Microglia and monocyte-derived macrophages: functionally distinct populations that act in concert in CNS plasticity and repair

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INTRODUCTION

Outside the central nervous system (CNS), macrophages are known to acquire distinct phenotypes, and accordingly, perform various different and even opposing functions. Macrophages are generally polarized into two major phenotypes: Th1-related cytokines, such as interferon-gamma (IFN-γ), and microbial challenge by products such as lipopolysaccharides (LPS) induce the classically activated M1 phenotype, driving macrophages toward a pro-inflammatory microbicidal function, whereas Th2 cytokines, such as interleukin-4 (IL-4) and IL-13, polarize macrophages to an alternatively activated M2 phenotype associated with wound healing and immune resolution (Gordon, 2003; Gordon and Taylor, 2005; Mantovani et al., 2009; Mosser and Edwards, 2008; Auffray et al., 2009; Martínez et al., 2009; Gordon and Martínez, 2010; Sica and Mantovani, 2012). These different macrophage populations act following various insults outside the CNS where the CCR2^+/−CX3CR1^+Ly6Chigh subset, corresponding to the M1 phenotype, is the first recruited to the damage site and is typically pro-inflammatory, whereas the CCR2^−/−CX3CR1^−Ly6Clow cells, matching the M2 phenotype, subsequently terminate the local inflammation as well as promoting regeneration and healing (Arnold et al., 2007; Nahirny et al., 2007). These two polarized phenotypes are further classified, based on their diverse surface markers, phenotypes and functions, into a more continuum spectrum of macrophage repertoire (Mosser and Edwards, 2008).

In the CNS, however, such diversity of macrophage functions was largely overlooked, as microglia, the innate immune cells of the CNS, were considered its exclusive innate components. Initially discovered by Cajal (1913) and his student Del Río Hortega (1919), microglia are currently accepted as self-renewing cells with a unique embryonic origin (Cinex et al., 2010; Schule et al., 2012; Gomez-Peñalver et al., 2013), distributed along CNS parenchymal tissues. Their primary roles are the maintenance of normal CNS functions (Elkabes et al., 1996; Nakajima et al., 2001; Aarum et al., 2003; Nimmerjahn et al., 2005; Hanisch and Kettenmann, 2007; Ransohoff and Perry, 2009; Walton et al., 2006; Ziv et al., 2006; Ramasahoff and Perry, 2009; Wake et al., 2009; Sierra et al., 2010; Tremblay, 2011) and the continuous search for alterations in homeostasis through their constantly scanning dynamic ramifications (Nimmerjahn et al., 2005; Neumann et al., 2006, 2008; Schwartz et al., 2006; Yin et al., 2005; Stadelmann et al., 2002; Streit, 2002; Shaked et al., 2004, 2005; Neumann et al., 2006, 2008; Schwartz et al., 2006; Yin et al., 2006; Majumdar et al., 2007; Muzio et al., 2007; Thorpe et al., 2009; Kettenmann et al., 2011), intensive acute activation (for example in spinal cord injury, optic nerve crush, or stroke) and chronic activation, which characterizes neurodegenerative diseases, render these cells neurotoxic, potentially impairing neuronal activity (Munn, 2000; Stalder et al., 2001; Vogel et al., 2003; Monje et al., 2005; Stirling et al., 2004; Block and Hong, 2005; Heppner et al., 2005; Block et al., 2005; Hanisch and Kettenmann, 2007; Muzio et al., 2007; Ovanesov et al., 2008; Centonze et al., 2009; Mazzara and Jin, 2010; Perry et al., 2010; Derecki et al., 2012, 2013; Scheffel et al., 2012). Such a phenotype not only prohibits...
microglia from resolving inflammatory damage but rather contributes to the vicious cycle of toxicity and calls for additional assistance to terminate the local inflammation.

As an immune privileged site, the CNS was, for decades, considered sealed for leukocyte entry, protected from the circulation behind the walls of the blood-brain barrier (Wilson et al., 2010; Ransohoff and Engelhardt, 2012). Any recruitment of immune cells to the CNS was perceived as either a technical artifact (Ajami et al., 2007; Midden et al., 2007) or as part of the ongoing inflammatory damage (McGeer et al., 1990; Popovich et al., 1999; Gris et al., 2004; Stirling et al., 2004; Boster et al., 2008). Further confusion resulted from the fact that blood-derived myeloid cells, recruited following CNS damage, were considered microglial reinforcements of comparable functions, and were accordingly termed “blood-derived microglia” (Eglitis and Mezey, 1997; Priller et al., Wake et al., 2009; Tremblay, 2011). Any recruitment of immune cells to the CNS was perceived as either a technical artifact (Ajami et al., 2007; Midden et al., 2007) or as part of the ongoing inflammatory damage (McGeer et al., 1990; Popovich et al., 1999; Gris et al., 2004; Stirling et al., 2004; Boster et al., 2008). Further confusion resulted from the fact that blood-derived myeloid cells, recruited following CNS damage, were considered microglial reinforcements of comparable functions, and were accordingly termed “blood-derived microglia” (Eglitis and Mezey, 1997; Priller et al., 2001; Bechmann et al., 2005; Simard et al., 2006). A series of recent innovative studies demonstrated that such infiltrating cells, which we defined as monocyte-derived macrophages (mo-MΦ), perform indispensable roles that cannot be provided by their resident counterparts (Shechter et al., 2009, 2011; London et al., 2011). These studies challenged the traditional perception of macrophages in the CNS as a functionally homogeneous population. Moreover, they set the ground for a new era of research employing sophisticated techniques including parabiosis, head-protected bone marrow chimeras, transgenic mice, and fate mapping analysis (Carson et al., 2007; Ginhoux et al., 2010; Sacerdop et al., 2010; Ajami et al., 2011; Middendorf et al., 2011; Prinz et al., 2011; Butovsky et al., 2012; Derecki et al., 2012; Scholz et al., 2013; Gomez Perdiguero et al., 2013), aimed at revealing the differential origin, phenotype, and function of distinct myeloid populations within the CNS. In this perspective, we will focus on the functional heterogeneity of microglia/mo-MΦ, addressing microglial functions as the first immunological support, the failure of these cells to provide significant protection under intensive acute or chronic activation, and the subsequent unique contribution of the mo-MΦ.

MICROGLIA IN MAINTENANCE AND DEFENSE

Similar to other tissue-resident macrophages outside the CNS, the primary role of microglia is to support normal tissue function, in this case neuronal integrity (Nimmerjahn et al., 2005; Hansich and Kettenmann, 2007; Ransohoff and Perry, 2009; Kettenmann et al., 2011; Scheffel et al., 2012). The development of in vivo two-photon microscopy revolutionized our understanding of microglial functions under steady state. It allowed the study of non-activated microglia in intact brains of living animals (Davalos et al., 2005; Hanisch and Kettenmann, 2007). Microglia have been reported to support neuronal function, to secrete neurotrophic factors, e.g., nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4 (Elkabes et al., 1996; Nakajima et al., 2001). Under certain conditions microglia upregulate their brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) expression; both factors have protective and growth-promoting effects and are essential for learning and memory skills (Mizuno et al., 2006; Hsieh et al., 2004; Lee et al., 2004; Butovsky et al., 2006c; Wang et al., 2012).

Being the native immune cells of the CNS, microglia act as the first line of defense, protecting the CNS from invading agents as well as internal enemies; microglia are involved in infection, inflammation, autoimmune disease, trauma, ischemia, and neurodegeneration. After initial exposure to a danger signal, microglia become activated; they upregulate expression levels of certain molecules such as CD11b and Iba1, and gain expression of molecules associated with antigen presentation, such as major histocompatibility complex (MHC)-II, B7.1, and B7.2 (CD80/86), which are absent in naive microglia. Microglia then lose their ramified morphology and surveillance mode, and convert to amoeboid-like, functional cells (Kettenmann et al., 2011).

Microglial functions under pathological conditions may reflect their diverse phenotypes acquired contingent to their activation signals. For example, activation of microglia by T cells that recognize CNS antigens or T cell-derived cytokines such as IFN-γ (at low concentrations) and IL-4 supports differentiation of NPCs and provides neuroprotection by regulating IGF-1 and tumor necrosis factor-alpha (TNF-α) levels. However, stimulation with LPS, amyloid-β or high concentrations of IFN-γ diminishes these effects. Moreover, activation of microglia by IL-4 prior to the LPS stimulation prevents the LPS-mediated inhibition of the microglial neuroprotective effects (Avidan et al., 2004; Shaked et al., 2004; Butovsky et al., 2005, 2006b, Scheffel et al., 2012). Thus, microglia are highly versatile cells; their regulated activation and proper termination might help in tissue preservation, repair, and renewal, while intensive acute or chronic activation may result in irreversible tissue loss.

Microglia exert several protective roles. These include removal by phagocytosis of pathogens and microbes, as well as clearance of toxic molecules, cell debris, remains of extracellular matrix, myelin derivatives, and protein deposits (e.g., amyloid-β or p-tau), all of which further contribute to the local inflammation
and are inhibitory to regeneration and repair (Chung et al., 1999; Magnus et al., 2001; Ravichandran, 2003; Shaked et al., 2005; Liu et al., 2006; Majumdar et al., 2007; Kettenmann et al., 2011). Microglia can promote regeneration, rather than removal of growth-inhibitory compounds (Kettenmann et al., 2011), these cells produce classical growth factors required for remyelination and regeneration (Kotter et al., 2001; Stadelmann et al., 2002). Microglia were reported to support regeneration of the optic nerve as well as sensory axons in the injured spinal cord (Prewitt et al., 1997; Rabchevsky and Streit, 1997; Yin et al., 2006) and to induce dopaminergic sprouting in the injured striatum (Batchelor et al., 1999; Thored et al., 2009).

Microglia not only fail to provide the needed functions, but there are ample evidence implying that they can be actively deleterious; these cells secrete reactive oxygen species, nitric oxide (NO), and pro-inflammatory cytokines that can endanger neurons, oligodendrocytes, or essential structures of the extracellular matrix (Monje et al., 2003; Stirling et al., 2004; Block and Hong, 2005; Block et al., 2007; Haniuch and Kettenmann, 2007; Perry et al., 2010). Microglial malfunction was suggested as a possible etiology in schizophrenia, resulting in impaired pruning during neurodevelopment, disturbance of normal neurotransmitter function, and uncontrolled production of pro-inflammatory cytokines such as TNF and IL-6, as well as failure in clearance of neuronal corpses (Mann, 2000). Microglial abnormal response is also evident in Rett syndrome, a neurodevelopmental disease resulting in reduced disease progression (Boillée et al., 2006). In experimental autoimmune encephalomyelitis (EAE), a neurodegenerative disease model, microglial activation was inhibited by administration of ganciclovir to chimeric mice in which only the microglia express thymidine kinase that converts this drug into its cytotoxic form. Such specific microglial paralysis inhibits disease development and attenuates inflammatory CNS lesions (Heppner, 2005). Moreover, in Alzheimer’s disease, characterization of fibrillary plaque development in brains of transgenic APP(SW) mice revealed that microglia are not only unable to clear amyloid-β deposits, but rather, contribute to plaque formation (Stadler et al., 2001; Wegiel et al., 2001). Additionally, microglia-derived chronic inflammation was shown to precede neuronal loss in neonatal borna disease virus (BDV) infection (Ovanesov et al., 2008).

Collectively, these evident suggest that under intensive acute or chronic activation microglia fail to acquire the desired phenotype, lose their essential functions and turn actively deleterious, and thus cannot provide immune resolution and subsequent CNS protection. In such scenarios, the recruitment of additional myeloid cells from the blood, comparable to microglia, is not likely. Rather, there is a need for peripheral intervention, in the form of unique cells, capable of providing the functions that cannot be delivered by the resident microglia.

**FUNCTIONAL MACROPHAGE HETEROGENEITY**

Indeed, intensive acute or chronic microglial activation drives these cells to produce a chemotactic profile favoring the recruitment of monocytes and lymphocytes (Haueter et al., 2002; Sargynt et al., 2009; Kamura et al., 2012). However, as the CNS is an immune privileged site, it was assumed to exclude leukocyte trafficking (Wilson et al., 2010; Ramsdohl and Engelhardt, 2012). Consequently, several studies suggested that the recruitment of myeloid cells to the CNS reflected non-physiological origin imposed by the unnatural experimental model (Ajamii et al., 2007; Mildner et al., 2007). Other studies, although recognizing leukocyte entry to the CNS, interpreted their presence as a sign of pathology or malfunction that is detrimental and should be avoided (McGeer et al., 1990; Popovich et al., 1999; Gris et al., 2004; Stirling et al., 2004; Boster et al., 2008). Moreover, the previous technical limited ability to distinguish between the infiltrating blood-derived cells and the resident microglia resulted in the view of the newly recruited cells as part of the microglial reservoir, leading to their inaccurate tagging as “blood-derived microglia” (Eglitis and Menez, 1997; Poller et al., 2001; Bechmann et al., 2005; Simard et al., 2006). This misleading nomenclature resulted in the erroneous perception of these cells as phenotypically and functionally comparable to microglia. Since then, advanced techniques have been developed to allow the blood-derived cells to be distinctly tracked and manipulated (Popovich and Hickey, 2001; Wright et al., 2004; Carston et al., 2007; Rolls et al., 2008; Shechter et al., 2009; Ajami et al., 2011; Colston, 2013). A series of recent studies used head shielded [Cx3cr1<sup>APP<sup>+/→WT</sup></sup> bone marrow chimeric mice, whose wt bone marrow was replaced with that of Cx3cr1<sup>+/→</sup> mice (Jung et al., 2000). This approach allows the infiltrating myeloid cells, derived from donor bone marrow and labeled with GFP, to be distinguished from their resident counterparts, while avoiding any artifacts related to brain irradiation (Shechter et al., 2009). These studies revealed the unique and non-redundant functions of the newly recruited cells and suggested the term “monocyte-derived macrophages (mo-MΦ)” to identify these cells as an entity separate from the resident microglia (Shechter et al., 2009, 2011; London et al., 2011). mo-MΦ restrict amyloid-β plaques in a mouse model of Alzheimer’s disease (Simard et al., 2006; Butovsky et al., 2007), contribute to motor function recovery following spinal cord injury (Shechter et al., 2009), promote survival of neurons and cell renewal in the injured retina (London et al., 2011), and were recently shown to arrest disease progression in Rett syndrome (Derecki et al., 2012). These cells display immune-resolving characteristics and
express anti-inflammatory cytokines, which are crucial for their neuroprotective function. Moreover, they restrict accumulation of other inflammatory leukocytes including neutrophils and resident microglia (Schecter et al., 2009; London et al., 2011), mediate debris clearance by phagocytosis (Derecki et al., 2012), and regulate the extracellular matrix and glial scar surrounding the damaged area (Schecter et al., 2011). Importantly, inhibition or attenuation of the infiltration of mo-MΦ results in exacerbated damage, indicating that the resident microglia, which were spared in these experiments, cannot fulfill the protective functions provided by the mo-MΦ (Butovsky et al., 2007; Schecter et al., 2009, 2011; London et al., 2011).

Additional reinforcement for the disparity of these two myeloid populations is the fact that resident microglia and mo-MΦ development is dependent on different transcription factors. While development of both microglia and mo-MΦ requires the transcription factor, Pu-1 (Mckercher et al., 1996), the latter necessitates Myb and FLT3, whereas microglial development is cfls-receptor-dependent and FLT3- and Myb-independent (Ginhoux et al., 2010; Schulz et al., 2012; Gomez Perdiguero et al., 2013). Each of these two myeloid populations has a unique set of transcription factors and regulators leading to a diverse pattern of gene expression. Advanced analysis methods compared the profile of gene expression, microRNAs (miRNAs) and transcription factors, of splenic Ly6Chi monocytes and CD39+ anti-inflammatory cells, which acquire their phenotype via their trafficking route to the CNS (Shechter et al., 2013). Thus, it will be interesting to characterize these cells, which acquire their nature via their trafficking route to the CNS, in these experiments, cannot fulfill the protective functions provided by the mo-MΦ (Butovsky et al., 2007; Schecter et al., 2009, 2011; London et al., 2011).

FUNCTIONAL RELATIONSHIPS BETWEEN THE MICROGLIA AND mo-MΦ – A CASCADE OF EVENTS

Based on the data reviewed above, we suggest here a cascade of events representing microglial functions within the CNS and the distinct contribution of mo-MΦ. Microglia enter the CNS during early developmental stages. By continuous scanning and sampling their environment via their dynamic processes, microglia are able to maintain CNS homeostasis; they preserve and modify (upon need) the synapse complex, support neurogenesis, secrete essential growth factors, and sustain normal CNS performance. Once encountering an unbalanced milieu, microglia become fully activated; retraction their long ramifications, proliferate and shift toward a “ready to act” mode. Their subsequent function is very much dependent on their activation signal. A short and moderate stimulus will direct microglia to rapidly eliminate the source of damage without evoking a further immune response. Such stimuli are part of routine CNS maintenance and are generally resolved without activating or affecting other systems in the body. Even when the stimulus is stronger but short-lived, microglia can potentially cope with the danger signal, performing clearance of neurotoxic factors, supporting regeneration, and secreting neurotrophic factors supportive of remyelination. However, when the stimulus is intense or chronic, microglia can no longer handle the ongoing damage; these cells become neurotoxic and release reactive oxygen species, NO, proteases and pro-inflammatory cytokines, all of which endanger neuronal activity. Such microglial malfunctions result in signals for recruitment of mo-MΦ to the damage site, which provide functions that cannot be delivered by the resident cells; mo-MΦ restrict the local inflammation, attenuate accumulation of misfolded proteins or any other intruders, restore homeostasis, and support healing and renewal. Unfortunately, the spontaneous response of mo-MΦ is often insufficient to achieve complete recovery. Thus, several therapeutic attempts to boost such a protective response by either direct administration of monocytes or indirectly augmenting their recruitment are currently underway (Figure 1).

LESSONS FROM OTHER TISSUE-SPECIFIC RESIDENT MACROPHAGES

Although unique, microglia are not the sole tissue-specific resident myeloid-derived cells. Many organs in the body contain...
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FIGURE 1 | microglial and mo-MΦ functions – cascade of events.
(a) Resident microglia originate from yolk sac macrophages that repopulate CNS parenchyma during early development and are self-renewed locally, independent from bone marrow-derived monocytes, by proliferation of primitive progenitors. (b) In the steady state microglia are constantly scanning their environment through their highly motile processes. These cells facilitate the maintenance of synapses (c) and neurogenesis (d), as well as secrete growth factors essential for normal CNS performance (e). Upon recognition of a danger signal, microglia retract their branches, become round and ameboid, and convert into an activated mode (f). A short or moderate signal directs microglia toward a neuroprotective phenotype; these cells clear debris by phagocytosis (g), secrete growth factors associated with remyelination (h) and support regeneration (i). Intense acute or chronic activation renders microglia neurotoxic; under such conditions microglia fail to acquire a neuroprotective phenotype. Instead, these cells produce reactive oxygen species (ROS), nitric oxide (NO) proinflammatory cytokines such as IL-1, IL-6, and TNF-α, all of which endanger neuronal activity (j). Microglial malfunction results in the recruitment of mo-MΦ to the damage site (k). mo-MΦ secrete anti-inflammatory cytokines such as IL-10 and TGF-β, express factors associated with immune resolution such as mannose receptor and arginase 1 (ARG1), and promote neuroprotection and cell renewal (l), all of which are functions that cannot be provided, under these conditions, by the resident microglia.  

FIGURE 2 | Lessons from other tissue-specific resident macrophages. (A) Langerhans cells (LCs), the resident myeloid cells of the epidermis share with microglia their scanning capacity, their activation mode and possibly, their embryonic origin. Different from microglia these cells migrate to the lymph node where they act as antigen presenting cells. (B) Analogous to microglia, intestinal macrophages act as the first line of defense, protecting the mucosa from harmful pathogens and removing dead cells and debris. Unlike most other tissue macrophages, upon activation by certain stimuli, these cells produce immune-resolving factors. Distinct from microglia, circulating monocytes are largely accepted as the source of intestinal macrophages, however, the possibility of local self-renewal by embryonic precursors, under steady state, was also raised. (C) Kupffer cells are the macrophages of the liver. Similar to microglia, these cells perform clearance of host-related debris and pathogens. Kupffer cells are classical antigen presenting cells; however, can also display immune-resolving functions. Moreover, they are largely assumed to be self-renewed independently from circulating monocytes, but a certain Kupffer cell subset was reported to originate from hematogenous precursors.
distinctive resident macrophages whose properties are tailored to the host tissue (Figure 2). Langerhans cells (LCs), for example, are the resident myeloid cells of the epidermis. Similar to microglia, they have extended dendritic processes that embrace neighboring keratinocytes (Langerhans, 1868; Bilzer et al., 2006) and scan the epidermis for pathogens and toxic molecules (de Jong and Geijtenbeek, 2010). These cells are endowed with the C-type lectin, Langerin, used for interaction with bacteria, fungi, and viruses (Turville et al., 2002; de Witte et al., 2007; Merad et al., 2008; de Jong and Geijtenbeek, 2010). Like microglia, LCs descend from embryonic precursors; possibly yolk sac macrophages or fetal liver monocytes, and are renewed independently of the bone marrow, by in situ proliferation upon need (Merad et al., 2002, 2006; Chorro et al., 2009; Chorro and Geissmann, 2010; Höfler et al., 2012). Moreover, as in microglial activation, upon capture of pathogens, LCs undergo phenotypic changes including increased expression of MHC-I and II, and of the co-stimulatory molecules CD80, CD86, and CD40 (Merad et al., 2008; de Jong and Geijtenbeek, 2010). However, unlike microglia, which are restricted to the CNS parenchyma, LCs upregulate the lymph node-homing receptor, CCR7, which eventually leads to their migration to peripheral lymph nodes where they induce a specific adaptive immune response against skin invading pathogens (Merad et al., 2008). Intestinal macrophages are the largest population of mononuclear phagocytes in the body (Smith et al., 2005; Varol et al., 2010; Mowat and Bain, 2011). Similar to microglia, they have essential functions under both normal and pathological conditions; intestinal macrophages preserve a delicate equilibrium between commensal bacteria and the host, maintaining epithelial integrity and mucosal homeostasis. These cells act as the first line of defense protecting the highly exposed mucosa from harmful pathogens, removing dead cells and debris, and modulating the local inflammatory response (Smith et al., 2005; Varol et al., 2010; Mowat and Bain, 2011). Unlike other tissue macrophages, upon activation, for instance by certain Toll-like receptor (TLR) ligands, intestinal macrophages do not express high levels of co-stimulatory molecules nor do they secrete pro-inflammatory cytokines (Kogler et al., 1998; Hirotsune et al., 2005; Uematsu et al., 2006; Mowat and Bain, 2011; Smith et al., 2011). Rather, they produce anti-inflammatory mediators such as IL-10 and prostaglandin E2 that restrict the local immune response (Mowat and Bain, 2011). Unlike microglia, the replenishment of intestinal macrophages is mostly associated with the recruitment of circulating monocytes. However, the possibility of self-renewal under steady state has also been raised (Mowat and Bain, 2011). Kupffer cells are the macrophages of the liver. These cells are mainly involved in clearance of pathogens and host-derived waste; they are constantly exposed to bacterial endotoxin (LPS) and microbial debris delivered from the gastrointestinal tract (Naito et al., 2004) and are involved in removal of senescent or malformed red blood cells and phagocytosis of soluble immunoglobulin G (IgG) complexes, microorganisms and eukaryotic cells (Naito et al., 2004; Parker and Picat, 2012). In addition to their role as phagocytes, Kupffer cells act as effective antigen presenting cells; upon Hepatitis C virus infection, human Kupffer cells elevate MHC-I and II expression, upregulate co-stimulatory molecules, and interact with T cells (Busgro et al., 1998). However, several studies also demonstrated the immune-resolving nature of Kupffer cells, which were shown to suppress lymphocytes in culture (Callegy et al., 1991), secrete IL-10 in response to LPS challenge (Knolle et al., 1995) and facilitate Fas ligand (FasL)-mediated apoptosis of T cells in a liver transplant model (Miyagawa-Hayashino et al., 2007). Thus, similarly to CNS heterogeneous macrophages, Kupffer cells seem to perform highly versatile functions. These cells, like microglia and LCs appear to self-renew independently of bone marrow-derived precursors (Schultz et al., 2012; Gomes Pardeganaru et al., 2013). However, a study addressing Kupffer cell heterogeneity identified two subsets of Kupffer cells; one of them is radioresistant and rapidly replaced from hematogenous precursors (Elden et al., 2007), indicating that the issue of Kupffer cell renewal is still unresolved.

CONCLUSIONS AND FUTURE DIRECTIONS

The evidence collected in this perspective supports the concept of functional macrophage heterogeneity within the CNS. Due to their similar morphology, previously assumed shared origin and subsequent misleading nomenclature, as well as the lack of available techniques to distinguish between the two populations, microglia and mo-MF were erroneously assumed to comprise a single population. Alternatively, and based on the ample findings addressed above, our model suggests that when it comes to CNS macrophages initial impressions can be deceiving; although they appear similar, mo-MF and microglia present different gene expression patterns and phenotypes, and are functionally distinct. Additional research is needed in order to further reveal the different function of these two distinct populations and the conditions that determine their unique phenotype. Such research will help resolving the misunderstanding that resulted from the previously held blanket view of these cells as homogenously destructive, and might assist in employing specific manipulations of the two subsets as a potential therapeutic approach.
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and glial cell line–derived neurotrophic factor. J. Neurosci. 19, 1786–1796.
Bechmann, I., Goldmann, J., Korsu, A. D., Borusan, E., Simberg, E., Nathun, F., et al. (2005). Circulating monocyte cells infiltrate layers of amnion during amniotic fluid degradation when they transform into microglia. FASEB J. 19, 667–649.
Boas, D. R., Henkel, J. S., Xiao, Q., Zhang, W., Jiang, T., Xin, A. A., et al. (2006). Wild-type microglia extend survival in P1L1 knockout mice with familial amniotic fluid leakage. Proc. Natl. Acad. Sci. U.S.A. 103, 16021–16026.
Bilzer, M., Bergstr, G., and Gerstl, A. L. (2006). Role of Kupffer cells in host defense and liver disease. J. Pathol. 206, 1175–1186.
Block, M. L., and Hong, J. S. (2005). Microglia and inflammation mediate macrophage generation in the mouse. Proc. Natl. Acad. Sci. U.S.A. 102, 77–80.
Bostock, A., Edan, G., Frohman, E., Boillée, S., Yamakawa, K., Lobsiger, C., Butovsky, O., Koronyo-Hamaoui, M., Butovsky, O., Hauben, E., and Schwartz, M. (2005). Microglia and inflammation mediate macrophage generation, proliferation and persistence in CNS injury. J. Neurosci. 25, 173–183.
Bouwmeester, W. J., Smit, J. A., Chen, Y., Becher, B., Abmayr, S. M., Meg记者表示，2005年被评选为国家自然科学奖一等奖，是该年度在科学界最受欢迎的一个奖项。2006年再次获得了国家科技进步二等奖。2007年获得国家自然科学二等奖，是当年该领域唯一一个奖项。2008年获得国家科技进步一等奖。2009年入选国家“百千万人才工程”第一层次人选。2010年当选中国科学院院士。2011年被评为全国优秀科技工作者。2012年获得国家自然科学基金委员会杰出青年科学基金资助。2013年入选“青年千人计划”。
Jung, S., Aliberti, J., Graemmel, P., London et al. Macrophage heterogeneity within the CNS.

London, A., Itskovich, E., Benhar, I., Langerhans, P. (1868). Über die Ner-

Kettenmann, H., Hanisch, U. K., Noda, W., Sher, A., et al. (2000). Analy-

Moser, T., Mayer, J., McGeer, E., Rogers, L., and Siely, S. (1990). Anti-inflammatory drugs and Alzheimer disease. Lancet 335, 1037.

Mizuno, M., Yamada, K., Olariu, A., Nawa, H., and Nabeshima, T. (2001). Neuroprotective effects of microglia in hippocampus. J. Neurosci. 21, 3047–50.

Mosser, D. M., and Edwards, J. P. (2009). The phagocyte: common features and functional diversity. Immunity 30, 31–40.

Mueller, B., Wunsch, S. A., Topham, J., Baribault, H., et al. (1996). Targeting gene insertion. Mol. Cell. Biol. 16, 1496–1499.

Muravev, I., Ueda, T., and Inoue, C. (2000). Cerebral macrophages are essential for binding and dissemination of scrapie agent. Nat. Med. 6, 5658.

Muzio, L., Martino, G., and Furlan, M. (1989). Inflammatory and immune functions of microglia. Trends Biochem. Sci. 14, 154–158.

Mzoughi, H., Harzallah, L., and Bouchelouche, T. (2012). Neuronal injury induces macrophage production of macrophage inflammatory protein-1 alpha in rat cortical neuronal cultures. J. Neurosci. Res. 90, 2127–2133.

Nakamura, T., Katayama, T., Ohnaka, C., Ito, Y., Chiba, Y., Kobayashi, H., et al. (2012). Neuronal injury induces macrophage production of macrophage inflammatory protein-1 alpha in rat cortical neuronal cultures. J. Neurosci. Res. 90, 2127–2133.

Neumann, J., Sauerzweig, S., Ronicke, R. J. (2001). Macrophage depletion impairs oligodendrocyte remyelination following lysolecithin-induced demyelination. Glia 35, 204–212.

Negishi, H., Yonezawa, M., and Nakajima, K. (2012). Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 334, 843–846.

Niederau, C., Hugel, S., Klee, M., and Hackel, M. (2001). Microglia and function of Kupffer cells. and function of resident and recruited macrophages in the role of microglia. J. Neuroimmunol. 119, 39–44.

Nishiyama, A., Ishikawa, T., and Ogawa, H. (2001). ESR1 gene transcripts in multiple hematopoietic abnormalities. EMBO J. 15, 5697–5708.

Nishimura, T., Matsumoto, H., and Nishimura, I. (2000). Anti-inflammatory and immune functions of microglia: an immunologic functional perspective. Annu. Rev. Immunol. 18, 453–483.

Nishio, K., Shirts, K., and Luster, A. D. (2000). Langerhans cells renew in the skin throughout life under steady-state conditions. Nat. Immunol. 1, 339–345.

Nishizuka, Y. (1986). Cyclic nucleotide-regulated protein kinases. Annu. Rev. Biochem. 55, 153–176.

Nishizuka, Y., and Simms, C. (1987). Role of protein phosphatases in cellular processes. Annu. Rev. Biochem. 56, 1021–1058.

Nishio, K., Shirts, K., and Luster, A. D. (2000). Langerhans cells renew in the skin throughout life under steady-state conditions. Nat. Immunol. 1, 339-345.

Nieto, C., Gage, F. H. (2004). IGF-I instructs OPCs to become oligodendrocytes. J. Neurosci. 24, 164–174.

Norton, M. J., Kreutzberg, G. W. (1983). Microglia: a specialized form of mononuclear phagocyte in the central nervous system. Science 220, 714–716.

Nourissat, G., Dejager, L., Marcq, S., and Barnabé-Heider, F. (1995). Non-tyrosine kinase function by targeted deletion and gene insertion. Nat. Cell Biol. 20, 413–418.

Nott, J. M., Brown, D., Millward-Sadler, S. M., Wood, A. J., and Howlett, P. (2002). Lysozyme as a marker of recruited versus resident and cultured microglia. Cell Tissue Res. 314, 193–199.

Ogawa, H., Ishikawa, T., and Nishio, K. (2000). ESR1 gene transcripts in multiple hematopoietic abnormalities. EMBO J. 15, 5697–5708.

Okabe, A., Tsuchida, S., and Date, T. (2004). Macrophages and mast cells in central nervous system inflammation. Innate Immun. 8, 44–52.
microglial engraftment. Nat. Med. 7, 1556–1561.
Prine, M. P., Pullen, J. S., Swidra, S. S., and Ransohoff, R. M. (2011). Homing of CNS myeloid cells and their roles in neurodegeneration. Nat. Neurosci. 14, 1227–1235.
Rahbek-Collin, A. G., and Streit, W. J. (1997). Grafting of cultured microglial cells into the lateral spinal cord of adult rats enhances neurite outgrowth. J. Neurosci. Res. 47, 34–48.
Ransohoff, R. M., and Engelhard, B. (2012). The anatomical and cellular basis of immune surveillance in the central nervous system. Nat Rev. Immunol. 12, 623–635.
Ransohoff, R. M., and Perry, V. H. (2009). Microglial physiology: unique stimuli, specialized responses. Annu. Rev. Immunol. 27, 119–145.
Ravindranath, K. S. (2005). "Recruitment signals from apoptotic cells initiate a quiescent state." Cell 113, 817–822.
Regel, G., Hausmann, M., Vogl, D., Aschenbrenner, E., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
Rolf, A., Shchter, R., London, A., Seger, Y., Jacob-Hirsch, J., Amarghi, N., et al. (2008). Two faces of cholinergic sustentacular protopodocytes in spinal cord repair: a role in microglial/macrophage activation. PLoS Med. 5, e1000115. doi: 10.1371/journal.pmed.1000115
Sauvage, N., Andus, T., Falk, A., Segev, Y., Jacob-Hirsch, J., Aschenbrenner, E., and Smythies, L. E. (2005). Intestinal bacteria by Toll-like receptor activation orchestrate brain-cell renewal: the nervous system tightrope: mononuclear phagocyte activation. Nat. Rev. Immunol. 5, 149–159.
could be construed as a potential conflict of interest.

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