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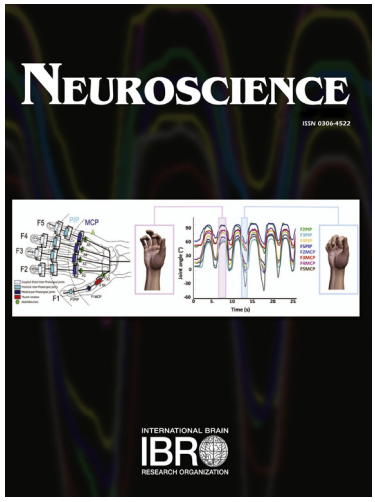

The evolving dialogue of microglia and neurons in Alzheimer's disease: microglia as necessary transducers of pathology

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The evolving dialogue of microglia and neurons in Alzheimer's disease: microglia as necessary transducers of pathology

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Abstract

The understanding of the contribution of microglial cells to the onset and/or progression chronic neurodegenerative diseases is key to identify disease-modifying therapies, given the strong neuroimmune component of these disorders. In this review, we dissect the different pathways by which microglia can affect, directly or indirectly, neuronal function and dysfunction associated with diseases like Alzheimer's. We here present the rationale for proposing a model to explain the contribution of microglia to the pathophysiology of Alzheimer's disease, defining microglial cells as necessary transducers of pathology and ideal targets for intervention.

Introduction

Microglia and neurons participate in a dynamic bi-directional communication that is essential for brain development and homeostasis, with its disturbance potentially contributing to disease. The two-way communication between these cell types includes neurons modulating microglial activation states by the release of factors such as chemokines, neurotransmitters and purinergic signalling, as well as microglia influencing neuronal function and connectivity either by direct physical contact with neuronal elements or by releasing paracrine signals.

Microglia originate from yolk-sac derived progenitors that invade the brain during early embryonic development and are long-lived cells which maintain their population by local self-renewal **(Lawson et al. 1992, Ginhoux et al. 2010, Mizutani et al. 2012, Askew et al. 2017)**. Under physiological conditions, they are considered to be highly dynamic cells, in contrast to the previously termed "resting" state, showing constant surveillance of their local microenvironment with their highly motile processes **(Davalos et al. 2005, Nimmerjahn et al. 2005)**. Microglia function is critical to maintain normal brain homeostasis and, beyond their main role as neuroimmune hubs during brain pathology, they have been recently described to participate in a variety of functions involving neuronal circuit formation and plasticity during development and also in adulthood. Microglia are involved in shaping neuronal circuits in perinatal and postnatal stages, by the regulation of developmental and adult hippocampal neurogenesis **(Sierra et al. 2010, Cunningham et al. 2013, Ueno et al. 2013, Reemst et al. 2016)** and in remodelling neuronal circuits and synapses in an activity-dependent manner to facilitate learning and memory in the developing and the adult brain **(Wake et al. 2009, Paolicelli et al. 2011, Parkhurst et al. 2013, Schafer et al. 2013, Squarzoni et al. 2014, Reemst et al. 2016)**. In return, neurons can regulate the activation state of microglia by secreting factors that influence the microglial phenotype, which are thought to keep microglia in a homeostatic state in the healthy brain **(Paolicelli et al. 2014)**. Neuronal activity has been shown to impact microglial behaviour, since increased neuronal firing can cause increased motility and physical contact of microglial processes with neuronal elements **(Wake et al. 2009, Tremblay et al. 2010)**, a response that might be regulated directly by the release of neurotransmitters **(Nimmerjahn et al. 2005, Fontainhas et al. 2011)**. Furthermore, microglia sense purines like adenosine trisphosphate (ATP), released by damaged neurons, via

purinergic receptors, which leads to a chemotactic response of microglia towards the site of injury **(Davalos et al. 2005, Kurpius et al. 2007)**.

In order to maintain brain homeostasis, intercellular communications must be tightly controlled, and a dysregulation of this intercommunication is known to occur in disease. Many brain diseases are characterized by inflammatory responses controlled by microglia **(Gomez-Nicola and Perry 2015)**, which disturb physiological interactions between microglia and neurons and could directly contribute to neurodegeneration via the production of neurotoxic substances. In this review, we discuss changes in the microglia-neuron cross-talk in Alzheimer's disease (AD) and how these changes might contribute to neurodegeneration, placing microglia as necessary effectors of AD-related pathology.

Direct microglia-neuron interactions in AD

Microglia are the brain's main resident immune cells and remain "immunologically silent" with limited immune function in the healthy brain. Microglia are believed to be kept in this homeostatic state by neuronal immunomodulators, such as CX3CL1 and CD200, which bind to their cognate receptors present on microglia. This intercommunication via inhibitory signals seems to be dysregulated in neurodegenerative disease **(Sheridan and Murphy 2013)**. CD200 is a type I membrane glycoprotein present on neurons in the rodent brain and interacts with the CD200 receptor (CD200R) which is a myeloid cell receptor found on microglia **(Wright et al. 2000, Barclay et al. 2002)**. CD200 and CD200R have been shown to be decreased in human AD tissue **(Walker et al. 2009)** and in mouse models of chronic and acute neuroinflammation **(Lyons et al. 2007)**, indicating a dysregulation of this pathway in disease. The interaction of CD200 with its receptor can attenuate Aβ-induced glial activation **(Lyons et al. 2007)**. CD200-deficient mice show signs of microglia activation and accelerated inflammatory response upon injury and experimental autoimmune encephalomyelitis, which suggests that CD200 silences immune function of microglia under physiological conditions **(Hoek et al. 2000)**. CX3CL1 (Fractalkine, Neurotactin) is released by neurons in the CNS, while its receptor CX3CR1 is expressed on microglia. Genetic ablation of CX3CR1 showed increased microglia activation in different models of inflammation **(Cardona et al. 2006, Bhaskar et al. 2010)**, suggesting that the CX3CL1/CX3CR1 signaling axis keeps microglia in a homeostatic phenotype under physiological conditions. In

different models of AD-like pathology, the genetic deletion of CX3CR1 has proven to have divergent effects, depending on the model investigated. On one hand, the lack of CX3CR1 lead to beneficial effects in models of amyloidosis by causing a reduction of amyloid-β (Aβ) deposition **(Lee et al. 2010, Liu et al. 2010, Lee et al. 2014)** and in a triple transgenic mouse harbouring both tau and Aβ mutations by preventing neuron loss **(Fuhrmann et al. 2010)**. On the other hand, detrimental effects have been observed in a toxin-induced model of Parkinson's disease and a transgenic model of amyotrophic lateral sclerosis (ALS), demonstrating increased microglial neurotoxicity and neuronal loss in the absence of CX3CR1 **(Cardona et al. 2006)**. Furthermore, CX3CR1 knock-out mice demonstrated accelerated phosphorylation and aggregation of microtubule associated protein tau (MAPT), which was accompanied with behavioural impairments **(Bhaskar et al. 2010, Lee et al. 2010, Maphis et al. 2015)**, further complicating the understanding of the impact of the CX3CL1/CX3CR1 signaling axis on the different aspects of AD pathology. CX3CR1 has been recently described as one of the markers establishing the homeostatic transcriptomic signature of microglia **(Gautier et al. 2012, Hickman et al. 2013, Butovsky et al. 2014)** and was found to be downregulated in disease-associated microglia in models of AD **(Holtman et al. 2015, Keren-Shaul et al. 2017, Krasemann et al. 2017)**, further indicating that dysregulated neuron-microglia communication is a feature of neurodegenerative disease and might contribute to the activated and possibly detrimental phenotype of microglia in AD.

Another example of ligand-receptor interaction that suppresses microglia activation is the neuron-derived factor CD22, which binds to microglial transmembrane protein-tyrosine phosphatase CD45 and inhibits the production of pro-inflammatory molecules in response to lipopolysaccharide (LPS) **(Mott et al. 2004)**. Furthermore, signal regulatory protein α (SIRPα) expressed on myeloid cells, neurons and astrocytes, and CD47 expressed on microglia and neurons, can interact and signal bidirectionally to suppress expression of proinflammatory cytokines **(Matozaki et al. 2009)**.

Apart from surface receptor interaction, neurons may also modulate microglial function through the release of neurotransmitters **(Sarlus and Heneka 2017)**. For example, tyrosine hydroxylase$^+$ (TH$^+$) neurons in the locus coeruleus (LC) regulate microglial cytokine and chemokine release and Aβ clearance in their projection areas, including the hippocampus and neocortex, through the release of

norepinephrine **(Heneka et al. 2010)**. Norepinephrine is considered to be an anti-inflammatory molecule that acts via β-adrenergic receptors, which have been shown to be present on the cell surface of microglia **(Chalermpalanupap et al. 2013)**. Early LC degeneration and subsequent loss of norepinephrine is a dominant feature in AD and leads to increased immune responses and Aβ accumulation in the respective brain regions **(Chalermpalanupap et al. 2013, Sarlus and Heneka 2017)**.

Neuron-to-microglia communication via purinergic signalling is also well established and might be highly relevant in pathological conditions such as neurodegenerative disease, when neuronal damage leads to the release of adenosine triphosphate, an ubiquitous energy source normally present in the cytoplasm of metabolically active cells. During neuronal injury, ATP and its metabolites adenosine diphosphate and adenosine are released from the cell into the extracellular space and bind to ionotropic (P2X) or metabotropic (P2Y) receptors many of which are located on the cell surface of microglia **(Inoue 2008)**. In the healthy brain, neuron-derived ATP release regulates microglial branch dynamics and induces rapid chemotactic response towards the site of neuronal injury **(Davalos et al. 2005, Kurpius et al. 2007)**, a process that is regulated by P2Y12 receptor (P2RY12) activation on microglia **(Haynes et al. 2006)**. P2RY12 is highly expressed by microglia in physiological conditions, but its expression is reduced in disease-associated microglia in mouse models of AD **(Keren-Shaul et al. 2017, Krasemann et al. 2017)**, indicating that microglial response towards neuronal purinergic signals might be compromised in neurodegenerative disease.

In the healthy brain microglia-to-neuron crosstalk is best illustrated by the ability of microglia to establish direct physical contacts with neuronal elements, participating in shaping developing neuronal circuitries through synaptic pruning. Upon brain disease such as AD, microglia induce an inflammatory response that develops alongside neuropathological features, likely influencing neuronal integrity and function and, consequently, contributing to neurodegeneration. Some of the first indications that activated microglia produce neurotoxic molecules that can directly harm and kill neurons come from *in vitro* experiments **(Boje and Arora 1992, Chao et al. 1992, Meda et al. 1995)**. Inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin 1β (IL-1β), interferon γ (IFNγ) and interleukin 6 (IL-6) have long been known to be increased in the brain of AD patients and are produced by microglia in response to Aβ peptides **(Akiyama et al. 2000, Heneka and O'Banion**

2007). For example, pro-inflammatory cytokines TNFα and IFNγ have been shown to have toxic effects on neurons, but also reducing levels of a major Aβ-degrading protease insulin degrading enzyme (IDE), increasing the production of Aβ by cortical neurons as well as impairing the Aβ-degrading abilities by microglia, which potentially contributes to Aβ deposition **(Rojo et al. 2008)**. In contrast, TNFα has also been shown to have protective effects against Aβ-induced neurodegeneration of rat cortical neurons **(Barger et al. 1995)**. This discrepancy could be explained by either diverse effects of TNFα on different subpopulations of neurons, or by TNFα eliciting its biological effect via distinct receptors (type I and type II TNF receptor) that have contrasting downstream effects in terms of neuroprotection and neurotoxicity **(Akiyama et al. 2000)**. Several other inflammatory mediators and cytokines have been implicated in contributing directly to the degeneration of neurons, affecting Aβ metabolism or tau pathology **(Griffin et al. 1998, Akiyama et al. 2000, Heneka et al. 2015)**, but results have been partially conflicting and one factor can have a variety of effects depending on the exact experimental conditions. This speaks for the complex interplay of the different microglia-induced inflammatory factors in mediating beneficial or detrimental effects on neuronal integrity during different stages of the disease.

Indirect microglia-neuron interactions in AD

Microglia as active players in the spread of Tau pathology

Since the initial hypothesis of the amyloid cascade postulated in 1992 **(Hardy and Higgins 1992)**, studies analysing the temporal dynamics and brain distribution of Aβ plaques and tau aggregates have lightened our understanding of the pathogenesis of AD. It is well established now that the accumulation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau begins to appear in the locus coeruleus, the transentorhinal and the entorhinal regions as early as age 20 **(Braak et al. 2011)** being one of the earliest hallmarks in AD patients. These accumulations can occur decades before significant Aβ deposition, without causing any impairment of the cognitive function. It has been shown that by age 50, the accumulation of NFTs in the transenthorinal region (called “transentorhinal” stage or Braak stage I–II pathology), is found in 50% of subjects but remains clinically silent **(Braak and Del Tredici 2011)**. After this silent period, NFTs appear to spread into neuronal projections towards other brain regions. Thus, cognitive decline coincides with the

spreading of tau pathology to allocortical regions ("limbic" stage of Braak Stages III–IV), and later to neocortex ("isocortical" stage or Braak stages V and VI) **(Braak and Braak 1995)**.

Consequently, stopping or limiting the propagation of tau aggregates appears as a relevant therapeutic target in the fight against AD. Numerous studies focused on the mechanisms involved in the spreading of tau aggregates have supported a model of trans-synaptic transmission. Using a transgenic mouse model that expresses a human tau mutation specifically in the entorhinal cortex it has been shown that misfolded tau spreads through anatomically connected regions **(de Calignon et al. 2012, Liu et al. 2012)**. But those studies explain only part of the model of propagation of tau pathology, as there is evidence supporting that the trans-synaptic transmission requires microglial cells. In 2012 Harris *et al.* shown in mice overexpressing mutant human tau, predominantly in layer II/III neurons of the entorhinal cortex, that their cognitive functions remained normal at 4, 8, 12 and 16 months of age, despite early and extensive tau accumulation in the entorhinal cortex, suggesting that the trans-synaptic transmission alone is not sufficient to induce the pathology **(Harris et al. 2012)**. Asai *et al.* provided support to this hypothesis, using a mouse model of rapid tau propagation from the entorhinal cortex to the dentate gyrus in 4 weeks, and showing that depleting microglia dramatically suppressed the propagation of tau aggregates and reduced excitability in the dentate gyrus **(Asai et al. 2015)**. Moreover, Bolos *et al.* demonstrated that microglia colocalize with NFTs in postmortem human brain tissue **(Bolos et al. 2016)**. An independent line of evidence showed that activated microglia (present in $CX3CR1^{-/-}$ mice) facilitated the propagation of tau, in an IL1R-dependent manner, suggesting that reactive microglia are sufficient to drive tau pathology in the brain **(Maphis et al. 2015)**. Consequently, the mechanisms involving microglia in the spreading of tau pathology have been further investigated in recent years. Evidence suggests that microglia facilitate the spreading of tau proteins by phagocytosing and exocytosing them at the synaptic cleft, stimulating research on microglial exosomes. Exosomes are 50-100 nm diameter extracellular vesicles that can be released by numerous cell types, including neurons **(Faure et al. 2006)** and microglia **(Yuyama and Igarashi 2017)**. In healthy conditions, exosomes are released in the intercellular space as an envoy, helping to shuttle molecules for long distances. They contain a wide range of molecules including proteins such as cytokines, lipids, genetic material but can also

contain prions, Aβ peptides **(Rajendran et al. 2006)**, tau protein **(Saman et al. 2012)**, and other misfolded proteins according to the pathological or physiological conditions. Asai *et al.* showed that tau is propagated through microglial exosomes in a model of AD, leading the inhibition of exosome synthesis (sphingomyelinase-2) to a suppression of tau propagation **(Asai et al. 2015)**. Bolos *et al.* demonstrated *in vitro* and *in vivo* that microglia internalize tau protein, after intracerebral injection of human tau (soluble (monomeric or small aggregates) and insoluble (aggregates)) in mice **(Bolos et al. 2016)**. Similarly, after intracerebral injection of human brain homogenates from AD patients in mice, different forms of tau colocalized with microglia **(Bolos et al. 2016)**. These studies suggest that microglia take up tau, regardless of the aggregation state of the protein, and support the notion that these cells play a key role in its clearance or its propagation, acting as necessary intermediates of pathology.

Microglia as necessary effectors of Aβ-mediated pathology in AD

It is well described now that, together with the deposition of NFTs and Aβ plaques, neuroinflammation is a major hallmark of AD. A line of evidence suggesting that microglia play a key role in the process of neuroinflammation, and consequently in progression of AD, is their tight association with Aβ deposits **(Condello et al. 2015, Olmos-Alonso et al. 2016)** and their involvement in Aβ uptake and degradation *in vitro* **(Frackowiak et al. 1992, Paresce et al. 1996, Chung et al. 1999, Koenigsknecht and Landreth 2004, Mandrekar et al. 2009)**, *in vivo* **(Frautschy et al. 1998, Mandrekar et al. 2009)** and in AD patients **(Perlmutter et al. 1992, Sheng et al. 1997)**. Microglia are able to clear soluble forms of Aβ via different direct and indirect mechanisms such as phagocytosis **(Frackowiak et al. 1992, Koenigsknecht and Landreth 2004)**, micropinocytosis **(Mandrekar et al. 2009)** and proteolytic degradation through the production of various Aβ degrading enzymes, such as IDE, neprilysin (NEP) and matrix metalloproteinase-9 (MMP-9) **(Qiu et al. 1998, Dolev and Michaelson 2004, Shimizu et al. 2008, Tamboli et al. 2010, Miners et al. 2011)**, which could be secreted in order to degrade Aβ extracellularly **(Tamboli et al. 2010)**. The expression of IDE, NEP, and MMP-9 has been shown to decline in microglia of aged APP/PS1 mice, which may contribute to their functional impairment in later stages of AD **(Hickman et al. 2008)**. Moreover, the relevance of NEP and IDE has been proven using APP/NED-deficient and APP/IDE-deficient

mice in which the Aβ deposition was increased in the brain **(Iwata et al. 2001, Farris et al. 2003)**. Conversely, overexpression of these proteases has been shown to reduce Aβ deposition **(Leissring et al. 2003)**.

The role of triggering receptor expressed by myeloid cells 2 (TREM2), and its adaptor protein TYRO protein tyrosine kinase-binding protein (TYROBP, also known as DAP12) in microglia-mediated Aβ clearance has been highly investigated recently as they are required to initiate signal transduction pathways that promote microglia activation **(Poliani et al. 2015, Wang et al. 2015)** microglial phagocytosis of apoptotic neurons, bacteria, lipoproteins and Aβ deposits **(Takahashi et al. 2005, Hsieh et al. 2009, N'Diaye et al. 2009, Kleinberger et al. 2014, Atagi et al. 2015, Yeh et al. 2016)**. Polymorphisms in TREM2, highly and exclusively expressed by microglia **(Zhang et al. 2014, Srinivasan et al. 2016)**, directly link impaired microglial phagocytosis of Aβ and increased susceptibility to AD **(Jin et al. 2014, Lue et al. 2015, Sirkis et al. 2016)**. Aβ plaques accumulation has been shown to be exacerbated in APP/PS1/TREM2-deficient and APP/PS2/TREM1-deficient mice at later ages (8+ months) **(Wang et al. 2015, Jay et al. 2017)**.

The reduction in the number of microglia or their depletion provides beneficial consequences, including a prevention of synaptic dysfunction, independently of the level of Aβ deposition. The neuroinflammatory mechanisms in AD involve the proliferation and activation of microglia, leading to the release of a wide range of inflammatory mediators **(Gomez-Nicola and Perry 2014)** (Fig. 1). Using APP/PS1 mice, our group demonstrated that microglial proliferation is progressively increased in proximity to Aβ plaques, suggesting that activation and proliferation of microglia is triggered by Aβ deposition **(Olmos-Alonso et al. 2016)**, correlating with previously reported findings **(Marlatt et al. 2014)**. These results were recently confirmed by live imaging of microglia, showing a 3-fold increase in the proliferation of neocortical microglia in APP/PS1 mice **(Fuger 2017 Microglia turnover with).** This intimate crosstalk of nascent Aβ pathology and microglial proliferation was also demonstrated using in vivo imaging of microglia around nascent plaques **(Condello et al. 2015)**.

The main system controlling the proliferation of microglia in disease is the colony stimulating factor 1 receptor (CSF1R) pathway, being its inhibition an efficacious way to test the contribution of microglia to prion disease **(Gomez-Nicola et al. 2013)** and ALS **(Martinez-Muriana et al. 2016)**. Our group showed that a prolonged inhibition

of CSF1R in the APP/PS1 model of AD-like pathology led to the decrease in microglial proliferation and to the shift of their profile to an anti-inflammatory phenotype. The inhibition of CSF1R prevented synaptic degeneration and caused a partial preservation of memory and behavioural performance, without modifying the levels of Aβ **(Olmos-Alonso et al. 2016)**. Similarly, in studies using 5xfAD or 3xTg mice treated with a potent CSF1R inhibitor for 1 month, it has been shown that the depletion of the microglial population (around 80%) led to the reduction of neuroinflammation, to the prevention of the loss of dendritic spines and neurons and to the improvement in memory, without modifying Aβ levels or plaque load **(Dagher et al. 2015, Spangenberg et al. 2016)**. These studies provide strong and independent support to the hypothesis that the pathophysiological trajectory of AD is modifiable through targeting microglia, making these cells a necessary effector of Aβ-mediated neuropathology.

This hypothesis has also been recently supported by studies targeting microglia activation through the complement cascade in AD models. Activated microglia, along with immunoglobulins and complement components, are closely associated with Aβ deposits in brains from AD patients and AD mouse models **(Eikelenboom and Stam 1982, McGeer et al. 1987, Griffin et al. 1989, Tooyama et al. 1990, Frautschy et al. 1998)**. Although the complements C1q and C3 localize to synapses during physiological development and mediate synapse pruning by phagocytic microglia **(Stevens et al. 2007, Schafer et al. 2012)**, their expression is also increased in pathological context as they colocalize with synapses and neuritic plaques in familial AD-mutant APP J20 transgenic mice and in APP/PS1 mice **(Fonseca et al. 2004, Hong et al. 2016)**. Microglia seem to have a central role in this complement-mediated process as studies have shown that *C1qa* expression is increased in microglia in primary motor cortex and the spinal cords of ALS patients **(McGeer and McGeer 2002)**. More recently Hong *et al.* demonstrated by fluorescent *in situ* hybridization an upregulated *C1qa* expression in microglia in hippocampi of J20 mice and Aβ oligomer-treated WT mice supporting microglia as a major source of C1q in synapses and pre-plaque brains in disease **(Hong et al. 2016)**. Maier *et al.* shown an accelerated Aβ plaque deposition, neurodegeneration and a modification in activated microglia profile in APP/C3-deficient mice **(Maier et al. 2008)**. On the other hand, APP/C1q-deficient mice had no change in Aβ plaque burden but showed decreased glial activation surrounding plaques and a slowing of neuronal pathology,

suggesting a detrimental effect of C1q on neuronal integrity **(Fonseca et al. 2004)**. Oral delivery of a C5a receptor antagonist (PMX205) for 2-3 months resulted in substantial reduction of fibrillar amyloid deposits and activated glia in two mouse models of AD (Tg2576 and 3xTg mice) **(Fonseca et al. 2009).** The reduction in pathology was correlated with improvements in behavioural tasks in Tg2576 mice. In 3xTg mice, PMX205 also significantly reduced hyperphosphorylated tau **(Fonseca et al. 2009).** Recently, Hong *et al.* have shown that the microglia-mediated engulfment of synapses, in mice challenged with soluble Aβ oligomers, was inhibited in CR3-knockout mice **(Hong et al. 2016)**. Shi *et al.* have demonstrated that 16-month-old APP/PS1/C3-deficient mice displayed reduction in proinflammatory mediators in the brain and performed better on a learning and memory task than APP/PS1 mice, despite having more cerebral Aβ plaques deposition **(Shi et al. 2017)**. Interestingly, APP/PS1/C3-deficient mice presented less microglia around hippocampal Aβ plaques and were protected against loss of synapses and neurons compared to APP/PS1 mice **(Shi et al. 2017)**.Together, those studies showed the indirect role of microglia in the loss of synapses suggesting that normal developmental synaptic pruning pathway is activated early in the AD brain and mediates synapse loss.

Aging- and environmental-related alterations in the microglial profile as a key effector in AD progression

Aging and environmental factors modifying the profile and the fate of microglia by be important components in the development and the progression of AD **(Shah 2013, Delpech et al. 2016, Grabert et al. 2016, Abate et al. 2017, Galatro et al. 2017, Janssen et al. 2017)**. Hefendehl *et al.* shown, using *in vivo* 2-photon microscopy, that surveying microglia in the neocortex exhibited an age-related soma volume increase, shortened and less motile processes, and a disruption in their tissue distribution. Furthermore, the mobility of microglial processes and the dynamic of microglia response significantly decreased with age **(Hefendehl et al. 2014)**. Several recent studies investigating the transcriptomic profile of human and mouse microglia have highlighted an age-related modification in the gene expression associated with pathways such as regulation of adaptive immune response, cell adhesion, cell cycle, axonal guidance or cell surface receptor expression **(Grabert et al. 2016, Galatro et al. 2017, Soreq et al. 2017)**. Similarly, environmental factors can influence the

profile of microglia very early in life. Mattei *et al.* shown that microglia from the adult offspring of a mother that had suffered from maternal immune activation (MIA) during pregnancy had an altered transcriptional profile and phagocytic function, associated with behavioural abnormalities. Interestingly, the changes in microglial phagocytosis on a functional and transcriptional level were similar to those observed in APP/PS1 mice **(Mattei et al. 2017)**. Microglia from wild-type mice exposed to chronic early-life stress (ES) from postnatal day (P)2 to P9 have been shown to present modifications in the expression of microglial markers including IBA-1, CD68 and cytokines, including IL-1ß and IL-6, with age. APP/PS1 mice exposed to the same type of ES were shown to display an exacerbated Aβ plaque deposition at 10 months of age **(Hoeijmakers et al. 2017).** A new phenotype of microglia, referred to as "dark microglia," was found in conditions such as chronic stress, also present in the APP/PS1 mouse model of AD. Notably, dark microglia exhibited a highly activated phenotype with strong expression of CD11b and TREM2 and extensive encircling of synaptic clefts when the microglia were associated with Aβ deposits **(Bisht et al. 2016)**.

Increasing evidence has correlated priming microglia with exacerbated disease (Fig. 1). The phenomenon of priming is characterized by effect of a pre-exposition of microglia to stress that will further potentiate the neuroinflammatory response to a second immune challenge **(Perry 2007, Hoeijmakers et al. 2016)**. The stimuli leading to microglial priming are multiple. Holmes *et al.* have demonstrated that both acute and chronic systemic inflammation, evidenced as an increase in serum TNFα, was associated with an increase in cognitive decline in AD patients **(Holmes et al. 2009)**. In murine models of neurodegenerative diseases, repeated injection of LPS led to an exacerbated tau pathology **(Kitazawa et al. 2005)**, Aß deposition **(Brugg et al. 1995)** neuronal death and induced acute cognitive impairment **(Cunningham et al. 2005, Cunningham et al. 2009)**. Moreover, injection of LPS during brain development enhances microglial activity and results in increased levels of pro-inflammatory cytokines IL-1β, IL-6 and TNFα **(Cai et al. 2000, Paintlia et al. 2004, Liverman et al. 2006)**. Altogether these studies suggest that microglial priming can affect brain development and, later, the onset and progression of neurodegenerative diseases.

Phenotypic diversity of microglia in AD: different roles for different cells?

The study of the role of microglia in AD has recently incorporated a regional and temporal dimension into the equation hypothesizing the presence of multiple microglial phenotypes with distinct functions and suggesting existence of microglial phenotypic trajectories **(Grabert et al. 2016, Janssen et al. 2017, Soreq et al. 2017)**. Keren-Shaul profiled microglia in 5xfAD mice, at the single-cell level, showing that the microglial phenotype evolves with the pathology, transitioning from a homeostatic phenotype to a disease-associated phenotype through downregulation of microglial checkpoints **(Keren-Shaul et al. 2017)**. Disease-associated microglia (DAM) emerge in a TREM2-dependent program, and represent a small subpopulation of cells present at late stages of the disease **(Keren-Shaul et al. 2017)**. The molecular signature of these DAM is strikingly comparable to that previously described for the, generally defined, plaque-associated microglia, characterised as $CD11c^+$ or $MHCII^+$ microglia **(Kamphuis et al. 2016, Yin et al. 2017)**, and its characterised by the increased expression of Cst7, Csf1, Trem2 or Clec7a, amongst others. Although these studies provide solid support for the time-dependent generation of microglial subpopulations, little is known about the contribution of these cells to disease, as the direct mechanistic association of DAM (plaque-associated microglia) is yet to be provided. However, follow up studies are emerging now, suggesting that the generation of such disease-associated phenotype is dependent on RIPK1, a kinase directly regulating Cst7 expression in microglia **(Ofengeim et al. 2017)**. Pharmacological or genetic inhibition of RIPK1 led to reduced pathology and improved behaviour in APP/PS1 mice, connecting RIPK1-mediated transcription in microglia to the progression of AD **(Ofengeim et al. 2017)**. This transcriptional trajectory of microglia in AD has also been shown by Krasemann *et al.*, demonstrating a TREM2-APOE-dependent switch of homeostatic to dysfunctional microglia **(Krasemann et al. 2017)**. This study provides solid mechanistic evidence to a model by which the exposure of microglia to Aβ plaques induces the emergence of the dysfunctional phenotype of microglia, associated with increased neurodegeneration and directly inhibiting the microglial tolerogenic (homeostatic) functions **(Krasemann et al. 2017)**. Interestingly, these results seem not to be restricted to Aβ-induced pathology, but recent data suggests the increased activity of APOE4 in glial cells also exacerbates tau-mediated neurodegeneration **(Shi et al. 2017)**. Taken together, these novel findings reinforce the view of the

progressive generation of a subpopulation of microglia with a detrimental contribution to the pathology, discussed in previous sections, which targeting may provide a beneficial impact in AD.

Conclusion

Increasing evidence suggest an essential, but bivalent, role of microglia in the development and progression of neurodegenerative diseases. The activation of microglia has been associated with neuroprotective effects by clearing cell debris, phagocytosing dead cells and releasing neurotrophic factors. On the other hand, microglial activation has also been correlated with chronic neuroinflammation contributing to neurodegeneration. Altogether, these studies confirm the dual role of microglia in the development and the progression of the disease and reveal the complexity of the factors regulating the balance of beneficial vs detrimental effects of microglia in neurodegenerative diseases. Despite its complex and dual role, it becomes obvious that microglia are a relevant target in neurodegenerative diseases, as neuroinflammation is involved in neurodegeneration in a direct or indirect way (Fig. 1). The remaining question is: which are the key pathways to target and during which time window in the disease?. We conclude that, in the future, a systematic probing of the mechanistic contribution of the individual molecular determinants of disease-associated microglia will provide a solid avenue into the pre-clinical domain. This will allow a deep and comprehensive evaluation of the model proposed in here, by which microglia are necessary transducers of AD pathology. Progressing the field into this domain will not only expand our understanding of microglia, but more importantly will open new avenues into devising the, long-due, disease-modifying therapies that provide a benefit to patients.

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Figure legend

Microglial cells as necessary effectors of pathology in AD. Through *direct interactions*, neurons contribute to maintaining microglia in a homeostatic phenotype. A dysregulation of the key pathways depicted in the figure leads to a shift in the microglial phenotype to an activated inflammatory profile. In the context of Alzheimer's disease, microglia can have *indirect effects* on neurons through the interaction with the main pathological hallmarks (Aβ and Tau). On one hand, Aβ can have indirect effects on neurons (right; black dotted line), causing abnormal synaptic function, initiating or pre-conditioning synaptic pathology. On the other hand, the accumulation of Aβ causes a progressive shift in microglia (left; grey dotted line), inducing a disease-associated phenotype that accelerates the progression of the pathology (direct effect, solid black line). Additionally, microglia is capable of promoting the spread of misfolded Tau (indirect effect, dotted black line), propagating the pathology in AD (direct effect). In this model, microglia would lead the executive phase of synaptic dysfunction and neurodegeneration, evidenced by recent data suggesting an uncoupling of Aβ from the beneficial effects observed after targeting microglia. Therefore, targeting the different steps of the sequence summarised in the left side of the figure (microglial route) provides a tantalising therapeutic opportunity, applicable to advanced stages of AD.

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Highlights

-Microglia undergo a progressive phenotypic transformation in Alzheimer's disease, associated to Amyloid β

-Microglia contribute to the spreading of Tau, propagating the pathology of AD

-Microglia are necessary effectors of pathology in Alzheimer's disease