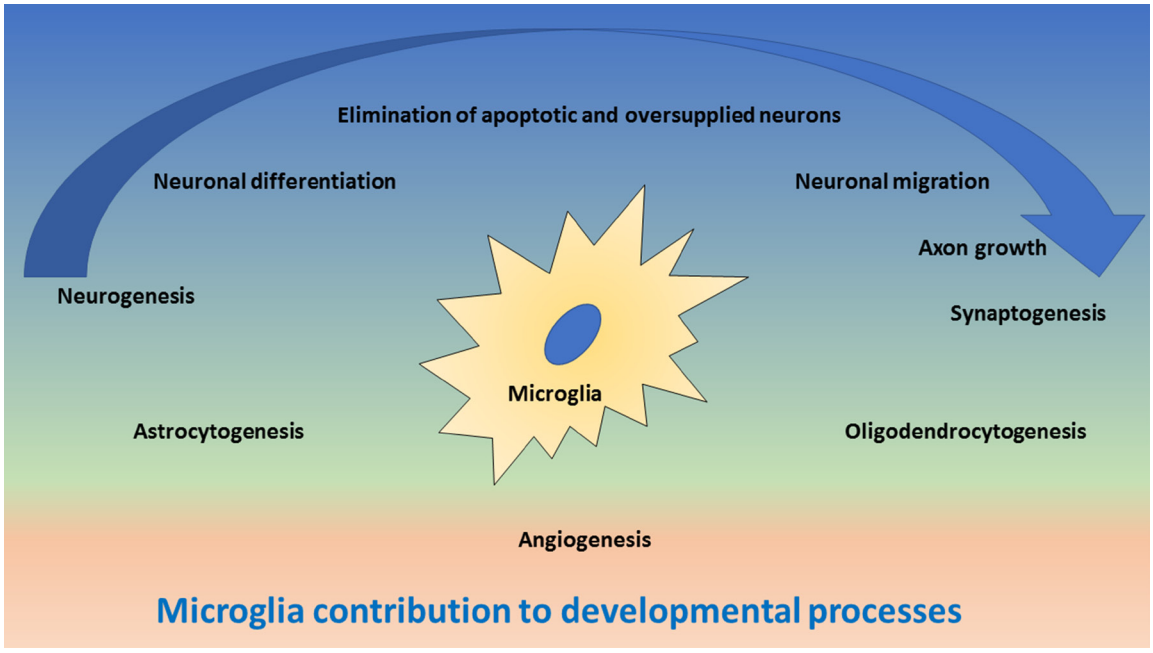

Figure 1: Schematic drawing of important functions of microglia during development of the central nervous system. In the upper blue area, the contribution of microglia to neurogenesis and synaptogenesis is depicted, including neuronal differentiation and elimination of apoptotic neurons, neuronal migration and axonal growth. The blue arrow indicates the direction of neuronal development. In the middle green area, the contribution of microglia to astrocytogenesis and oligodendrocytogenesis is depicted. In the lower red area, the contribution of microglia to angiogenesis is depicted.

vaccines [140] and vaccination [141], dietary factors [142], exercise [143] and aging [144]. Recently, there are also first experimental attempts to control the influence of microglia on adult neurogenesis via drug therapies, including with indomethacin [145] and minocycline [146]. However, more research is required to better understand the cellular and molecular mechanism of how microglia and systemic immune events influence adult neurogenesis.

Phenotype and function of microglia

Upon their discovery, microglia have been identified and differentiated from other CNS-associated myeloid cell populations morphologically through histology. Thereby complex shape and distribution patterns have been described, depending on animal species, location in the CNS and activation stage [87]. Despite their different origin by early immigration from the yolk sac, microglia share many markers with other macrophage populations, such as the blood-derived perivascular, choroid plexus and leptomeningeal macrophages, including F4/80 (Figure 2A), CD11b (Figure 2B) [118], but as microglia usually represent the majority of immune cells in the CNS, some of those markers are routinely used for their characterization [147–149]. Iba1 (ionized calcium binding adaptor molecule 1), which is highly conserved in mammals, has been useful as a specific marker for the detection of microglia, since its discovery [150, 151], as it is not expressed in blood monocytes, but often also in blood-derived tissue macrophages and dendritic cells [118, 152, 153]. Thus, to distinguish microglia from blood-derived immigrated macrophage populations, and from blood monocytes, reduced expression of the common leukocyte antigen CD45 as a marker has been suggested, although CD45 is upregulated in activated microglia [152]. More recently, a plenitude of membrane proteins has been identified in microglia. CX3CR1 (fractalkine receptor) is one important functional membrane protein, as its ligand (fractalkine, CX3CL1) is expressed on neurons [5, 90] and astrocytes [154]. CX3CR1 has been widely used as a marker for flow cytometry and immune histochemistry, as well as for developing a crucial CX3CR1-GFP mouse model, which is functionally very close to the Iba1-GFP model [155]. However, when it comes to identifying newly immigrated monocytic cells into the CNS and to differentiate them from resident microglia, reliable markers are still missing.

The transcriptome analysis of mouse microglia has revealed a unique signature for the freshly isolated brain-derived cells, whereas the cultured cells display properties of activated microglia [156]. In addition to some transcription factors (Rhox5, Cebpe, E2f6, Hoxc6, Phf17, Ppargc1b), several membrane proteins have been identified in microglia that are unique and not expressed in other macrophages, including the ion transporters Slco4a1, Slc30a5, Mcoln3, the lipid-metabolism associated cell

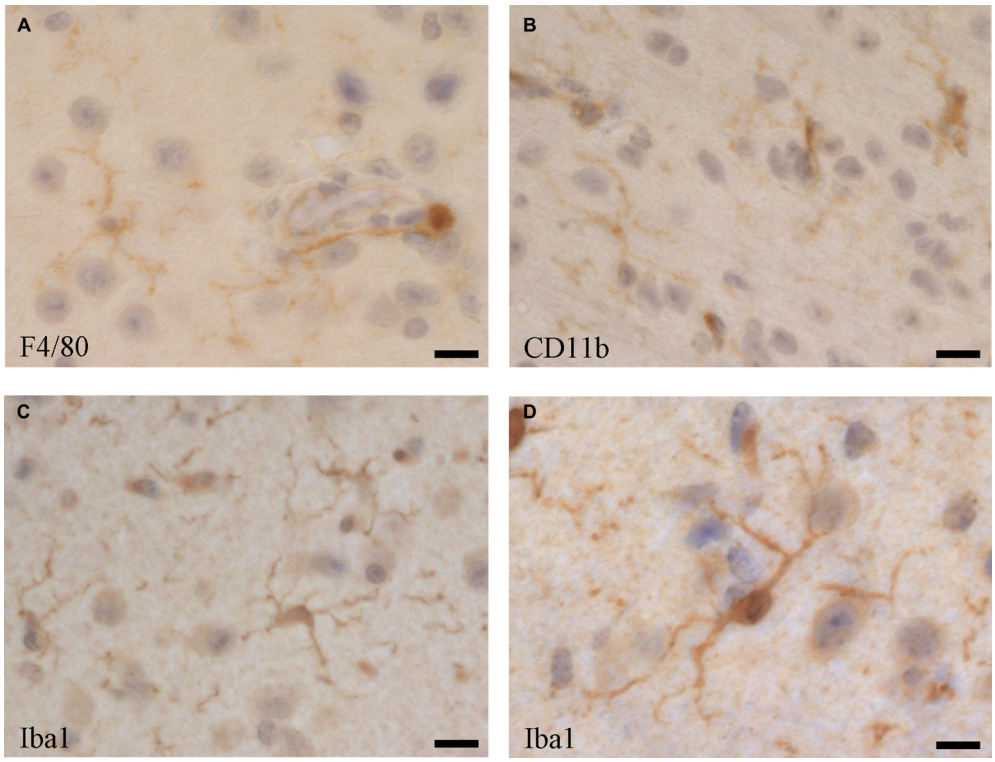

Figure 2: Microglia cells visualised by immune histochemistry in the mouse brain using antibodies directed against. (**A**) F4/80 (Serotec, Kidlington, UK, clone Cl:A3-1), (**B**) CD11b (BD Pharmingen, San Diego, USA, cat. no. 553308), and (**C** and **D**) Iba1 (Abcam, UK, cat. no. ab5076). Bars: (A and C) 25 µm, (B) 20 µm, (D) 40 µm.

membrane molecules Lrp8, Lpcat3, Stab1, Pap2c, and the putative efflux cell membrane receptor Mfsd10. Unfortunately, reliable antibodies against these proteins, for specific histological detection of microglia in the CNS, are still missing. Similar work has also been done with human brain-derived microglia, which shows substantial similarities to the mouse microglia under physiological resting conditions [157]. However, activated microglia and cells from aged individuals show significant differences between mouse and human, as well as depending on location and condition [158, 159], making comparison of transcriptome studies quite difficult [160].

Microglia build a 3-dimensional network in the CNS and they communicate also through hemichannels and gap junctions [161, 162]. The hemichannels allow secretion and uptake of glutamate and ATP, factors that are essential in the communication with neurons and astrocytes. The gap junctions allow microglia to react as a syncytium. However, the extent of such connections and their relevance need further investigation, also in respect of possible pharmacological treatment by using functional modulators or blockers.

Microglia are the professional phagocytes of the CNS. They are able to sense and take up extracellular material, like cell debris, apoptotic cells, as well as tumour cells and microbes. Consequently, they contribute substantially to the function and structure of the CNS. They express a variety of sensing and binding receptors on their surface membrane [163]. Phagocytosis is essential for the control of newly generated neurons during development and adult neurogenesis, as well as for synapse homeostasis. However, they are able to engulf whole or parts of neurons, which may become fatal if phagocytosis gets out of control and if live, functional neurons are eliminated [164–166]. Microglia use a variety of receptors for the recognition of molecules, particles and cells that they engulf [167]. Sialic acid binding immunoglobulin-like lectins (Siglecs) are important regulatory receptors expressed on microglia and binding to sialated ligands on neurons or CNS tumor cells [168–171]. Siglecs signaling modulates activation of microglia and thus also phagocytosis activity. Although they also serve as binding receptors, signaling through SIRPα (signal-regulatory protein alpha; CD172a), complement receptor 3 (CR3; CD11b), LRP (low-density lipoprotein receptor-related protein; CD90.2) and TREM2 (protein triggering receptor expressed on myeloid cells-2) also modulates phagocytosis by microglia, indicating that live neurons can control phagocytosis through expression of corresponding ligands [165, 172–179]. On the other hand, activated microglia secret inflammatory cytokines or other mediators that are able to regulate expression of those ligands on neurons, which may eliminate live and functional neurons and induce disease. Consequently, fine-tuning of the balance between eat-me and don't-eat-me signals, in the interaction between microglia and neurons, controls for whether neurons are engulfed and eliminated, or not [164]. Interestingly, there seem to be sex and age differences, when it comes to microglia functions, including phagocytosis, although the mechanisms are not well understood [180, 181]. For instance, in experimental autoimmune encephalomyelitis (EAE) mouse model for MS, which may present with reduced relapses during pregnancy, estrogen was found to promote anti-inflammatory, protective and regenerative microglia [182, 183]. Further, in experimental stroke, smaller infarcts and anti-inflammatory microglia were observed in female, but not in male mice [184]. Thus, phagocytosis by microglia is crucial for function and structure of the CNS, as well as in many pathologies. Therefore, more research on this topic is required in the future.

Continuous and sufficient blood supply to the CNS is essential and disruption of perfusion results in subsequent damage of function and structure [185, 186]. Regional perfusion of the CNS is tightly regulated at capillary level depending on oxygen and energy needs by the local neurons, which control regional perfusion indirectly via astrocytes. However, the molecular mechanisms for the regional perfusion control are still not well understood. Most important is also the tight separation of the CNS tissue and intercellular space from the intravascular space, which is given by the blood-brain-barrier (BBB) [187, 188]. The BBB is important to keep serum proteins (e.g. complement system, antibodies, etc.) and a plenitude of soluble factors (e.g. cytokines, microbial products, etc.) in the blood circulation out of the CNS tissue, as many of those factors induce immediate and strong activation of microglia that results in devastating neuroinflammation [189, 190]. In mouse, the CNS vascularisation starts at about E8 by endothelial cells forming a capillary network, at around the same time of microglia colonisation, but before astrocytes emerge. However, CNS pericytes that stabilise the endothelial capillaries emerge around the same time [191]. Yet unknown neuronal factors and the pericytes control differentiation of CNS capillary endothelial cells and thus the formation of the first line of the BBB by increasing the tight connections between endothelial cells and by forcing them to establish limited, CNS-specific transcytosis. The functional capillary system, forming the internal part of the BBB, is composed of a continuous layer of endothelial cells interconnected through tight junctions and enclosing the lumen containing the blood. A distinct continuous basal lamina surrounds the endothelial cells in which pericytes are embedded without forming a continuous layer [192]. The basal lamina and the pericytes form the perivascular space which may also contain immune cells, including macrophages, often referred to as perivascular microglia, and lymphocytes. The perivascular space is peripherally completely covered by endfoot processes of the astrocytes forming the glia limitans, a second, external closure of the BBB interconnected through yet unknown adhesion

molecules [193, 194]. Occasionally, also processes of microglia also contribute to the glia limitans layer, called the juxtavascular microglia. Whereas the astrocytes control the transport of nutrients, oxygen and other molecules between the blood vessels and the neurons, the role of the perivascular and juxtavascular microglia is not well understood. However, they may monitor the interface between the first inner and second outer line of the BBB, and consequently mediate between the blood and the CNS environment, and vice-versa. Most important, activated microglia opens up the BBB by releasing inflammatory factors, resulting in enhanced neuroinflammation, by allowing serum components and immune cells entering the CNS tissue [36, 195, 196]. As most recently described [197] in healthy condition, the endothelial BBB is closed and enforced by claudin (CLDN) 5 and . In inflammation, the endothelial part of the BBB downregulates CLDN5 and opens towards the perivascular space, while the astrocytes of the glia limitans upregulate CLDN1, CLDN4, and junctional adhesion molecule A (JAM-A), and forms an enhanced second barrier, composed of reactive astrocytes with tight junctions containing CLDN1, CLDN4 and JAM-A subunits. Enhancement of the second barrier has been attributed to local microglia secreting IL-1β, a driver cytokine of lesion pathogenesis in multiple sclerosis and the corresponding EAE model. In addition to inflammatory diseases of the CNS, stroke and trauma of the CNS are extreme cases of the breakdown of the BBB with subsequent substantial activation of microglia [37, 198, 199]. Activated perivascular microglia may also be able to control repair of the damaged BBB [200, 201], as well as to induce or support angiogenesis, which is important in CNS tumours [202, 203] and vascular pathologies of the retina [204–207]. First experimental therapeutic approaches have been suggested [208], but more research is required. Substantial research of this topic has used live animal imaging [209, 210], often the retina model, as the blood vessels of the eye are easily monitored. However, more *in vivo* research about the influence of microglia on the BBB would be needed and new models ought to be developed.

Activation of microglia and their role in neuroinflammation, neurodegenerative conditions, mental diseases, aging and gender

Under physiological conditions, ramified, resting microglia provides a neuroprotective environment [211, 212]. However, most CNS pathologies, as well as regenerative efforts, include activation of microglia with corresponding inflammatory events (Figure 3) [213, 214]. Activated, inflammatory microglia are thus neurotoxic and kill neurons by engulfing them or releasing various neurotoxic molecules and factors, including reactive oxygen species (ROS), glutamate, Fas-ligand, tumour necrosis factor α (TNFα) and others [215–218]. On the other hand, activated neuroprotective microglia may secrete neurotrophins that support neuroregeneration [219]. Of note, microglia do not act on their own, but they coordinate their action with astroglia [27, 220]. Recently, a new type of microglia has been described under pathological conditions named the ¨dark microglia¨, due to their characteristic dark appearance in electron microscopy because of ultrastructural changes, which are proposed to reflect oxidative stress in a particularly hyperactive subset of microglia [221]. Morphologically, microglia activation results in increased dynamics of the cell processes that are extended and retracted according to corresponding signals. In addition, the cells may give up their home location and migrate towards the area of action close by, where they may accumulate and may form a protective enclosure around the pathological or damaged area usually seen around damaged CNS tissue after trauma or amyloid-β plaques in Alzheimer's disease [222, 223]. Similar to other tissue macrophages, microglia change upon activation the pattern of surface proteins and secrete various soluble factors [224]. In addition, phagocytosis is upregulated upon activation. Depending on continuous presence or absence of the cause for the activation, or on clearance of the problem, microglia may either display the inflammatory properties and remain chronically activated, or they may change towards a protective phenotype and function where they support tissue repair and restoration of structure and function of the CNS [20, 225, 226]. Interestingly, severe local or systemic events, external to the CNS, like systemic inflammation or bacterial infection with sepsis can open and cross the BBB and subsequently activate microglia [18, 227] and interfere with ongoing CNS processes [228]. On the other hand, activation of microglia and neuroinflammation may also result in the break-down of the BBB and corresponding leakage of complement into the CNS, which results in enhanced activation of microglia and neuroinflammation [229]. However, chronic neuroinflammation may result in neurodegenerative diseases.

Microglia express various pattern recognition receptors (PPRs) for sensing endogenous danger-associated molecular patterns (DAMPs: e.g. heat shock proteins) [230] and exogenous pathogen-associated molecular patterns (PAMPs: microbial proteins, saccharides, lipids, RNA and DNA) [231]. Toll-like receptors (TLRs) are such PPRs, transmit danger signals and strongly activate microglia in the context of CNS damage or infection [232, 233]. Interestingly, galectin-3 (Gal3) secreted by activated microglia is also a ligand of TLR4, which may result in chronic activation of microglia [234]. Amyloid-β, which is found in the context of Alzheimer's disease, as well as prions also activate microglia [235]. It has also been shown that chromogranin A, released by stressed neurons and recognized by scavenger receptors on microglia results in their activation [217]. Inflammatory activation signals in microglia are

then integrated in the inflammasome [236], which results in activation of transcription factors for the transcription of inflammatory genes [237]. Microglia activation can be such a deleterious and destructive event by harming structure and function of the CNS that many regulatory mechanisms ought to be built in this process, of which few have recently been discovered, including TREM2 [238, 239]. Interestingly, upregulation of macrophage colony-stimulating factor receptor (CD115, M-CSFR; c-*fms*) on microglia makes them rather neuroprotective [240], as well as signalling through P2X7 receptor [241]. Like for most immune cells, microglia respond to metabolic and energy-related events and activation results in metabolic reprogramming of the cells [242], which interestingly differs between different activation stages [23], which allows accordingly more detailed differentiation between microglia activation stages. In addition, chronic activated microglia may have substantial epigenetic changes of their chromatin, which may then be difficult to reverse [243].

Trauma of the CNS is a frequent pathology, including traumatic brain (TBI) and spinal cord (SCI) injury. Severity of the damage can range from very minute, e.g. in contusion, to substantial tissue damage resulting in deleterious loss of function, including paresis, paralysis and hemi- or tetraplegia. Microglia are immediately activated in such an event [26] and they try at first to enclose the damage and minimise the spread of it [223]. However, strong activation of microglia may damage viable neighbouring neurons [244]. In the course of the response to injury, microglia contribute first to cleaning debris [245] and later to tissue repair, usually resulting in non-functional scar tissue [21, 27]. Interestingly, minor recurrent trauma like concussion during sport (boxing, soccer, etc.), or injury in a distal CNS region, may also activate microglia in otherwise healthy tissue and result on a longer term in substantial mental disease or chronic pain [246, 247]. One has also to consider that injury breaks down the BBB and allows immigration of blood derived immune cells, including macrophages and lymphocytes that contribute to the acute inflammatory reaction and subsequent tissue repair [16, 248]. Various factors known to contribute to induction and regulation of neuroinflammation, as well as to tissue repair are involved in the course of CNS injury, including CX3CR1-CX3CL1 that mediate communication between microglia and neurons or astrocytes [249]. However, the detailed molecular mechanisms and the extent of the role of microglia in CNS trauma and repair are still not well understood and need further future research [250].

CNS ischemia and stroke are events with similar tissue responses seen in traumatic injury of the CNS, although the cause is different. Correspondingly, microglia reacts very similarly to tissue damage and similarly supports tissue repair mechanisms [13–15, 251–254], also including immigration of peripheral blood leucocytes [255, 256]. Most important is of course to consider

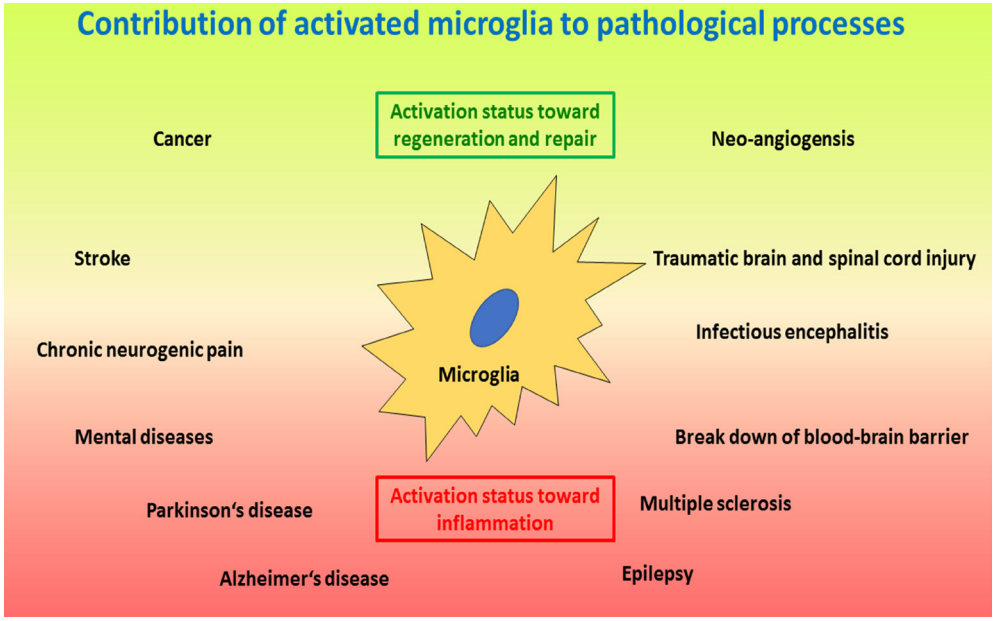

Figure 3: Schematic drawing of important processes where activated microglia play a crucial role. The lower red area depicts pathologies induced and/or sustained by microglia activated along the inflammatory and neurotoxic pathway, including neurodegenerative and autoimmune-like diseases, as wells as neurogenic pain, infectious encephalitis and break-down of the blood-brain barrier. The upper green area depicts microglia activated along the regenerative pathway where the focus is on tissue repair, including injury and repair, as well as tumour growth and angioneogenesis. Of note, microglia activation status can be different at different locations at the same time. In addition, microglia activation status may change from one polarized status to the other polarized status over time for certain pathologies; e.g. in infections at first the inflammatory status is required to eliminate the infectious agent, whereas later a regenerative status will support repair of damage caused by the infection.

the underlying systemic metabolic and inflammatory condition, usually contributing to the cardiovascular disease and subsequent stroke, which may also influence microglia response to ischemia and tissue damage and which increases the complexity of the pathology of stroke [257, 258].

Activated microglia driving chronic neuroinflammation have also been shown to substantially contribute to aging of the CNS [259, 260], epilepsy [261], chronic neuropathic pain [262], mental diseases [35, 263, 264] and neurodegenerative diseases, including Alzheimer's disease [222], Parkinson's disease [265], amyotrophic lateral sclerosis (ALS) [34] and multiple sclerosis [33]. Aging goes in parallel with systemic chronic activation of the immune system and polarization towards a low-level inflammatory status [266, 267]. This process also affects the CNS and thus microglia [259, 268], which interferes with CNS homeostasis, especially adult neurogenesis [269], the function and structure of myelination [270] and synapses, as well as the BBB. Mental and neurodegenerative diseases have then probably to be seen as focal processes of age-related activated and dysfunctional microglia [45, 271–274]). However, better understanding of the molecular and cellular mechanisms in the activation of microglia and the regulation of inflammatory processes in the CNS is required and more research is therefore needed in these areas of neuroimmunology.

The role of microglia in viral encephalitis and in brain tumours

Virus infections are the most frequent reason for encephalitis. A variety of viruses affect the CNS and induce encephalitis, including flaviviruses such as Dengue [275, 276], hepatitis C [277], Japanese encephalitis [278, 279], West Nile [44] and Zika [280–282], as well as herpes viruses such as herpes simplex [283], varicella Zoster [284] and Kaposi's sarcoma associated herpes virus [285], as well as HIV [286, 287]. All the viruses mentioned above may infect microglia [276–278, 280, 281, 288], whereas flaviviruses and herpes viruses, but not HIV [289], may also infect neurons and/or astroglia. Infected neurons and astroglia usually respond with inflammatory signals that activate surrounding microglia. Infected microglia are usually also activated and may substantially contribute to the anti-viral immune response in the CNS, which results in the recruitment of blood monocytes and T-lymphocytes and in the clearance of the virus. Virus-dependent neuroinflammation often results in the local break-down of the BBB. However, damage of the BBB may not be the initial event for the transmission of the virus from the blood to the CNS tissue and cells, but other mechanisms can be involved. E.g. in the case of Japanese encephalitis, somehow astrocytes and microglia are first infected, before the BBB opens up [290]. Thus, the virus could either get into the CNS via infected capillary endothelial cells which release infectious viral particles towards the CNS, or via infected leucocytes (in HIV) [291] that enter into the CNS and transmit the virus to susceptible microglia [292]. There is also a broad variety of reactivity between different individuals in humans, resulting in a broad spectrum between low and severe neuroinflammation and neuronal infection and cell death. Correspondingly, the infection outcome may vary between asymptomatic and fatal consequences, with a broad spectrum between minor mental disorder and severe cognitive deficiencies. Viral infection of the developing CNS results usually in severe malformation which may even result in a non-viable foetus and thus lead to abortion, as it has been recently documented for Zika [282, 293]. Viral infections of microglia may also interfere with their function, which may result in enhanced, uncontrolled inflammation and/or immune deficiency, of which the mechanisms are still not well understood. Fortunately, vaccines have been successfully established for some viruses, e.g. Japanese encephalitis, which prevents infection in the first instance. However, for many of the mentioned viruses, there is still no vaccine available and substantial more research is required to better understand the role of microglia in corresponding viral encephalitis.

Glioma, especially glioblastoma, is the most frequent primary brain tumour [50]. Therefore, glioma is covered here, representing the principal mechanisms of microglia in CNS primary tumours and metastases. Gliomas develop from genetically aberrant glia cell precursors and are usually monoclonal [294]. Microglia play a role in establishing a growing glioma tumour, and certainly help glioma to grow together with its vascular supply [295–297]. The vascular bed of gliomas has to be considered different from the functional BBB [298] and allows substantial immigration of CCR2 + blood derived monocytes, as well as regulatory/suppressive lymphocytes and other leucocytes into the tissue, due to CCL2 production of the tumour [299, 300]. Interestingly, there is a more immune-suppressive, tumour growth promoting population of residential microglia, as well as an inflammatory, monocytes-derived macrophage population [202]. Together, in the interaction with the tumour cells, they provide an optimal environment for survival and growth of glioma, by preventing an effective anti-tumour immune response, generating space in the healthy tissue and providing growth factors [301–303]. However, future therapies have probably to target, in addition to the tumour cells, also microglia and macrophages, as well as the vascular cells [304]. In addition to mouse and human *in vitro* models, the zebrafish *in vivo* model has become very helpful to investigate the role and interaction of microglia with glioma [305].

Microglia research models

Microglia research still relies heavily on *in vivo* [51] and *ex vivo* cellular and tissue models [241], including mouse [32, 70, 209, 306, 307], rat [308] and zebrafish [70, 309], as these cells are unique and very different from other tissue macrophages and bone marrow derived cells. However, for research in humans, two *in vitro* approaches have been successfully envisaged: (1) isolation of primary microglia from surgical specimens of the brain [310] or post-mortem tissue samples [147, 278, 311, 312], or (2) differentiation of microglia-like cells from embryonic stem cells [313], induced pluripotent stem cells (iPS) [314–316], bone marrow stem cells or blood monocytes [317–319]. Although all those *in vitro* human models have their limitations, they have so far been very useful to investigate cellular and molecular mechanisms related to cellular structure and function in the context of inflammation, infection and immune response. Recently, microglia from different models have been better characterized using modern transcriptomic methods [320] and compared, indicating that all cultured cells used for *in vitro* models are probably at an activated stage [147], and only *in vivo* models represent physiological resting microglia. However, it may be possible in the future to also develop better *in vitro* models of resting microglia [321] once the *in situ* tissue conditions and molecular and cellular properties are better known. Interestingly, microglia depletion models [322] that can also be replenished with different kinds of modified cells [241] have more recently been developed. It is thus expected that more new models will be developed in the near future in microglia research, adding new knowledge and new aspects of the very versatile and important CNS macrophages, the microglia.

CONCLUSIONS

Microglia are thus unique cells of the central nervous system, linking it to the immune system. They participate in the biology and pathology of the CNS from early on through-out development and later in CNS homeostasis. Their origin and many of their functions have only recently been discovered, but much more is still not known. Consequently, microglia will remain for the years to come on the centre stage of research in neuroimmunology.

Abbreviations

Central nervous system (CNS), induced pluripotent stem cells (iPS), multiple sclerosis MS), Chemokine ligand (CCL), Chemokine receptor (CCR), tumour necrosis factor alpha (TNFα), macrophage colony-stimulating factor receptor (CD115, M-CSFR; c-*fms*), reactive oxygen species (ROS), blood-brain barrier (BBB), human immune deficiency virus (HIV), interleukin (IL), complement receptor 3 (CR3, CD11b).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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