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The microglial phagocytic role with specific plaque types in the Alzheimer disease brain

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Abstract

Alzheimer disease (AD) involves glial inflammation associated with amyloid plaques. The role of the microglial cells in the AD brain is controversial, as it remains unclear if the microglia form the amyloid fibrils of plaques or react to them in a macrophage-phagocytic role. Also, it is not known why microglia are preferentially associated with some amyloid plaque types. This review will provide substantial evidence to support the phagocytic role of microglia in the brain as well as explain why microglia are generally associated with specific plaque types that may be explained through their unique mechanisms of formation. In summary, the data presented suggests that plaque associated microglial activation is typically subsequent to specific amyloid plaque formations in the AD brain.
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Keywords: Alzheimer's disease; Amyloid plaques; β-Amyloid; Microglia; Astrocytes; Transgenic mice; Neuropathology; Inflammation; Plaque formation; Phagocytosis; Dense-core plaques; Diffuse plaques; Cerebellum; Entorhinal cortex

1. Introduction

Amyloid plaques are the most investigated neuropathological feature associated with Alzheimer disease (AD) even though they have been detected in non-demented, age-matched control brain tissues. The origin of these plaques has been attributed to extracellular 'deposition' of beta-amyloid (Aβ), which eventually leads to neuronal death by unknown mechanisms. Although alternative mechanisms of amyloid plaque formation have also been proposed, including models of neuronal or vascular origin, microglia have also been hypothesized to play a seminal role in amyloid plaque formation. Here, we first exploit the relationship between activated microglia and amyloid plaque types as it pertains to the role of microglia in plaque formation, then we focus on the microglia's phagocytic role and suggest that microglial activation is subsequent to particular amyloid plaque formations.

1.1. AD plaque heterogeneity

Extracellular amyloid in plaques exists in many shapes and sizes that could be related to multiple mechanisms of formation [11,12], and/or to technical factors such as the staining methods, post-mortem time delay, specificity of reagents and so forth [14,17]. As an example, not only was plaque size increased using formic acid pretreatment on serial sections of an AD brain (as compared to no pretreatment), but the amyloid was presented as plaques in the brain of an apparent middle-aged, normal, non-demented male using formic acid, which were presented only as intraneuronal labeling in the next serial section without the use of formic acid [17]. Unfortunately, the AD research literature is hampered by the lack of an accepted and comprehensive amyloid plaque nomenclature that include such descriptive plaque terms as senile, compact, star, diffuse, mature, classical, immature, dense-core and others. Of all of these confusing descriptive plaque labels, the diffuse and dense-core terms appear the most referenced and will be used in this review.

Historically, it was proposed that diffuse and dense-core (senile) amyloid plaques differ with respect to glial activity, with the latter primarily being associated with highly reactive microglia [40]. In fact, as far back as 1934, microglial

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"reactions" of the diffuse plaque types were weaker and "rarer" than those seen in the dense-core (classic) plaques [63]. In support, it was reported that HLA-DR positive activated microglia were not associated with diffuse plaque types in the molecular layer of the AD human entorhinal, temporal and occipital cortex [62] nor in the AD retrosplenial cortex [65]. Similarly, such activated microglia were not associated with diffuse plaque types in the APP23 transgenic mice brain tissues, in contrast to their preferential association with dense-core plaques [58]. Similar observations were reported in Down syndrome brain tissues where activated microglia were only associated with particular types of plaques [43].

In reference to plaque formation, the possibility that microglia could create any plaque type de novo is even more unlikely since they do not express detectable levels of amyloid precursor protein (APP) mRNA, implying that these cells are incapable of synthesizing or producing significant Aβ from endogenous APP [32,54]. Therefore, microglia cells are not necessary for the production of Aβ plaques. In fact, the Aβ deposition in Down syndrome brains was attributed to gene dosage of Aβ precursor [34] not microglial involvement.

If microglia are not creating plaques, then why do they preferentially, but not exclusively, associate with dense-core plaques? Can it be attributed to unique amyloid species, or is the composition between these plaques different because they arose from unique mechanisms of formation?

1.2. Unique mechanisms of plaque formation

Many studies fail to support the hypothesis that diffuse plaques evolve into dense-core plaques over time [2,38,60,65,72] suggesting that all plaques are not created equally, and that distinctive plaque types do not exchange in the brain [11,12,14,46,72]. For example, the majority of the Aβ deposits in the APP22 mice are the diffuse type, while those detected in the APP23 mice develop almost exclusively the dense-core, congophilic at their first appearance making it very difficult to reconcile the diffuse plaque types form a precursor for the dense-core congophilic plaques [60]. Therefore, if plaques originate by exclusive mechanisms, then the some of the contents in these plaques could be unique providing a straightforward explanation why microglia are only associated with the dense-core plaque types.

Contrary to the popularized dogma that all amyloid plaques arise from extracellular deposition, plaques may originate from vessels [44], neurons [11–17], Purkinje cell dendritic processes [67] and astrocytes [46]. In one example, recent attention has turned towards pathological events within the neuron suggesting that cell death could come from inside the cell, leading to lysis of Aβ-filled neurons to deposit their contents as dense-core plaques in the brain [11–13,15]. In another example, our lab discovered the presence of astrocytic plaques (lysed astrocytes) in the AD brain tissues [46] thereby supporting the existence of distinctive plaque types in the AD brain.

The AD cerebellum provides a clear-cut example where diffuse and dense-core plaques co-exist in predictably, mutually exclusive areas [22]. The diffuse plaques are only observed in the molecular layer, and the striatum of the APP23 mice, while the dense-cores are only observed just below the Purkinje cell layer, which further supports the claim that diffuse plaques are not necessarily a precursor of dense-core amyloid plaques [21,58,67]. So why are these plaques in exclusive areas? It was suggested that these microglial-associated dense-core plaques arise from lysed Golgi type II neurons (Fig. 1A), which are typically located just below the Purkinje cell layer [67]. In contrast, in the molecular layer of the same section, the non-microglial-diffuse plaques (Fig. 1B) appear to have been formed from degenerating Purkinje cell dendritic processes [67]. Fig. 2 presents similar examples in the AD cerebral entorhinal cortex where microglia are again associated with dense-core (Fig. 2A), not diffuse (Fig. 2B) amyloid plaques in different areas of the same AD cerebellar cortical tissue.

These explanations make it logical to suggest that microglia are associated with lysed cell bodies (dense-core plaques) where lysosomal enzymes, cellular DNA and other factors such as advanced glycation endproducts [68] known to be sufficient to induce microglial activation are released from injured or dying neurons and become accessible to cause the microglial activation. In support, in vitro activation of microglia by Aβ aggregate in the absence of co-factors is typically weak [41] as the material in the diffuse plaques, perhaps only amyloid, lack these important and potent microglial-activating materials.

Therefore, if cellular lysosomal enzymes are released, which are enzymatically active in post-mortem tissues, then they should be able to digest focal areas of proteolytically sensitive parenchymal proteins in the brain. One such proteolytically sensitive protein, microtubule-associated protein (MAP)-2, was not immunohistochemically detected through the entire volume of the dense-core plaques, but presented normal patterns among the diffuse amyloid plaques in the same sections of AD entorhinal cortex brain tissues [12]. In support, enzymes such as cathespin D were not detected in diffuse plaques but were prominent in dense-core plaques (personal observations, MRD). The differential presence of these enzymes in the dense-core, not diffuse, amyloid plaques can also explain the easy immunohistochemical

Fig. 2. Triple immunohistochemical labeling using specific antibodies to Aβ42, HLA-DR and GFAP to detect amyloid, microglia and astrocytes, respectively according to previously published methods [16] in different areas of the same AD entorhinal cortex. Open arrows indicate red-labeled amyloid plaques. Large arrowheads identify blue-labeled microglia and small arrowheads identify astrocytes: (A) presence of a microglial embedded within an amyloid dense-core plaque in the AD entorhinal cortex; (B) presence of a diffuse plaque without associated microglia in the same tissue of the AD entorhinal cortex. Note the presence of intracellular Aβ42 within nearby pyramidal neurons (N) as well as in nearby astrocytes (small arrowheads). (Bar = 40 μm).

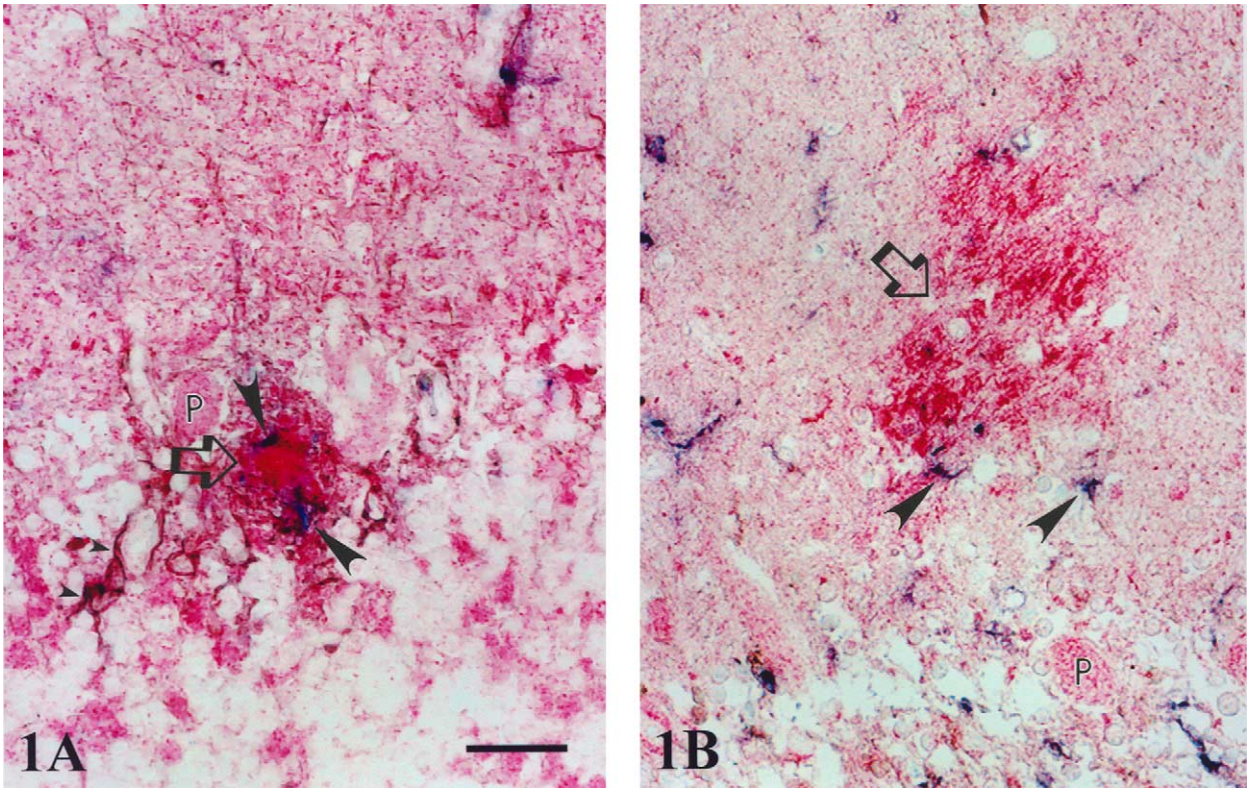
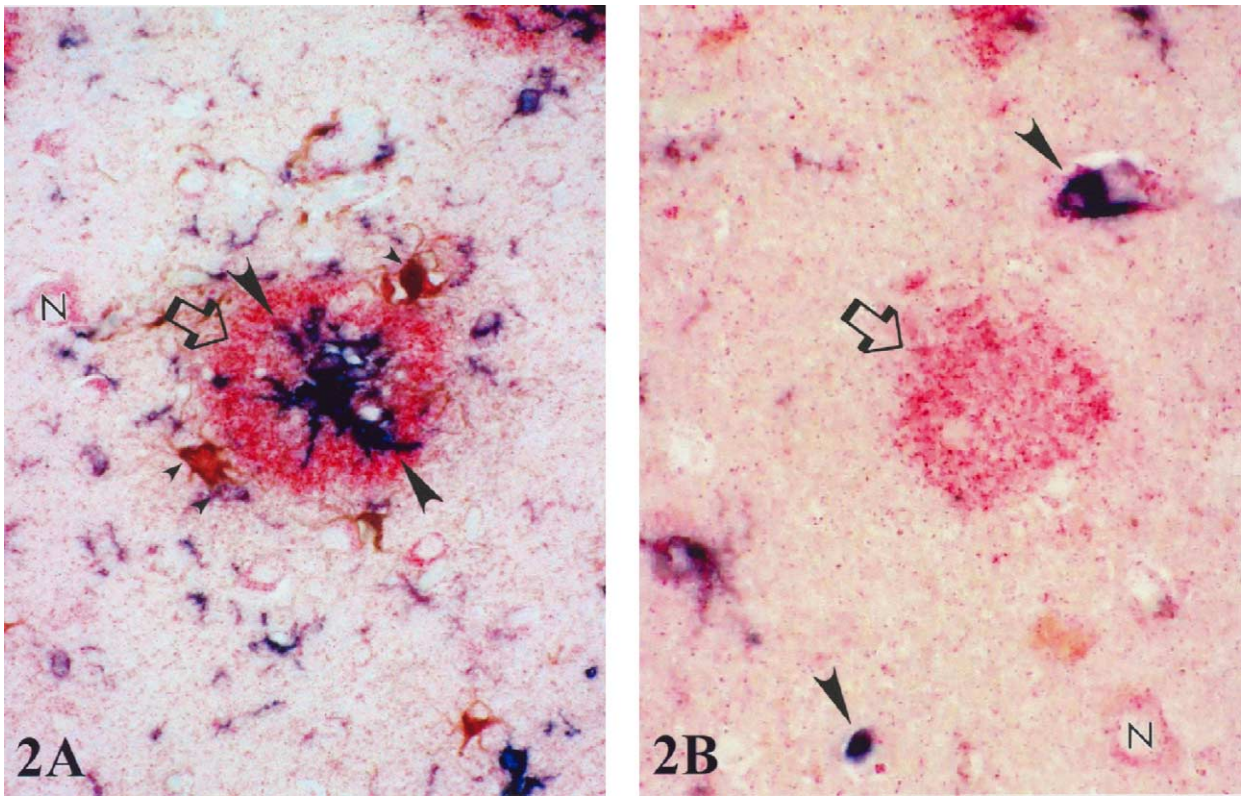


Fig. 1. Triple immunohistochemical labeling using specific antibodies to Aβ42, HLA-DR and GFAP to detect amyloid, microglia and astrocytes, respectively according to previously published methods [16] in different areas of the same AD cerebellum. Open arrows indicate red-labeled amyloid plaques. Large arrowheads identify dark blue-labeled microglia and small arrowheads identify brown-labeled astrocytes: (A) presence of a microglial associated dense-core plaque just below the Purkinje cell (P) layer of the AD cerebellum; (B) presence of a diffuse plaque without associated microglia in the molecular layer of the AD cerebellum of the same tissue. (Bar = 100 μm).



detection of proteolytically resistant proteins (e.g., tau, amyloid, cathepsin D and ubiquitin) in dense-core plaques [12].

Other than released enzymes, cellular nucleotides will also be released, which are diffusible and may play a role in microglial chemotaxis [16,23,27,47]. One such example of microglial-activating material detected in dense-core but not diffuse plaques is a nuclear remnant [11,13,15] as ATP or ADP can induce chemotaxis for cultured microglia through $G_{i/o}$-coupled P2Y receptors [27], which is completely blocked by either AR-C69931MX, a potent and selective antagonist against $P2T_{AC}$ receptors or pertussis toxin pretreatment [27]. Similarly, neurons make complement components and their message is dramatically induced in AD brain neurons [56]. Complement opsonized Aβ is readily recognized and phagocytized by microglia contributing to their activation (next section).

Hence, it is logical to propose that activated microglia are preferentially associated with specific plaque types based on their content, which is dependent upon their mechanism of formation. The existence of unique plaque types can also explain the characteristic morphologies of these plaques and suggests the need to distinguish plaque types in related studies to determine which types correlate to dementia.

1.3. Microglia as phagocytes

The phagocytic role of microglia has been well documented within plaques [32,61]. In fact, the characteristics of activated microglia resemble peripheral macrophages after injury in peripheral tissue, which is consistent with the shared developmental origin of these two cell types [25,32,33]. In vivo studies that include the direct injection of plaque cores into the rat cerebral cortex, result in phagocytosis, not deposition, of the beta-amyloid cores [24,51].

A number of cell surface receptors bind Aβ and mediate microglial activation, and there is evidence that complement opsonizes Aβ fibrils, facilitating their removal by microglial phagocytosis. Pre-aggregated Aβ can be modestly phagocytosed by microglial class A scavenger receptor and the class B scavenger receptors B1 and CD36 [5,8,9,42,50], but when opsonized, it is more aggressively phagocytosed by Fc receptors and complement receptors [53]. Phagocytosis activates the cells, and Aβ binding to the RAGE (receptor for advanced glycation end-products) is also a powerful activator of microglial inflammation [69]. Finally, amyloid also exerts chemotactic effects through binding to formyl peptide receptor-like 1 (FPRL1), which contributes to microglial activation [10].

Phagocytosis of fibrillar Aβ may be less successful in vivo where large aggregates of fibrils are not completely enclosed by microglial pseudopodia. This type of attempt at frustrated phagocytosis is modeled in vitro by attaching fibrillar Aβ to the surface of the culture plate, which has been shown to stimulate a variety of microglial inflammatory responses [37,39]. Electron micrographs of microglia associated with plaques in AD brain tissue are therefore inconclusive as to whether amyloid fibrils are being phagocytized or being secreted, since fibrils are only partially engulfed by microglial cytoplasmic extensions [30,61]. There is little evidence from cell culture studies to favor the proposition that microglia take up Aβ aggregate, as found in diffuse plaques, and form it into fibrils, as found in dense-core plaques. Microglia in vitro actively phagocytose Aβ monomer, oligomer, and fibrils. Clearance of monomer leads to formation of oligomers of approximately 18 kDa molecular weight, presumably tetramers. The newly formed oligomers are associated with the cells and in electron micrographs appear to be internalized in secondary lysosomes [1]. However, formation of fibrils was not seen in microglia cultures incubated with either monomeric or oligomeric Aβ1–42. Microglia in these cultures contained immunolabeled nonfibrillar Aβ in cytoplasmic granules that appeared to be secondary lysosomes, and nonfibrillar Aβ was also seen at the cell surface in the process of being phagocytosed (unpublished data, MDA: Fig. 3). Aβ fibrils, on the other hand, appeared only in cultures incubated with pre-formed fibrils. In these cases, immunolabeled Aβ fibrils were seen in the process of being phagocytosed or contained within intracellular vacuoles (unpublished data, MDA: Fig. 4). It is interesting to note that fibrillar Aβ, the predominant Aβ species in dense-core plaques is associated with microglia in the brain but is not associated with microglia in congophilic angiopathy [66]. These reports strengthen the notion that materials specific to dense-core plaques, other than fibrillar Aβ, can activate microglia.

1.4. Glial activation and amyloid plaque formation in APP transgenic models

APP transgenic mice lack neurofibrillary tangle formation and extensive neurodegeneration but are excellent models for plaque formation [29,57]. Exclusively, neuronal expression of the APP transgenes with neuron-specific promoters resulted in plaques with a regional distribution and characteristic relationships with glia that strongly resemble AD [24,28,57] providing compelling evidence for a neuronal source of the Aβ in deposits. Manipulation of these models has also provided solid evidence that two of the astrocyte protein products, ApoE [4] and α1-ACT [45,49], play an important role in amyloid plaque deposition. Therefore, one must cede the point that astrocytes "contribute" to plaque formation or progression although there is also strong evidence for an astrocytic role in amyloid clearance [46,71]. We know a great deal about these two pro-amyloidogenic factors that are "contributed" by glia and how they are regulated. Because microglia also make substantial amounts of ApoE [4] and stain for ApoE in plaques [64], it is theoretically plausible that they also "contribute" to plaques and that their activation could play a role, but does it? Empirical evidence suggests otherwise.

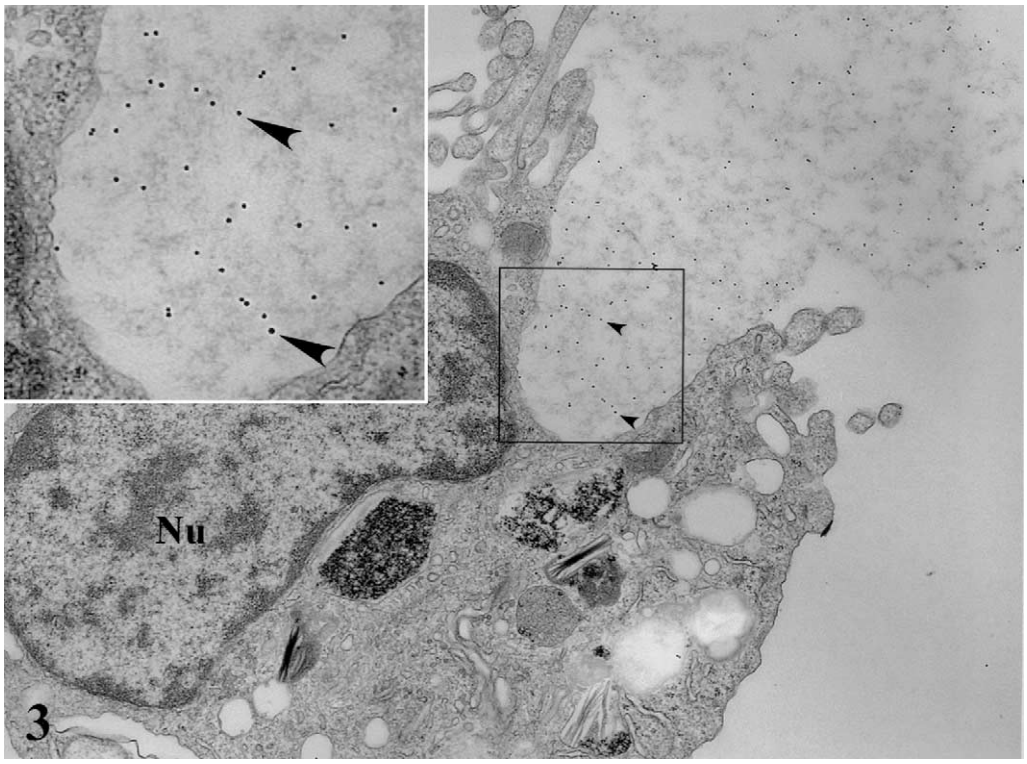


Fig. 3. Microglia extending pseudopodia to phagocytose a nonfibrillar aggregate of Aβ immunogold labeled (arrowheads) using anti-Aβ primary and 15 nm gold-conjugated secondary antibodies (postembedding) according to previously published methods [2]. Original magnification: 7700× (inset: 15,400×).

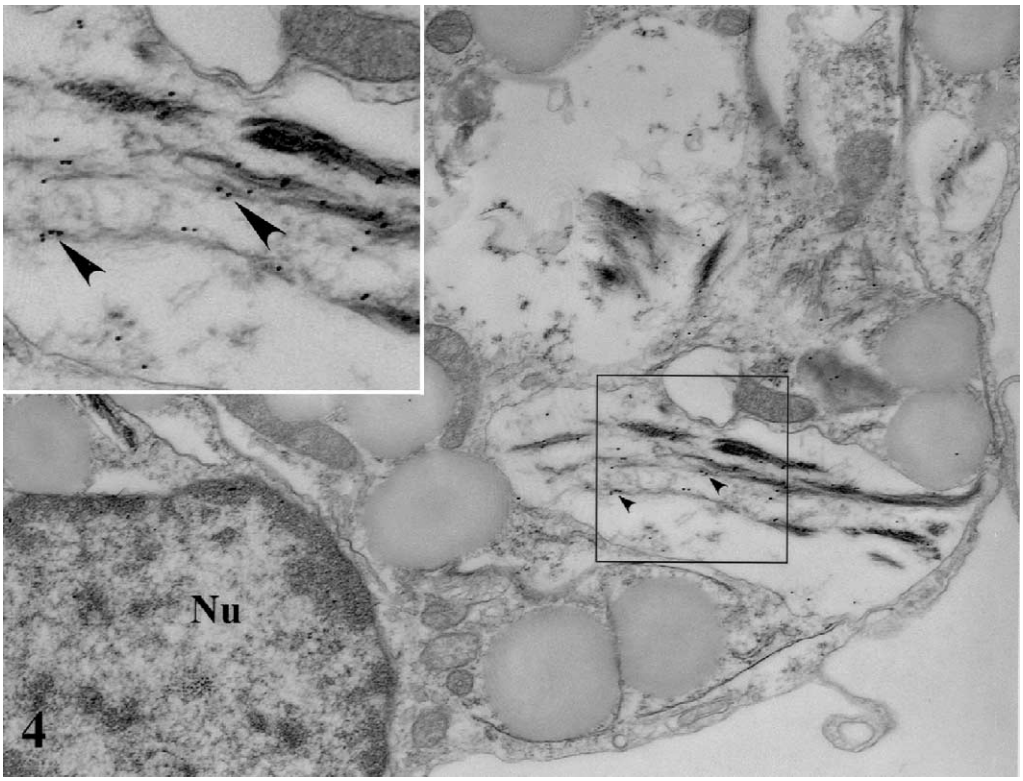


Fig. 4. Microglia in the process of phagocytosing immunogold-labeled Aβ fibrils (arrowheads). A completely extracellular bundle of Aβ fibrils is seen adjacent to the cell on the right. Within the cell is immunogold-labeled amyloid fibrils enclosed in vacuoles according to previously published methods [2]. Original magnification: 10,000× (inset: 20,000×).

1.5. Microglial activation reduces amyloid

When one examines experiments with APP transgenics in which microglial activation has been stimulated by widely varying methods (entorhinal cortex lesion, passive and active Aβ vaccine, LPS injection, trauma, nitroflurbiprofen) amyloid deposition has been consistently reduced rather than increased [6,7,20]. In fact, rapid microglial activation and plaque clearance after application of Aβ antibody have been monitored in vivo using multiphoton microscopy [3]. Direct ultrastructural evidence implicated microglial amyloid phagocytosis in vaccinated animals in vivo. Finally, the one case of a similarly Aβ vaccinated human to come to autopsy showed evidence of extensive microglial activation and amyloid removal [48] while available evidence mitigated against other possibilities [26]. While diffuse plaques are more readily removed, all types of plaques appear to be reduced, again arguing that microglial activation does not result in progressive conversion of one type of plaque to another. Thus, activation of microglia consistently leads to a loss of amyloid rather than more amyloid plaques of a particular type providing additional evidence against the hypothesis that activated microglia play a major role in plaque formation.

1.6. Inhibiting microglial amyloid clearance can increase amyloid

If activated microglia formed plaques, one would predict that anti-inflammatory agents should effectively prevent plaque formation. However, there is no evidence that the most powerful anti-inflammatory agents like dexamethasone have any beneficial impact on amyloid or AD. In fact, experiments from Wyss-Coray et al. [69] have shown that glial overexpression of a major "anti-inflammatory" cytokine, TGFβ1, markedly reduced plaques but increased microglial activation in APP transgenic mice. Once again, microglial activation is associated with reduced rather than increased amyloid. Further examination of this effect revealed that TGFβ1 increased expression of complement C3 and that specifically blocking C3 conversion to C3b/iC3b with sCrry prevented microglial removal of C3b opsonized Aβ aggregates leading to a doubling of amyloid burden [70]. These studies provide strong evidence for a normal amyloid clearance role for microglia rather than a role in making plaques.

Studies with non-steroidal anti-inflammatory drug (NSAID) treatment in APP transgenics including our own have shown the expected reduction in activated microglia in ibuprofen treated APP mice [35,73], but most of the reduction appears secondary to the reductions in plaque numbers and therefore plaque-associated microglia. While it might be thought that NSAIDs like ibuprofen may be reducing amyloid by inhibiting microglial activation, recent data from Dr. Takashi Morihara in the author's lab (GMC) has shown the surprising result that ibuprofen treated animals with fewer plaques actually show no evidence for reduced mRNA associated with microglia activation (Morihara et al, submitted). In fact, another profen, nitroflurbiprofen, was reported to not only inhibit but to robustly activate microglia around plaques; nitroflurbiprofen actually reduced plaques better than flurbiprofen or ibuprofen, which failed to increase the CD11b positive activated microglia [31]. Similarly, the antioxidant/NSAID curcumin reduced amyloid, but increased microglia per plaque [36]. So the NSAID studies do not support a role for activated microglia in making plaques, but are consistent with a role in their removal.

Finally, ongoing experiments in which CNS microglial activation has been genetically suppressed in APP transgenics by the op/op mutation [52] which has fewer microglia appear to result in more rather than less amyloid (unpublished results, GMC), again supporting the concept that microglia play a role in normal amyloid clearance while suppression of microglia activation or clearance leads to more rather than less amyloid.

While glia (especially astrocytes) obviously contribute some important plaque-associated proteins to amyloid deposits, microglial activation data from many labs using a range of paradigms consistently show a role in clearance, not deposit formation. If there is also a role in deposit formation, additional data are required to show it.

1.7. Astrocytic role

Intracellular Aβ has also been detected in subpial astrocytes in the form of lysosomal granules possibly indicating phagocytic and lysosomal activity [46,62], and the Aβ detected in plaque-associated astrocytes appeared degraded because the Aβ was truncated [72]. Eventually, like the Aβ overburdened neurons (section on unique mechanisms of plaque formation), these astrocytes also lyse [46], which may activate microglia to phagocytize the debris. In fact, we observed microglia cells in very close association with some astrocyte-derived amyloid plaques (unpublished observation, MRD). It is interesting to note that Aβ has also been found intracellularly in astrocytes associated with both neuritic (apparently dense-core) (Fig. 2A) and diffuse plaques [62], suggesting differential involvement of astrocytes and microglia.

1.8. Microglia then astrocyte activation

Some studies have indicated that astrocyte activation occurs subsequent to microglia activation suggesting a cause and effect relationship [25]. When human-derived dense-core amyloid plaques were injected into the rat brain, astrocytes were activated subsequent to the microglia activation [24]. Interestingly, the local presence of astrocytes inhibited the microglial ability to ingest plaques or Aβ in vitro [19,54]. Without the astrocytes in the cultures, microglia rapidly (within 2 h) phagocytosed, broke apart and cleared the senile plaques. Amazingly, this activity was suppressed after the introduction of astrocytes. Furthermore, astrocytic-derived IL-4 inhibited microglial phagocytic

activity in vitro [59]. Similarly, cultured astrocytes were incapable of clearing Aβ fibril deposits, and these cells released glycosaminoglycase-sensitive molecules that inhibited the subsequent removal of Aβ by cultured microglia [54]. Inhibition of microglia was also observed in a separate study where nitric oxide (NO)-related oxidative brain damage was promoted by the microglial cytokine TNF-α [41], whereas astrocytes exerted, via the release of TGF-β, a negative feedback that inhibited microglial NO production [55]. Taken together, these studies suggest that the function of subsequent astrocyte activation may be to temper or regulate the phagocytic microglial activity [16,55,59] perhaps in an effort to more easily form a "scar" of fibrotic processes to heal the necrotic area by providing structural support to the residual tissue like that observed in cases of brain injury involving localized cell death [25]. Similar astrocytic "wraps" were reported in Mongolian gerbils 17 days after transient forebrain ischemia where they formed a structure that was described as a glial scar [18]. Such an astrocyte wrap or scar may explain the persistence of the amyloid plaques in AD brains creating additional difficulty in removing them.

Considering together, these data show a sequence with initial plaque formation, followed by microglial and then astrocytic activation, which together secrete neurotoxic factors to contribute to local secondary cell death consequences. From this vantage, it is ironic that the cells empowered to remedy the pathology, instead contribute to a self-perpetuating pathological cascade [21,25,58,66] (Fig. 5).

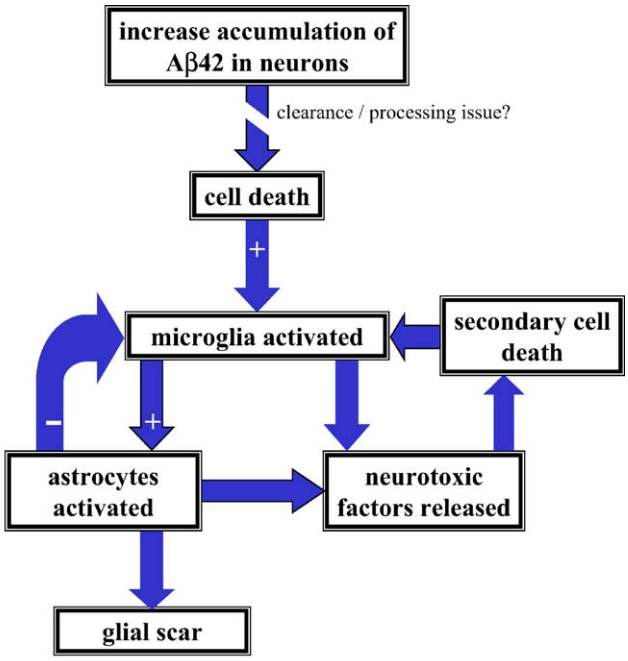


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Fig. 5. A proposed pathway of inflammation in the AD brain showing inhibitory (−) and stimulatory (+) pathways of primary and secondary cell death consequences. Based on substantial evidence, we propose that one of the primary activators of microglial activations originates from dying or lysed cells. Subsequent microglial activation can trigger astrocyte activation (+) (although astrocytic activation may occur independent of microglial activation), which in turn can inhibit microglial activation (−). However, both activated microglia and astrocytes secrete factors that are toxic to neurons, thereby contributing to a pathological cascade.

2. Summary

The literature presented in this review provides compelling data to suggest that (1) the known role of the microglial cell is to phagocytose like its peripheral monocytic counterpart; (2) microglial cells are activated by material specific to dense-core plaques, which may include perikaryon and nuclear factors (debris) known to be powerful stimuli to microglial activation; (3) microglial activation is subsequent to amyloid plaque formation; and (4) microglial activation can in turn activate astrocytes, which can inactivate microglial phagocytosis. It is important to note that the activated microglia and reactive astrocytes can secrete factors that are neurotoxic to surrounding neurons creating a vicious cascade of cell death (Fig. 5). Furthermore, it may be too simplified to assume that all amyloid plaques have common etiologies, as specific ones might correlate with dementia (dense-cores), while others (diffuse) may have no impact on cognitive impairment.

Therefore, microglia represent a natural mechanism of protein aggregate and debris removal, and non-selectively blocking their functions could break the pathways of increased local inflammation but may not affect the primary causes of amyloid plaque formation in AD and may even aggravate plaque accumulation.

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