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COGNITIVE FUNCTION AND AGING (DAVE MORGAN, SECTION EDITOR)

Animal Models of Alzheimer's Disease: Utilization of Transgenic Alzheimer's Disease Models in Studies of Amyloid Beta Clearance

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Abstract Glial cells in Alzheimer's disease (AD) have been shown to be capable of clearing or at least restricting the accumulation of toxic amyloid beta (Aβ) deposits. Recently, bone marrow (BM)–derived monocytic cells have been recognized in experimental studies to be superior in their phagocytic properties when compared to their brain endogenous counterparts. In human AD, BM-derived monocytic cells may have deficiencies in their capacity to restrict plaque growth. Therefore, enhancement of phagocytic properties of cells of monocyte origin, both brain endogenous microglia and BM-derived monocytic cells, offers an attractive therapeutic approach to fight off AD. Transgenic mouse models with aberrant Aβ deposition offer a valuable tool for discovery of novel pathways to facilitate cell-mediated Aβ uptake. This article reviews the most recent findings on the phagocytic capacity of cells with monocytic origin in various transgenic AD models and describes the methods to study phagocytic activity of these cells.

Keywords Alzheimer's disease · Amyloid precursor protein · Amyloid beta · Presenilins · Transgenic mice · Inflammation · Cytokines · Chemokines · Phagocytosis · Lysosomes · Microglia · Bone marrow · Macrophages · Aging · Cognitive function

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Introduction

Microglia and bone marrow (BM)–derived monocytic cells have been implicated in Alzheimer's disease (AD) pathogenesis. The role of microglia in the development of AD has for long been under debate. As AD progresses, the magnitude of proinflammatory microglia-secreted cytokines increases, contributing to the vicious cycle of inflammation and following neuronal damage. In addition, some evidence suggests that microglia may actually promote Aβ deposition. On the other hand, whereas microglial phagocytosis of Aβ in vivo may be rather limited, microglia in vitro are efficient Aβ phagocytes. A subpopulation of brain monocytic cells enters the brain from the circulation upon brain damage. Infiltration of BM-derived cells is very limited in healthy brain and in AD transgenic mice [1, 2••] but this infiltration is increased upon injury associated with blood–brain barrier (BBB) disruption, and infiltrated monocytic cells have been detected in brains of AD patients who quite often suffer from comorbidities such as small cerebral infarcts [3]. BM-derived cells have been shown to be superior in phagocytosing and clearing Aβ in several different models developed to assess phagocytic activity [4–7]. AD transgenic mice with aberrant Aβ accumulation have been the major cornerstone in studies revealing novel pathways to enhance Aβ clearance. This review article describes the most recent findings on the phenotype of phagocytic cells across different currently available transgenic AD models. In addition, development of methods for assessing the Aβ phagocytic properties is discussed.

Alzheimer's Disease Animal Models

AD research was clearly boosted by the development of transgenic mouse models, and to date, the availability of such models is ample. The obtained pathology of AD mice depends on the transgene, promoter, and mutation of choice; the integration site; and the achieved expression level of the transgene. Human amyloid precursor protein (hAPP) in different length, either 695, 751, or 770 amino acids, have been used as transgenes with several mutations and with either neuron-specific platelet-derived growth factor and Thy-1 promoters or nonneuronal hamster PrP promoter. The onset and severity of Aβ pathology has been indicated to depend on achieved Aβ 1–42 levels, with the mutations in APP augmenting the pathology (reviewed in [8]). Whereas mutated APP isoforms seem to be sufficient to cause Aβ deposition, presenilin (PS) 1 or 2 alone are unable to result in any detectable lesions despite the fact that elevation in Aβ levels is observed. Overexpression of mutated PS together with mutated hAPP isoforms aggravates the progression of Aβ pathology with earlier appearance of the plaques. In addition to the APP- and PS-based transgenic mice, transgenic mice carrying mutated tau also have been developed [9]. Overexpression of tau alone is not sufficient to result in plaques, but, together with APP and PS, recapitulates both neurofibrillary tangles and plaques.

Despite the transgene expressed, none of the currently available transgenic mouse models capture the full human AD pathology. However, they are suitable for studies of Aβ phagocytosis due to the facts that

(1) similar to human brain, Aβ deposition increases with aging;
(2) Aβ in mouse models occurs in similar form as in human AD brain; compared to human cases, the deposited Aβ in AD transgenic mice is similar in size, and stains with Congo red and Thioflavin S and also can be found around the vasculature as amyloid angiopathy;
(3) plaques are recognized by glial cells which are recruited around the deposits; and
(4) brain levels of Aβ in these models correlate, at least to some extent, with the severity of cognitive impairment (nicely reviewed by Duyckaerts et al. [8]).

Microglial Phenotype in Alzheimer's Disease Models

Microglia are the main immunological effector cells with phagocytic properties in the brain. The origin of microglia has long been suggested to lay on the hematopoietic progenitor cells; however, recent reports show that microglia derive from primitive myeloid progenitors at early embryonic life but later are maintained with minimal contribution of hematopoietic cells of peripheral origin [10, 11]. Microglia are difficult to be distinguished from other myeloid subsets, however, very recently microglia was reported to express fractalkine receptor CX3CR1, but not the chemokine receptor CCR2, from embryonic stage throughout life [11]. The phenotype of microglia had long been referred to as being either active or resting; however, it now is widely recognized that microglia display various forms of activation states and are never resting, but rather constitutively survey the brain parenchyma for pathogens. Microglial phenotypes are being categorized into M1 and M2; the latter also referred to alternative activation. M2 activation state has been further subcategorized into M2a, M2b, and M2c, but most likely any category is not able to fully capture the microglial function because microglia may have unique activation properties depending on the type of stimuli [12].

Microglia in AD mice have been proposed to exert proinflammatory phenotype. Exogenously added Aβ has been shown to promote the production of several proinflammatory mediators, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)–α, macrophage inflammatory protein-1 (MIP-1), Aβ degrading enzymes, prostanoids, complement proteins, and free radicals [13]. On the other hand, microglia recognize and respond differently even to different forms of Aβ. Oligomeric, the more toxic form of Aβ, has been shown to cause M1 shift in microglial phenotype compared to fibrillar form of the peptide [14]. In addition, preexisting activation state achieved with anti-inflammatory cytokines reduces microglial reactivity to Aβ [14].

Several proinflammatory cytokines, such as IL-6, TNF-α, and IL-1β, have been shown to be increased In brains of human AD patients [13, 15]. The situation is similar in AD transgenic mouse models. The overall levels of proinflammatory cytokines of microglial secretion seem to be upregulated, indicating a classical, cytotoxic activity of microglia, though detected cytokines and the time point of their upregulation may vary from model to model. Several studies have assessed microglial cytokine secretion [16–18] from whole brain homogenates or brain total microglia, but because other brain cells are equally capable in secreting the same cytokines as microglia and microglia may differ in their cytokine secretion depending on their surroundings, more cell-specific studies are clearly needed. Aging also may cause a shift in microglial phenotype [19]. Table 1 lists the cytokine expression profile of some commonly used AD transgenic models. In most models, Aβ accumulation precedes the upregulation of cytokines. Indeed, Aβ-laden milieu causes a shift in microglial phenotype, which may depend on not only the total brain Aβ pathology but also the microenvironment the microglial cell encounters [19, 20]. Bolmont et al. [20] showed that microglia in the vicinity of plaques are actively taking up additionally

Table 1 Microglial cytokine expression profiles in some Alzheimer's disease mouse models

Study	AD mouse model	Development of Aβ pathology	Detection method	Cytokine expression profile
Masoumi et al. [80]	APPswe/PS1dE9	4 months	IHC	TNF-α ↑ starting at age 8 mo and IL-1β, IL-6, and MCP-1 ↑ starting at age 10 mo
Hoozemans et al. [15]	APPswe/PS1dE9	4 months	Isolated microglia; qPCR	SRA, CD36, RAGE, insulysin, neprilysin, and MMP-9 ↓; IL-1β and TNF-α↑ starting at age 8 mo
Farfara et al. [81]	Tg2576	9–11 months	IHC; in situ hybridization	IFN-γ and IL-12 ↑ and IL-4 ↓ starting at age 9 mo
Jankowsky et al. [16]	APPswe; APP/PS1	11 months in APPswe; 10 weeks in APP/PS1	Organotypic slice cultures; multiplex cytokine assay	IL-1α, TNF-α, GM-CSF, and IL-6 ↑ at age 15 mo in both models. APP/PS1 brain slices produced significantly more IL-12p40, IL-1β, IL-1α, TNF-α, GM-CSF, and IL-6 compared to APPswe brain slices. Cytokine levels correlated with brain Aβ in both models
Hickman et al. [17]	PS1(M146L) x APP751sl	3–4 months	Brain homogenates; qPCR	TNFα, iNOS, IL-1β, FASL, TRAIL, nox1, and Cox2 ↑ at age 18 mo. IL-1β ↑ at age 12 mo
Hickman et al. [17]	PS1(M146L) x APP751sl	3–4 months	IHC	Microglia in the near vicinity of Aβ plaques were shown to adopt an incomplete alternative activation state characterized by elevation of YM-1 and absence of TNF-α and iNOS at age 18 mo

Aβ beta amyloid; *AD* Alzheimer's disease; *FASL* Fas ligand; *GM-CSF* granulocyte-macrophage colony-stimulating factor; *IFN-γ* interferon-gamma; *IHC* immunohistochemistry; *IL* interleukin; *iNOS* inducible nitric oxide synthase; *MCP* monocyte chemotactic protein-1; *MMP-9* matrix metalloproteinase 9; *qPCR* quantitative polymerase chain reaction ; *RAGE* receptor for advanced glycation endproducts; *SRA* scavenger receptor A; *TNF-α* tumor necrosis factor alpha; *TRAIL* TNF-related apoptosis-inducing ligand

injected Aβ dye in contrast to microglia further away from the plaques and in brains of wild-type controls, suggesting a polarized surrounding-dependent activation and phagocytic capacity of microglia in AD mouse brain. Also, neurotransmitters and neuropeptides may modulate microglial activity and Aβ phagocytosis [21, 22]. A deeper knowledge of the microglial activation properties is urgently needed to fully understand how microglial activation status could be adjusted toward more efficient phagocytosis without risking other, important properties of microglia in AD brain.

Bone Marrow–derived Monocytic Cells in Alzheimer's Disease Models

Several studies have failed to show efficient microglial in vivo Aβ phagocytosis without additional stimulus, yet increasing evidence shows that peripheral macrophages and monocytic cells are competent phagocytes. These cells have their origin in the BM, where they develop from hematopoietic stem cells (HSC). Upon stimuli, monocytic cells are released from BM into the circulation. Monocytes in the bloodstream are rather short-living and infiltrate into the target tissues followed by cytokine and chemokine secretion. The $Ly6C^{+}CCR2^{+}$ monocytes have been shown to be the direct infiltrating precursors of BM-derived microglia in the brain, with the chemokine CCL2 being the major contributor in mediating the infiltration. Infiltrating COX-2 immunoreactive monocytic cells containing intracellular Aβ also have been found in human AD brain [23]. Similar to brain microglia, BM-derived cells also have been categorized based on their activation state and expression of cell surface molecules. Roughly, proinflammatory $Ly6C^{+}$ monocytes are recruited in inflamed tissue mediated by CCL2-CCR2 interaction, whereas $Ly6C^{-}$ monocytes are thought to be recruited at the resolving phase of the insult mediated by CX3CR1 and take part in wound repair and tissue remodeling processes [24, 25] .

Whether or not microglia phagocytose Aβ in AD brain or contribute to Aβ accumulation is not yet clear; however, several lines of evidence suggest that BM monocytic cells are efficient phagocytes in vitro and in vivo [26–28]. In addition, there is evidence that monocytes in patients with AD have deficient capacity to phagocytose Aβ [29]. Although Aβ pathology itself may not be sufficient in increasing the infiltration of BM-derived monocytic cells in AD transgenic mouse brain [2••], AD patients frequently

suffer from comorbidities such as cerebral infarcts, which are associated with BBB damage. Therefore, it is likely that BM-derived monocytic cell infiltration occurs in human AD. In addition, $CD11b^+$ myeloid cells have been shown to infiltrate into AD transgenic mouse brain when infused into the bloodstream [30•]. Even without parenchymal infiltration, BM-derived cells may have an important function as Aβ phagocytizing perivascular macrophages, the absence of which was associated with increased cerebral amyloid angiopathy (CAA) and mortality in CCR2-deficient AD mice [2••].

Aβ Phagocytosis and Degradation in Alzheimer's Disease

In familial cases of AD, imbalance in the production and clearance of Aβ leads to harmful responses to specific Aβ species in neurons and glia, Aβ accumulation, and, eventually, progressive neurodegeneration [31]. Even small chronic deficits in the mechanisms of Aβ reduction may lead to aberrant Aβ accumulation. Dysfunctions in Aβ clearance by microglia or BM-derived monocytic cells in the brain parenchyma, Aβ egress from brain to blood, or Aβ clearance by perivascular macrophages and peripheral blood monocytes may contribute to increased Aβ burden. Depending on the site of Aβ accumulation, it can be referred to as parenchymal Aβ deposition or CAA. Although these conditions have different appearances and possibly altered disease severity, they probably carry similar pathological mechanisms, which also may work in parallel.

The role of microglia in the regulation of Aβ levels in AD has been under intensive investigation. Depending on conditions, glial cells may have a role in AD by potentially contributing to increased Aβ burden [32]. However, microglia as brain mononuclear phagocytes have been shown to participate in Aβ reduction with multiple mechanisms. Microglia are able to secrete various proteases such as neprilysin, insulin-degrading enzyme, angiotensin-converting enzyme, cathepsin B, cystatin C, and matrix metalloproteases (MMPs), which may degrade Aβ, among other biologically active peptides [31]. After stating this, in this context we concentrate on Aβ removal by phagocytic mechanisms by myeloid cells including microglia.

Microglia take up soluble Aβ species through nonsaturable fluid phase macropinocytosis and traffic them into the late endosomes and lysosomes for degradation [33]. Oligomeric Aβ uptake by microglia involves recognition of Aβ by scavenger receptors, followed by Aβ internalization, trafficking to lysosomes, and degradation by lysosomal proteases including cathepsin B [34]. Fibrillar Aβ is recognized by cell surface innate immune receptors, including scavenger receptors and toll-like receptors (TLR), and taken up by receptor-mediated phagocytosis or endocytosis [35–37] . Also, some other receptors have been linked to fibrillar Aβ phagocytosis, such as a Dap12-associated receptor called signal regulatory protein-β1 (SIRPβ1) [38] or triggering receptor expressed on myeloid cells (TREM2) [39], low density lipoprotein (LDL) receptor, and apolipoprotein E (apoE), as reviewed by Bu [40]. Specifically, macrophages from ApoE2 mice are more efficient in degrading Aβ than ApoE3 macrophages, which in turn are better phagocytes than ApoE4 macrophages [41•].

Low activity of lysosomal enzymes in microglia in comparison to macrophages may account for the limited microglial degradation of Aβ [6]. The question remains as to what extent microglia are able to degrade fibrillar Aβ and whether monocytes derived from the periphery would outweigh parenchymal microglia in Aβ clearance in vivo. In addition to limited phagocytosis, microglial capacity for efficient Aβ degradation also may be limited [42]. Even though microglia in the AD brain and similarly in AD mouse brain can take up Aβ, their Aβ removal capacity is not sufficient to prevent the accumulation of plaques without any intervention. Thus, interventions aiming at facilitating the uptake and degradation of Aβ by microglial cell are an attractive therapeutic approach.

In Vitro Methods in Studying Aβ Phagocytosis in Alzheimer's Disease Models

The phagocytosis of Aβ is in its simplest form studied by incubating cells with recombinant Aβ peptides and quantifying uptake and degradation of Aβ peptide from the cells. The fact that Aβ peptides are prone to aggregation, the origin of Aβ preparation, and the way Aβ is solubilized may obviously cause a lot of variation in the outcome of the form of Aβ that is finally applied on the cells. This may explain high variation in the responses to Aβ detected between different cell culture studies. There are many secondary cell lines utilized as models of inflammatory cells, such as immortalized microglia cell lines BV-2, N9, MMGT12, and C8-B4 from mouse origin; HAPI from rat origin; and HMO6 and CHME3 from human origin, as well as macrophage cell line RAW264.7 of mouse origin and monocyte cell line THP-1 of human origin. BV-2 microglia is one of the most utilized cell lines in Aβ phagocytosis studies in vitro [43, 44].

Secondary cells have many similarities but also several differences to primary microglia [43–45], which are one step closer to native microglia. Primary microglia can be obtained from neonatal or adult rodents [46–48] as well as postmortem human brain [49]. Neonatal microglia, a model widely used to study microglia function, actually consist of subpopulations of cells displaying partially different functions [28, 50, 51]. Neonatal microglia also may have immature responses to inflammatory stimulus compared to adult

microglia, which have decline in proteasomal function and reduced Aβ phagocytosis [46, 52]. Also, microglia obtained from aged animals show altered responses to inflammation and decreased Aβ uptake and phagocytosis in comparison to microglia isolated from young adult animals [48]. Aged animals also have reduced expression of Aβ-binding receptors and Aβ-degrading enzymes [17]. Primary monocytes can be obtained from mouse BM or human peripheral blood, or from HSC by differentiation with macrophage colony–stimulating factor (MCSF) [28, 53]. Macrophages can be collected from mouse peritoneum after induced inflammatory stimulus or by spontaneous or MCSF-induced differentiation of primary monocytes in vitro [6, 28, 29, 41•, 54].

For the simplest Aβ uptake studies, cells are incubated with a fluorochrome-conjugated Aβ, which can be tracked inside the cells using fluorescent microscopy or quantified by flow cytometry [28, 29, 33, 41•]. To study degradation of internalized Aβ, quantification of remaining Aβ protein levels within the cells is recommended instead of fluorescence signal to ensure that the readout is true Aβ clearance and not just fadeout of the fluorochrome. Phagocytosis in general also can be studied by feeding the cells with fluorescent beads or latex beads; however this is a nonspecific assay for overall phagocytic activity.

Ex Vivo Methods in Studying Aβ Phagocytosis in Alzheimer's Disease Models

To expose the cells into a more authentic environment for Aβ phagocytosis, the cells may be applied on top of brain sections prepared from aged transgenic AD mice containing native Aβ deposits [28, 41•, 55, 56]. The reduction in Aβ burden can be determined by immunohistochemical Aβ staining as well as quantification of protein levels. The sections also may be obtained from postmortem samples from AD patients as a more suitable model for studying Aβ phagocytosis when cells of human origin are investigated. The ex vivo Aβ phagocytosis assay is superior to Aβ uptake assay in regard to the exposure of cells into native AD brain conditions, which may modulate the cell phenotype mimicking the in vivo situation. Preferably, cells of various origin and alternative methods should be combined when studying the mechanisms of Aβ phagocytosis.

In Vivo Methods in Studying Aβ Phagocytosis in Alzheimer's Disease Models

Finally, the most relevant model for Aβ phagocytosis is to utilize transgenic mouse models of AD. To study the role of specific factors involved in the Aβ clearance, transgenic AD mice have been crossbred with mouse strains lacking or overexpressing certain protein products. Because knocking out specific genes may have developmental consequences or, on the other hand, the gene function may be compensated by other factors, it is an advantage to utilize conditional transgene technology. With this technology, the expression of a particular gene is conditional to a specific stimulus and can be switched "on" or "off" as desired. This has been utilized with AD models in order to ablate a certain type of cell to study their contribution to AD pathology [4, 57, 58].

First studies showing the infiltration of peripheral myeloid cells in AD mouse brain have taken advantage of the chimeric mouse model. In this model, recipient mice are irradiated and their blood cell production is reconstituted by transplantation of either purified HSC or crude leukocyte population including HSC. Donor mice expressing a reporter gene, such as green fluorescent protein, have been utilized to track the peripheral derived cells from the brain. Although the method is widely used [4, 26, 59], the irradiation in the chimeric model has been legitimately criticized for causing preconditioning leading to increased permeability of BBB and excessive peripheral cell infiltration into the brain parenchyma [1, 2••]. Other approaches have been to transplant the cells to naive mouse circulation or locally into the brain to study their Aβ phagocytosis [28, 30•, 60].

Aβ burden in the brain can be quantified with immunohistochemical staining for total Aβ or with Congo red staining for fibrillar Aβ plaques. The levels of soluble and insoluble Aβ species may be determined from the brain and blood with enzyme-linked immunosorbent assay. Because AD pathology and Aβ deposition occur in transgenic mice within months and may require as long as 1–2 years to fully develop, there is a demand for methods that would allow monitoring the Aβ burden in longitudinal studies. Recent progresses in neuroimaging techniques enable this monitoring in vivo. Positron emission tomography with Aβ tracers can be utilized to directly visualize Aβ in vivo [61]. Also, the development of magnetic resonance imaging techniques has led to promising results in visualization of Aβ deposits [62]. Aβ deposition and interaction with cells can be monitored in brain in vivo utilizing multiphoton microscopy [20, 63, 64••]. In general, alterations in Aβ burden can be monitored in parallel with behavioral studies to link it to possible changes in memory deficits and anxiety. However, the Aβ burden and learning deficits do not necessarily correlate because other mechanisms or specific forms of Aβ may engage to these processes [65–68] . The findings on the mechanisms of Aβ phagocytosis in AD models will be discussed in more detail in the next paragraph.

Table 2 Role of specific myeloid cells or factors regulating myeloid cell migration or activity affiliated to Aβ clearance in the animal models of AD

Study	Cells	Model	Effect on Aβ burden
Mildner et al. [2••]	BM CCR2^{+} cells	CCR2$^{-/-}$BM cell chimera in APPswe/PS1 and Tg2576 mice	Irradiation preconditioning and CCR2 expression in BM cells are required for their brain engraftment. Peripheral macrophages rather than parenchymal microglia modulate Aβ deposition in AD mice
El Khoury et al. [5]	CCR2	CCR2$^{-/-}$mice crossed with Tg2576 mice	Absence of CCR2 impairs microglia accumulation and increases Aβ levels and mortality in AD mice
Magga et al. [28]	BM CD11b^{+} cells	Adoptive transfer of neprilysin-transfected BM CD11b^{+} cells into APP/PS1mice	BM CD11b^{+} cells home to AD mouse brain after adoptive transfer. Injection of CD11b^{+} cells expressing secreted form of neprilysin is associated with reduced Aβ burden
Koistinaho et al. [56]	Microglia/CD11b^{+} cells	CD11b^{+} cell ablation in APPPS1 and APP23 mice	Nearly complete ablation of CD11b^{+} cells did not alter Aβ levels in AD mice within the observation period of 4 weeks
Ruan et al. [82]	CD11c^{+} TGF-β^{+} cells	Dominant negative TGF-β in CD11c^{+} cells in Tg2576 and APPswe/PS1dE9 mice	TGF-β deficiency in CD11c^{+} reduced parenchymal and vascular Aβ burden involving infiltration of peripheral macrophages
Abbas et al. [83]	CD45	CD45$^{-/-}$crossed with APPswe/PS1dE9 mice	CD45 deficiency promotes proinflammatory microglial activation, reduces their phagocytic activity, and increases soluble and insoluble Aβ levels
Town et al. [84]	Myeloid differentiation factor 88	MyD88$^{-/-}$BM cell chimera in TgCRND8 and APPswe/PS1dE9 mice	MyD88 deletion in BM cells attenuates neuroinflammation, enhances Aβ phagocytosis, and reduces Aβ burden
Zhu et al. [85] and Hao et al. [86]	CX3CR1	CX3CR1$^{-/-}$crossed with APPPS1 mice	Absence of CX3CR1 leads to altered inflammation, enhancement of microglia Aβ phagocytosis, and reduction of Aβ burden
Lee et al. [87]	CD14	CD14$^{-/-}$crossed with APPswe/PS1dE9 mice	TLR co-receptor CD14 deficiency alters microglia activation and reduces microgliosis and Aβ burden
Liu et al. [88]	TLR4	TLR4 mutation mice crossed with APPswe/PS1dE9 mice	TLR mutation decreases microglia activation and increases Aβ deposition in early AD possibly involving reduced Aβ clearance
Reed-Geaghan et al. [89]	TLR9 ligand	TLR9 ligand CpG injection (i.c.v) into Tg2576 mice	TLR9 ligand CpG reduces Aβ burden and increases microglial production of degrading enzymes and reduction of Aβ
Song et al. [90]	EP2	EP2$^{-/-}$BM cell chimera in APPswe/PS1dE9 mice	EP2 deletion in BM cells reduces Aβ burden
Doi et al. [91] and Keene et al. [92]	Liver X receptor	LXR agonist p.o. into APP23 mice, LXR$^{-/-}$crossed with APPswe/PS1dE9 mice	LXR agonist reduces Aβ burden in AD mice on high-fat diet. Astrocytic LXR activation and the release of ApoE are involved in microglial Aβ phagocytosis
Terwel et al. [93]	Complement factor C3	C3$^{-/-}$crossed with APP mice	Absence of C3 drives microglia into M2 alternative activation phenotype and increases Aβ burden
Fitz et al. [94]	IL-6	AAV1-induced IL-6 overexpression in brain of TgCRND8 and Tg2576 mice	Overexpression of IL-6 leads to massive gliosis, and attenuates Aβ deposition by enhanced microglia activation and possibly by increased Aβ phagocytosis
Maier et al. [95]	IL-1β	Overexpression of IL-1β in brain of APPswe/PS1dE9 mice	Sustained overexpression of IL-1β enhances microglia activation and reduces Aβ burden
Chakrabarty et al. [96]	MCSF	Weekly i.p. injections of MCSF into APPswe/PS1	MCSF increases microgliosis and BM cell infiltration and reduces Aβ burden by phagocytosis

Aβ beta amyloid; *AAV* adeno associated virus; *AD* Alzheimer's disease; *apoE* apolipoprotein E; *BM* bone marrow; *EP2* prostaglandin E2 receptor subtype 2; *i.c.v.* intracerebroventricular; *IL* interleukin; *i.p.* intraperitoneal; *LXR* liver x receptor; *MCSF* macrocyte colony–stimulating factor; *p.o.* per oral; *TGF-β*$^{+}$ transforming growth factor beta; *TLR9* toll-like receptor 9

Mechanisms of Aβ Phagocytosis in Myeloid Cells in Alzheimer's Disease Models

Microglia-mediated clearance of Aβ in vivo may be rather limited, but it can be enhanced by opsonization of Aβ deposits obtained with active or passive immunotherapy. Enhanced Aβ clearance in turn associates with alleviation of AD-related neuropathological alterations (reviewed in [69]). The Aβ-antibody complex is identified with Fc receptors present in immune cells, including microglia and macrophages subsequently leading to Fc receptor–mediated phagocytosis (reviewed in [70]). However, microglia-mediated Aβ phagocytosis does not explain all the beneficial effects of immunization because other mechanisms, such as altered Aβ fibrillization in brain parenchyma or enhanced brain to blood efflux of Aβ also may occur (reviewed in [69]).

Although the immunotherapy treatment for AD is promising, it is hindered by severe adverse effects such as brain microhemorrhages observed in animal studies and encephalitis observed in clinical trials after passive and active immunization, respectively, as reviewed in [69]. It has been reported that macrophages laden with Aβ may get trapped to endothelial layer, inhibiting the monocyte emigration and Aβ export across BBB [53], possibly partly explaining the increased occurrence of hemorrhages. There are naturally occurring autoantibodies to Aβ in plasma and cerebrospinal fluid that exist in both healthy individuals as well as in AD patients although their levels may be decreased in advanced AD as well as within normal aging [71, 72] . Because these autoantibodies promote microglia-mediated uptake and clearance of Aβ [73, 74] and bind to Aβ deposits in human AD brain [75] and after peripheral administration in animal models in vivo [74], they may offer a more native therapeutical approach to combat towards Aβ. An alternative vaccination strategy also was described with glatiramer acetate, a weak agonist of autoantigens, involving recruitment of BM-derived dendritic cells and their regulation of Aβ deposition [57, 76].

Findings on certain cell types, receptors, or pharmacological treatments associated with Aβ clearance by microglia or monocytic cells in animal models of AD are represented in Table 2. Many pharmacological approaches such as galantamine [77], valproic acid [78], and cannabinoids [79] have been shown to enhance phagocytosis and potentially, clearance of Aβ in mouse microglial or monocytic cells in vitro. Pharmacological approach with curcuminoids also was shown to result in Aβ clearance by human monocytes obtained from AD patients [29, 80], suggesting that in vitro models of AD may be applicable to study monocytic function in AD. Furthermore, therapeutical approaches not directly associated with Aβ phagocytosis may have unexpected effects on microglial function as reported for galantamine and γ-secretase inhibitors increasing and inhibiting microglial Aβ phagocytosis, respectively [77, 81].

Conclusions

Transgenic AD mouse models have revolutionized the research of mechanisms leading to Aβ clearance by cells of myeloid origin. Several in vitro and ex vivo methods assessing the phagocytic capacity of microglia and BM-derived monocytic cells have been developed. Increasing knowledge of the heterogeneity of microglial function in AD has changed the course of research to not only dampen microglial reactivity but also to modulate their activation properties. Pinpointing such events leading to reduction in brain toxic Aβ levels offers an attractive tool for combating this devastating disease.

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- • Of importance
- •• Of major importance

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