Introduction

Alzheimer’s disease (AD) is the most common cause of dementia. The main pathological markers of this disease include amyloid plaques and neurofibrillary tangles. Research conducted over the last forty years has identified amyloid beta peptide (Aβ) as the main constituent of the plaques and characterized the abnormal metabolism of the amyloid precursor protein that leads to aggregation and deposition of these peptides in AD brains [1]. The intense preclinical and clinical research effort aimed at modulating Aβ metabolism as the means of slowing down or arresting AD has not, unfortunately, led to effective therapeutic agents or strategies, prompting questions about the suggested central or unique role of Aβ in AD [2]. Worldwide, more than 46 million people are affected by dementia. If no effective treatment is identified, this number is expected to double every 20 years. This illustrates the urgent need for identification and testing of alternative molecular and cellular targets that would allow effective modulation of AD pathological processes and clinical outcomes [1]. In the sections below, potential microglia-related targets are identified that could be used to design novel therapeutic agents for AD.

Microglia physiology

Microglia represent an ontogenetically distinct population of mononuclear phagocytes, which originate from yolk sac progenitors at the early stages of embryogenesis; therefore, they are considered the resident macrophages of the central nervous system (CNS) [3,4]. Microglia participate in a range of physiological processes during brain development and maturation. For example, they secrete brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and several other neurotrophic factors that support neurogenesis. Since many unwanted cells have to be removed during neurodevelopment, microglia are essential for elimination of such cells through phagocytosis [5,6]. Microglia also closely associate with the developing CNS vasculature and genetic ablation of these cells leads to a sparser vascular network, indicating the supportive role of microglia in angiogenesis. To promote angiogenic sprouts, thus facilitating the formation of the vascular network, microglia secrete factors different from vascular endothelial growth factor-A (VEGF-A) [7].

In the mature CNS, microglial growth factors are essential for the formation of new synapses, for example, as part of the hippocampal neurogenesis, but microglia also participate in synaptic pruning by phagocytosing inactive synapses that have been labeled with the complement proteins C1q and C3 [8,9]. Under physiological conditions, most microglia are characterized by highly branched processes displaying ramified morphology. Due to the observed tile-like network that microglia form covering the CNS parenchyma, it was initially hypothesized that these cells did not touch or overlap with each other. Recently, two-photon excitation microscopy has been used to demonstrate that these cells, initially believed to be in resting state, in fact are actively sampling CNS environment. They are touching neighbouring cells and blood vessels by extending and retracting their thin, branched processes; therefore, microglia are constantly surveying brain parenchyma and are able to react and move quickly to sites of injury or invasion by pathogens [10-12].

Microglia and the neuroinflammatory hypothesis of Alzheimer’s disease

Identification of reactive microglia in the post-mortem brain tissues of AD patients served as the initial evidence of the neuroimmune response being launched in the brain areas heavily invaded by plaques and tangles, the main histological markers of AD neuropathology. Up until then, AD was considered to affect neurons selectively. These initial studies demonstrated that the hippocampal and cortical structures affected by the disease were infiltrated by reactive microglia as well as astrocytes, which are another type of the non-neuronal glia of the brain. Reactive microglia were identified as having swollen, amoeboid shape. They were phagocytic, and were overexpressing the major histocompatibility complex (MHC) class II human leukocyte antigen (HLA)-DR isotype proteins on their surface as revealed by the immunohistochemistry techniques [13,14].

The neuroinflammatory hypothesis of AD, which states that glia-driven immune processes contribute to the onset and progression of this disease, is now supported by several other lines of evidence: 1) The reactive phenotypes of microglia and astrocytes in AD brains have been confirmed by identifying a range of other morphological and functional parameters [15]; 2) Biochemical and molecular biology studies have demonstrated upregulated inflammatory cytokines, chemokines, and complement in brain tissue affected by AD as markers of neuroimmune activation [16]; 3) More than a dozen epidemiological studies have identified reduced risk of AD in chronic users of anti-inflammatory drugs [17]; 4) Positron emission tomography (PET) techniques using a specific ligand for the mitochondrial translocator protein (TSPO, also known as the peripheral benzodiazepine binding site), which labels...
reactive microglia, show involvement of these cells at the early stages of AD pathogenesis [18]; 5) Upregulated inflammatory markers and glial activation are observed in the animal models of AD; however, it is important to note that there are significant phenotypic and functional differences between reactive microglia, as well as astrocytes, from human AD tissues and AD mouse model brains [19,20]; 6) Genome-wide association studies have revealed several inflammation-related genes as late-onset AD risk factors with low to moderate effect sizes. Examples of these genes, which are mainly expressed by microglia in AD brains, include triggering receptor expressed on myeloid cells 2 (TREM2); cluster of differentiation (CD) 33 (SIGLEC-3, sigl acid-binding Ig-like lectin 3); complement receptor 1 (CR1); phospholipase C gamma 2; and inositol polyphosphate-5-phosphatase [21,22].

**Pro-inflammatory activation of microglia in AD**

The initial reports of reactive microglia in AD demonstrated that these cells surrounded Aβ-containing senile plaques [13,14]. Since then, it has been shown by using cultured cells and animal models of AD that microglia can be adversely activated by Aβ, which leads to secretion of inflammatory mediators. Based on the previously described M1 and M2 activation states of peripheral macrophages [23], it has been proposed that Aβ can induce the so-called classical pro-inflammatory M1 phenotype of microglia. Such pro-inflammatory activation of microglia is also induced by established immune stimuli interferon (IFN)-γ and lipopolysaccharide (LPS) [24]. In addition to the evidence collected by using isolated microglia cultures and AD animal models, a significant support to the proposed adverse contribution of microglia to the disease pathogenesis comes from clinical PET imaging studies showing strong correlation between reactive microglia and cognitive decline in AD patients [25]. Since the inflammatory mediators and cytotoxins released by M1 microglia could be at least partially responsible for the neuronal death in AD, preventing or slowing down microglial transition from the "surveying" to M1 phenotype could be an effective strategy for attenuating AD progression [10,26,27].

Several molecular targets have been proposed for achieving this goal. As a result of an intense research effort, more than ten different microglia receptors have been identified that can mediate their pro-inflammatory activation by Aβ. They include receptor for advanced glycation end products (RAGE), toll-like receptors (TLRs) 2 and 4, macrophage receptor with collagenous structure (MARCO), CD36, formyl peptide receptor 2 (FPR2), peroxisome proliferator-activated receptors (PPARs) γ, δ, and α, and liver X receptors (LXR) α and β. It has also been established that microglial activation by Aβ depends on the polymerization state of this peptide with oligomeric soluble Aβ being more pro-inflammatory than its insoluble fibrillar forms. Several distinct intracellular signaling molecules mediate the pro-inflammatory transformation of microglia including dual specificity phosphatase 2 (DUSP2), nuclear factor (NF)κB, and the three main mitogen-activated protein kinases (MAPKs): extracellular signal-regulated kinase (ERK), c-Jun terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 MAPK (for reviews see [28-31]). Antagonists of the microglia receptors that are activated by the soluble oligomeric Aβ and inhibitors of key intracellular signaling pathways engaged by these receptors could be developed as therapeutic agents in AD.

Soluble Aβ oligomers are not the only microglial stimulants present in the extracellular space of AD brain parenchyma. Several different damage-associated molecular patterns (DAMPs) have been shown to be released from damaged neurons and/or glial cells. For example, the non-histone DNA binding protein high-mobility group box 1 (HMGB1), normally located in the cell nucleus, is released passively from dying cells or actively secreted through several different pathways by stimulated cells [32-34]. Cytochrome C and mitochondrial transcription factor A (TFAM), which are mitochondrial proteins, can also be released into extracellular space and activate microglia [35-37]. All these proteins act like typical DAMPs by binding to the pattern-recognition receptors (PRRs) expressed by microglia inducing their pro-inflammatory activation. Therefore, microglial PRRs such as RAGE, nucleotide-binding oligomerization domain-like receptors (NLRs), TLR 2 and TLR 4, as well as the intracellular signaling pathways associated with these receptors, could be targeted to inhibit adverse activation of microglia [38-40].

Reactive microglia can cause neuronal damage directly by phagocytosing stressed, but live, neurons, and by stripping dendritic spines in complement-dependent manner [41,42]. Pro-inflammatory microglia also release a mixture of neurotoxins whose composition most likely depends on the nature and concentration of stimulating agents present in the extracellular space. Even though significant interspecies differences have been noted [6], several well-characterized neurotoxins are secreted by microglia from different species. They include reactive oxygen species (e.g., superoxide anion), excitatory amino acids (e.g., L-glutamate), neurotoxic metabolites (e.g., quinolinic acid), phospholipases (e.g., secreted phospholipase A2 group IIA), and proteases (e.g., cathepsin B, prolyl endopeptidase) capable of killing neurons directly (reviewed in [43-48]). Designing selective therapeutic agents that scavenge or neutralize some of the toxins (reactive oxygen species), block neuronal receptors interacting with the neurotoxins (L-glutamate), or inhibit their enzymatic activity (proteases and phospholipases) could be a valid strategy for lowering the impact of adverse M1 activation of microglia.

In addition to their direct neurotoxicity, reactive microglia contribute to neuronal injury indirectly. Increased secretion of chemokine (C-C motif) ligand 1 (CCL1), CCL20, interleukin (IL) 1β, IL-6, and tumor necrosis factor (TNF) α is an established characteristic of the classical M1 activation phenotype of microglia [49]. Once released by reactive microglia, the above cytokines and chemokines can recruit and activate surrounding surveying microglia and astrocytes in paracrine manner. Interestingly, astrocytes have been recently shown to become neurotoxic in response to IL-1α, TNFa, and complement C1q secreted by reactive microglia. Such a neurotoxic state of astrocytes has been termed A1 phenotype and cells displaying this novel phenotype have been identified in brains of AD patients [50]. Neutralizing microglial pro-inflammatory cytokines and chemokines, as well as blocking their corresponding receptors on microglia and astrocytes, should be considered as a means of slowing down neuroinflammatory cascades in AD. A recent trend in new drug discovery effort should be noted, which involves multi-target directed ligand (MTDL)-based strategies incorporating two or more pharmacophores into a single drug molecule. In the MTDL drugs designed for AD, one or more of the pharmacophores could be directed at microglia-specific targets such as cytotoxic proteases, cell surface receptors, or intracellular signaling molecules [31].

**Anti-inflammatory activation of microglia in AD**

In AD brains, surveying microglia can transition not only to the M1 pro-inflammatory activation state but also to the alternative M2 anti-inflammatory/resolution activation state. The M2 phenotype can be induced by IL-4, IL-10, and IL-13, and is characterized by secretion of several anti-inflammatory cytokines including IL-10, IL-1 receptor
Microglia have been shown to switch from M2 to M1 phenotype as AD pathology progresses in a double-transgenic mouse model [55]. While the dominance of M1 microglia during late AD is consistent with their adverse effects on neuronal survival, M2 activation of microglia at the early disease stages indicates these cells could have upregulated protective functions aimed at restoring brain homeostasis. It has been proposed that M2 microglia, as well as possibly DAMP, are protective by phagocytosing Aβ deposits and degrading extracellular Aβ by secreting several different proteases, in addition to secreting anti-inflammatory cytokines [49,54,56]. While some of the microglia receptors, such as CD36, TLR2, and TLR4 have been associated with both Aβ phagocytosis and pro-inflammatory adverse activation, several receptors contribute to Aβ phagocytosis by microglia with relative selectivity; they include scavenger receptor A-1 (SCARA-1) and chemokine-like receptor 1 (CMKLR1) [30]. Thus, therapeutic agents that facilitate transition of microglia to M2 phenotype either from the surveying or M1 state could be beneficial in AD due to upregulated Aβ clearance capacity of microglia and secretion of anti-inflammatory cytokines.

The functional state of microglia can be regulated by a diverse set of soluble molecules as well as through direct contact with other cells and insoluble structures such as amyloid plaques [5,51]. In addition to DAMP discussed above, there is an emerging group of molecules termed resolution-associated molecular patterns (RAMPs), which inhibit the secretion of pro-inflammatory cytokines and cytotoxins by immune cells [57]. Thus far, RAMPs have been mainly studied in the context of peripheral diseases; however, evidence is accumulating that some of these molecules reduce adverse activation of microglia and facilitate removal of Aβ aggregates. For example, galectin-1 has been shown to deactivate M1 microglia [58], binding immunoglobulin protein (Bip, GRP78) stimulates Aβ clearance by microglia [59], and extracellular cardioliopin upregulates microglial phagocytosis and expression of neurotrophic factors, but decreases their secretion of inflammatory mediators and cytotoxins [60]. Furthermore, disease symptoms can be reduced in AD model mice by overexpressing heat-shock protein 27 (HSP27) [61] or administering cardiolipin-containing liposomes [62] illustrating that some of the RAMPs could have a potential as therapeutic agents in AD.

Conclusion

The contribution of neuroinflammation to AD pathogenesis as well as the central role of microglia in neuroimmune processes are becoming increasingly recognized. Reactive microglia can play both beneficial and detrimental roles in AD; therefore, future studies should identify therapeutic agents and strategies that can selectively downregulate or mitigate harmful activity of microglia, including their secretion of pro-inflammatory cytokines and neurotoxins, while preserving or even upregulating their beneficial functions such as phagocytosis and removal of Aβ. Development of such therapeutic agents and strategies is challenging due to the shifting balance between M1/M2 microglia in AD progression, the significant overlap of receptors and signaling molecules regulating the beneficial and the harmful functions of microglia, and the presence of blood-brain barrier, which restricts access of large molecules – including proteins and phospholipids – to microglial targets.

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