Monocytes and Alzheimer's disease

Yu FENG¹, Lei LI¹, Xiao-Hong SUN²

¹Department of Neurology, The First Affiliated Hospital, China Medical University, Shenyang 110001, China

²Department of Neurology, The Fourth Affiliated Hospital, China Medical University, Shenyang 110000, China

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by extracellular amyloid beta (A β) deposition and intracellular neurofibrillary tangle formation. Monocyte is part of the innate immune system and can effectively remove dead cells and debris. It has been suggested that A β can recruit monocytes into brain in AD mice, resulting in restriction of cerebral amyloidosis. However, monocyte may act as a double-edged sword, either beneficial (*e.g.*, clearance of A β) or detrimental (*e.g.*, secretion of neurotoxic factors). In addition, recent studies indicate that in AD patients, A β phagocytosis by monocytes is ineffective. The present review mainly summarized the current knowledge on monocytes and their potential roles in AD.

Keywords: Alzheimer's disease; amyloid beta; monocyte; inflammation; neurotoxic factors

1 Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly and is characterized by progressive dementia and presence of amyloid beta (A β) plaques and neurofibrillary tangles. Currently, it has affected 20–30 million people worldwide^[1]. Although A β has been considered to play a key role in AD pathogenesis^[2,3], the precise neuropathogenic mechanism remains largely unknown. Accumulative evidence suggests that A β accumulation in the brain of AD patients is due to its overproduction (familial AD) and the deficiency in its clearance from the brain (sporadic AD)^[4]. The detrimental effects and lack of beneficial effects tilt the balance between A β production and clearance to neuronal pathology. Monocytes, which constitute part of the innate immune system and play a ma-

jor role in immune surveillance in the body, can effectively remove dead cells and debris^[5]. Immunohistochemical studies of the frontal lobe and hippocampus of AD brain have shown perivascular and intraplaque infiltration by blood-borne macrophages containing intracellular A β , but inefficient A β clearance^[6]. Besides, recent evidence indicates that deficiency in chemokine (C-C motif) receptor 2 (CCR2) can lead to impaired recruitment of mononuclear phagocytes and increased cerebral amyloid burden in AD mice, while increased recruitment of these cells into the brain of AD mice can result in restriction of cerebral amyloidosis^[7]. These findings suggest that monocytes play an important role in the clearance of A β . However, Fiala M *et al.*^[6] reveal that unlike control monocytes, the monocytes in AD patients exhibit poor differentiation into macrophages and only surface uptake of A β . Besides, they suffer apoptotic cell death. The intracellular cytokine assay further suggests that the cytokines interleukin (IL)-10 and interferon γ (IFN- γ) are over-expressed in T cells, and the cytokine IL-12 is over-expressed in monocytes of AD

Corresponding author: Yu FENG

Tel & Fax: 86-24-83282315

E-mail: fengyu_1976@163.com

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patients. Thus, it is hypothesized that increased neuroinflammation and decreased A β phagocytosis play important roles in AD development.

2 Monocytes

Circulating blood monocytes are the precursors of tissue macrophages, osteoclasts and antigen-presenting cells (APCs)^[5,8,9]. They are derived from myelomonocytic stem cells in the bone marrow and then are released into circulation^[10]. Monocytes show not only morphological heterogeneity regarding the size, granularity and nuclear morphology, but also immunophenotypic and functional heterogeneity^[11]. They can be divided into at least 5 subsets with different surface expressions of lipopolysaccharide receptor CD14, Fc γ receptor I (CD64), Fc γ receptor II (CD32), Fc γ receptor III (CD16), the neural cell adhesion molecule (NCAM) CD56, the sialoadhesin CD33, the co-stimulatory molecule CD40, and the receptor tyrosine phosphatase CD45^[12–14]. The classical monocyte subpopulation 1 is characterized by a high expression level of CD14 but without CD16 expression. Approximately 60% of the monocytes belong to this subpopulation. These CD14⁺⁺CD16[–] cells also express CD64 and CD32, possessing a high phagocytic activity and producing large amounts of cytokines. Approximately 25% and 9% of the monocytes belong to the subsets 2 and 3, respectively, both having a high capacity of phagocytosis and different from subset 1 in their expression of CD16. Subset 3 also expresses CD14 at a low level. Precursors of dendritic cells, which constitute approximately 4% of the monocytes, are categorized into subset 4 (CD14^{dim}CD33⁺), with a high expression level of the co-stimulatory molecule CD40. The smallest subset of monocytes, subset 5, which is comprised of approximately 2% of the monocytes, overlaps with subset 1 and differs from the predominant population of CD14⁺⁺CD16[–] cells in the additional expression of the NCAM CD56, a marker correlated with immaturity. Additionally, CD14⁺⁺CD16[–] monocytes express CCR2 whereas CD14⁺CD16⁺ monocytes express CCR5^[14,15]. After entering the tissues and organs, monocytes differentiate into macrophages, a process regulated by the macrophage

colony-stimulating factor (M-CSF)^[16]. Macrophages are important for the removal of dead cells and debris during inflammation. They can internalize and degrade proteins, and release a variety of cytokines upon activation^[17]. The secreted cytokines and chemokines recruit immune cells to the sites of infection and inflammation. Macrophages are part of the innate immune system and are also characterized by a high degree of heterogeneity depending on the tissue microenvironment, such as osteoclasts in the bone, alveolar macrophages in the lung and microglia in the brain. *In vitro*, 2 activation states or phenotypes of macrophages can be distinguished^[18]. Classically activated macrophages (M1) induced by pro-inflammatory mediators are characterized by enhanced productions of pro-inflammatory cytokines and reactive oxygen species (ROS). Alternatively activated macrophages (M2) which are generated *in vitro* by IL-4 and IL-13, secrete high amounts of anti-inflammatory cytokines, inhibiting inflammation and promoting tissue repair. Monocytes/macrophages are involved in the pathogenesis of several diseases and their abnormal activation can result in acute and chronic inflammation. In atherosclerosis, monocytes are attracted to the sites of modified lipoprotein accumulation in vessel walls^[19,20]. After entering the vessel wall, they differentiate into macrophages, and by uptaking and storing modified lipoproteins such as enzymatically degraded LDL (E-LDL) and oxidized LDL (ox-LDL)^[21], these monocyte-derived macrophages become foam cells, a hallmark of atherosclerosis^[20,22]. Dendritic cells derived from subset 4 monocytes are specialized APCs^[14]. In addition, tissue macrophages are involved in antigen presentation. Following phagocytosis and degradation of pathogens, antigenic peptides are coupled to major histocompatibility complex (MHC) class II molecules and then presented on the cell surface to T cells, thereby activating the adaptive immune system^[23].

3 Monocytes and microglia

3.1 Microglia Microglia are resident macrophages in the central nervous system (CNS) and the spinal cord. They constitute approximately 12% of the total cells in the

CNS^[24] but are not uniformly distributed. A large proportion of microglia are found in gray matter, with the highest concentrations in the hippocampus, olfactory telencephalon, basal ganglia and substantia nigra, where they are located in close vicinity to neurons. In the white matter of the CNS, microglia are localized between fibre tracts. In close contact with blood vessels, the perivascular microglia, a specialized type of microglia, can be found^[25]. Ramified microglia that are believed to be resting cells, can permanently detect minor tissue injury in CNS^[26]. Microglia are considered as the immune cells of the CNS and their response to pathology is termed microglial activation. Microgliosis describes the focal accumulation of activated and proliferating microglia. Once activated, the microglia undergo morphological changes from the ramified state to an amoeboid state, and the surface molecules such as CD14, MHC molecules, and chemokine receptors are up-regulated. In mature brain, the ramified processes of microglia extend into the surrounding tissue. Importantly, in the normal brain, the interactions of microglia with both neurons and other glia cells suppress the activation of microglia, and dampen their responses to pro-inflammatory signals and spurious induction of an immune response^[27]. Besides, they have similar functions as tissue macrophages, including phagocytosis, antigen presentation, as well as production and release of cytokines, eicosanoids, complement components, glutamate, and reactive oxygen and nitrogen species. Microglial cells exert several beneficial effects in the CNS, such as enhancing neuronal survival by clearance of toxic cellular debris as well as releasing trophic and anti-inflammatory factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). During brain development, microglia are also involved in programmed neuronal death. In mature brain, they play a role in lesion repair through attracting stem cells to the site of inflammation or injury^[28].

3.2 Microglia derived from monocytes Despite the intensive studies, whether microglia are lifelong residents in the brain remains obscure. Besides, whether they normally renew themselves through proliferation within the brain or take myeloid progenitors that normally infiltrate the brain

as sources is still a matter for debate. Unlike macroglia (astrocytes and oligodendrocytes) and neurons derived from neuroectoderm, microglial progenitors arise from peripheral mesodermal (myeloid) tissue. This is supported by the fact that microglia express the myeloid-specific transcription factor PU.1^[29] and the stem cell/progenitor cell marker CD34^[30].

During development, microglial progenitors which are derived from mesenchymal myeloid lineage progenitor cells, immigrate into the embryonic brain early in gestation^[31]. They proliferate *in situ* and exhibit a motile amoeboid phenotype, populating the brain before the development and closure of the blood-brain barrier (BBB). This population is thought to be distinct from fetal macrophages that are also myeloid in origin but arise from monocytes in the fetal circulation. The fetal macrophages also invade the developing brain and contribute to the microglial population, particularly at later developmental stages^[32]. In the normal mature brain, turnover of microglia is at a low level, and these cells are renewed by proliferation of endogenous microglia^[31,33]. Under normal conditions, infiltration of peripheral blood cells is normally prevented by the BBB. Specifically, the infiltration of peripheral monocytes into the normal brain is infrequent and the levels of these cells are very low. A number of CNS disorders are accompanied by brain infiltration by peripheral monocytes, macrophages, or T lymphocytes, which is influenced by cytokines and chemokines^[34]. For example, D'Mello *et al.* have shown that peripheral tumor necrosis factor α (TNF- α) signaling can stimulate the production of monocyte chemoattractant protein (MCP)-1/CCL2 by microglia, which drives the subsequent infiltration of CCR2-expressing monocytes into the brain^[34]. This is supported by experimental models of stroke and neuronal injury whose BBB is compromised^[35] and models whose BBB is not compromised (*e.g.*, in the hypoglossal nucleus after lesion of its innervating nerve). Data from Schwartz and colleagues have shown that the spatial organization of the infiltrating monocyte-derived cells around the lesion site has a direct impact on functional indices of recovery following spinal cord injury^[27]. In another study, this group

showed that infiltrating blood-derived macrophages play a novel anti-inflammatory role in recovery from spinal cord injury, which cannot be provided by activated resident microglia^[36], suggesting that the bone marrow stem cells are able to populate the CNS and to differentiate into microglia. However, there are certain differences between resident microglia and blood-derived microglia. Unlike normal microglia, the perivascular microglia are regularly replaced by bone marrow-derived precursor cells^[37] and express immune activation markers, such as hemoglobin-haptoglobin scavenger receptor (CD163), mannose receptor (CD206), CD4 and MHC class II antigens^[38]. In addition, CD45, which is expressed at a low level in endogenous microglia but at a high level in blood-derived monocytes (CD45^{hi}), distinguishes the blood-derived monocytes from the endogenous microglia^[39]. By using immunohistochemical staining for CD45 and the adhesion receptor CD11b, a marker for microglia and mononuclear phagocytes, researchers found that in the whole brain of Tg2576 mice, an AD model expressing the 695-amino acid isoform of human amyloid precursor protein (APP), the percentage of CD11b⁺CD45^{hi} cells shows a 10-fold increase compared with that in the wild-type brain^[40]. It is reliable, if CD45 is restricted to infiltrating cells and is unaltered for a significant period of time once the cells are resident in the tissue. In addition, some experimental strategies have been proposed to discriminate between peripheral and CNS-resident mononuclear phagocytes, such as generating chimeric mouse models expressing green fluorescent protein in the bone marrow compartment^[7].

3.3 Activation of microglia Microglia and macrophages express receptors specific for innate immunity, such as Toll-like receptors (TLRs), the lipopolysaccharide receptor CD14, MHC class I and II antigens, Fcγ receptors I-III (CD64, CD32 and CD16), complement receptors (CR1, CR2 and CR4), β2-integrins, intercellular adhesion molecule-1 (ICAM-1), and co-stimulatory molecules B7-1 and B7-2^[41–43]. Engagement of the host defense mechanisms provokes the conversion of microglia from a “resting” state into an “activated” phenotype, which is associated with a robust and coordinated response involving those

cytokines and chemokines, production of free radicals, and the generation of acute-phase proteins^[44]. Although effective in eliminating pathogens, it is maladaptive when these mechanisms are engaged by disease processes that originate within the tissue itself, especially in the CNS. In AD brain, the formation of amyloid fibrils and their deposition elicit the phenotypic activation of microglia and the panoply of responses that accompany the activation of host defense mechanisms. Quiescent microglia, however, do not express CD163, MHC class II or CD14. Upon activation, microglial cells up-regulate the surface expressions of CR3, MHC class I and II antigens^[37].

4 Monocytes in AD

4.1 Involvement of monocytes in AD The role of peripherally derived monocytes in AD has been widely studied, but controversy still exists. In a postmortem study using immunohistochemistry method, Fiala M *et al.* revealed perivascular and intraplaque infiltration of blood-borne macrophages containing intracellular Aβ, but only with inefficient clearance of Aβ deposits, in the frontal lobe and hippocampus of AD patients^[6]. Simard *et al.*^[45] have reported infiltration of significant numbers of bone marrow-derived macrophages in the brain of AD murine model, and that importantly, selective elimination of these cells by genetic and pharmacological manipulations results in increased plaque burden. More compelling evidence comes from the study of Hickman SE *et al.*, who reported that *ccr2* deficiency impairs recruitment of mononuclear phagocytes and increases cerebral amyloid burden in APP Tg2576 mice, and increased recruitment of these cells results in restriction of cerebral amyloidosis^[40]. Furthermore, in the study of Town T *et al.*^[46], C57BL/6 mice with expression of CD11c promoter-driven dominant-negative TGF-β receptor type II (CD11c-DNR) were crossed with APP Tg2576 mice. In the generated Tg2576-CD11c-DNR mice, researchers find that brain plaque pathology is dramatically attenuated, and this is associated with increased infiltration of Aβ-containing peripheral macrophages around cerebral vessels and Aβ plaques. Guerreiro RJ *et al.* even suggest peripheral inflammatory cytokines as bio-

markers in AD and mild cognitive impairment^[47]. All these above findings strongly support that the bone marrow-derived monocytes are involved in the course of AD.

4.2 Clearance of A β by monocytes As already mentioned, monocytes play a beneficial role against AD pathogenesis by degradation of A β peptides. Indeed, monocyte attachment is an initial step to clear these deposits and stop or delay their neurotoxic effects. In transgenic animals, many microglia that infiltrate amyloid plaques originate from the bone marrow and are attracted by A β peptides. Recently, Heneka MT *et al.* have revealed that the focal activation of microglia including monocyte-derived microglia becomes apparent in 3-month-old APP V717I transgenic mice, but A β usually starts to deposit in plaque-like structures much later around 10–12 months^[48]. They propose that the soluble A β and the secreted APP may cause this early microglia activation. In another study, Meyer-Luehmann M *et al.* used *in vivo* multiphoton microscopy to sequentially image 5–6-month-old olf B6C3-YFP transgenic mice (bearing *APP^{swe}* and *PS1d9xYFP* genes) and found that microglia can be recruited by A β plaques^[49]. Furthermore, various chemokine pathways can contribute to the recruitment of mononuclear phagocytes in the CNS. Besides, Hickman SE *et al.*^[7] have demonstrated that chemokine receptor CCR2 can induce the recruitment of mononuclear phagocytes to A β plaques in Tg2576 mice. In addition, IL-16, receptor for advanced glycation end products (RAGE) and platelet endothelial cell adhesion molecule 1 also contribute to the recruitment of these cells across the BBB induced by A β . Clodronate-mediated depletion of perivascular macrophages *in vivo* can significantly increase cerebral amyloid angiopathy in TgCRND8 AD transgenic mice, whereas chitin stimulates perivascular macrophage turnover and promotes A β clearance. After being attached, the monocytes egress from the bone marrow into the blood, and cross the BBB to the perivascular areas, entering the brain parenchyma, where they produce neurotoxic cytokines, bind and phagocytize A β . The phagocytosis of soluble A β involves scavenger receptors A and B, IFN- γ , ILs, complements and NF- κ B, but the underlying mechanism is unclear^[50]. It has been shown that blood-de-

rived microglia play a beneficial role in CD14-dependent phagocytosis and degradation of A β peptides^[51]. In a recent study, using a microglial ablation system through herpes simplex virus thymidine kinase expression under the control of the CD11b promoter and ganciclovir treatment *in vivo*, ablation of microglia in an AD mouse model that develops plaque pathology at 2–3 months of age, does not affect plaque load^[52]. One interpretation for this finding is that the existence of toxic amyloid species and inflammatory mediators may lead to an early loss of key functions of microglia including phagocytosis, resulting in paralysis of these cells. Apparently, ablation of these paralyzed microglia would not result in any change of A β plaque load, since these cells have by far earlier stopped to limit plaque build-up in such a scenario.

4.3 Defective clearance of A β in AD Although blood-derived monocytes in AD patients are able to migrate across the BBB and phagocytize A β , more and more studies report that their ability of A β clearance is impaired. In contrast to the monocytes from normal subjects, monocytes from AD patients show disturbed transport of A β into endosomes and lysosomes and defective A β clearance. Moreover, AD monocytes display poor differentiation and only surface uptake of A β compared to the cells from age-matched controls^[6]. AD monocytes also display abnormal expression of cytokines and suffer apoptosis. Current results indicate that the defective A β phagocytosis may be due to the down-regulation of several genes, including the glycosyltransferase gene *MGAT3* and *TLRs* genes. IL-10 is a cytokine that strongly inhibits the function of monocytes/macrophages and plays a role in abnormal phagocytosis of A β in AD. Fiala M *et al.*^[6] suggest that the crucial defect of AD macrophages does not lie in A β binding but in intracellular signaling through NF- κ B.

4.4 Increased inflammation of monocytes While the innate immune system can ward off A β , this comes at a cost, as the engagement of the innate immune response also results in inflammatory damage to the tissue. Moreover, A β itself is pro-inflammatory and can activate microglia to release neurotoxic factors^[53]. Products of activated mononuclear phagocytes may be also involved in AD pathogenesis.

Nearly all the cytokines that have been studied, including IL-1 α / β , IL-6, TNF- α , IL-8 and TGF- β , are up-regulated in AD compared to those in healthy age-matched individuals. Some reports have demonstrated increased plasma levels of these cytokines in patients with mild AD, and the levels, however, gradually decrease with disease progression.

Epidemiological studies indicate that medication with nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease the risk of AD by nearly 50% and delay AD onset by 5–7 years^[54]. Although NSAIDs do not necessarily affect the activation of mononuclear phagocytes^[55], they may reduce inflammation-mediated neuronal injury by suppressing COX-1- and COX-2-mediated synthesis of prostaglandins from arachidonic acid. Another drug for AD treatment is Memantin, an NMDA receptor antagonist with a relatively low affinity. Memantin acts by inhibiting NMDA receptor function to abrogate the neurotoxic damage caused by increased glutamate level in response to mononuclear phagocyte activation. The anti-inflammatory drug minocycline can also reduce microglial activation and improves behavioral performance in AD mice, although it does not affect A β deposition. These results, together with other observations, indirectly demonstrate that mononuclear phagocyte-mediated inflammation in AD is excessive.

5 Conclusion

Monocytes constitute the principal elements in the clearance of A β and play a crucial role in AD progression. Paradoxically, as discussed above, in AD brain, neuroinflammation is excessively increased but A β phagocytosis is defective. Concomitantly, a number of pro- and anti-inflammatory cytokines are dysregulated in AD patients. Also, there is an increase in incompetent memory T cells and a corresponding decline in macrophages in these patients.

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单核细胞和阿尔茨海默病

冯昱¹, 李蕾¹, 孙晓红²

¹ 中国医科大学附属一院神经内科, 沈阳 110001

² 中国医科大学附属二院神经内科, 沈阳 110000

摘要: 阿尔茨海默病(Alzheimer's disease, AD)是神经退行性疾病中最常见的类型。胞外 β 淀粉样蛋白(amyloid beta, A β)的沉积和胞内神经原纤维的缠结是典型的AD神经病理学特征。单核细胞是天然免疫细胞,可以有效清除坏死细胞及碎片。在AD模型鼠上的许多实验研究表明, A β 可以使单核细胞向大脑募集,从而限制脑内的淀粉样变性。然而,单核细胞也是一把双刃剑:一方面它可以清除A β ,另一方面它又能分泌神经毒性因子,损伤神经细胞。此外,近来也有研究表明,在AD患者脑内,单核细胞并不能有效清除A β 沉积。本综述主要对单核细胞及其在AD中的潜在角色进行讨论。

关键词: 阿尔茨海默病; β 淀粉样蛋白; 单核细胞; 炎症; 神经毒性因子