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# Microglia in protein aggregation disorders: friend or foe?

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## Abstract

Microglia cells have been implicated, to some extent, in the pathogenesis of all of the common neurodegenerative disorders involving protein aggregation such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis. However, the precise role they play in the development of the pathologies remains unclear and it seems that they contribute to the pathological process in different ways depending on the specific disorder. A better understanding of their varied roles is essential if they are to be the target for novel therapeutic strategies.

### Keywords

Microglia; protein aggregates neuroinflammation; cytokines; neurotoxicity; Alzheimer's; Parkinson's; ALS

## Introduction

Microglia are the resident immune cells of the central nervous system and, contrary to the description of them as being "resting" when in their highly ramified form, they are constantly monitoring the environment for any signs of change (1, 2). In this role they are inevitably activated to some extent by any brain pathology and this is particularly evident in those neurodegenerative disorders which involve protein aggregation events such as Alzheimer's and Parkinson's disease. However, what remains unclear is the precise nature of that activation and whether it is similar in different diseases. One of the key questions is, do they simply react to external stimuli to phagocytose and remove protein aggregates or do they have an active role in the development and progression of protein aggregate pathology? Furthermore, while they might intuitively have a role in dealing with extracellular protein aggregates in the brain parenchyma do they also react to intracellular protein aggregations such as neurofibrillary tangles and Lewy bodies? In this short review we will address these and a number of other questions related to the neuropathology of the main protein aggregation disorders.

## Alzheimer's disease (AD)

The potential roles of microglia in neuroinflammation and the progression of pathology have been studied to varying degrees in all of the common neurodegenerative disorders but the most extensive literature relates to AD. Two papers published back-to-back in 1989 were instrumental in highlighting the potential role of inflammatory cytokines in driving AD pathology. Griffin and colleagues showed that there was a 30 fold increase in the number of interleukin 1(IL-1) immunoreactive microglia in AD and Down's syndrome brains as

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compared to age-matched controls (3). Furthermore, Goldgaber and colleagues showed in human umbilical vein endothelial cells that IL-1 upregulates amyloid precursor protein (APP) gene expression (4). Processing of APP gives rise to the Aβ peptide that is the main constituent of the senile plaques found in the AD brain (5). Taken together these two observations raised the possibility that, rather than having a purely reactive phagocytic role, microglia could drive the formation of Aβ plaques. Since then there has been a lot of interest in exactly how microglial phenotype correlates with plaque type, progression and distribution (6, 7). In terms of plaque type there appears to be a particular association between IL-1 immunoreactive microglia and diffuse Aβ plaques whereas the dense plaque cores, presumed to be the end-stage of plaque formation, do not show any such association (8). There is also correlation between microglia with a neuroinflammatory phenotype and the anatomical distribution of neuritic plaques (9) suggesting perhaps a role for cytokines in the formation of this type of plaque (10). These observations were brought together by Sue Griffin when she postulated the existence of a “cytokine cycle” whereby glial cells in a positive feedback cycle of cytokine release drive the development of AD pathology (11) (Fig 1). Such a sustained pro-inflammatory activation can have significant neurotoxic effects (12).

An alternative view is that the microglial cells do not drive pathological change at all but are in fact themselves impaired. More specifically, it is suggested that the microglial cells associated with the plaques are not activated but are actually dystrophic or senescent (13). Streit and colleagues carried out a detailed morphological examination of microglia in a series of AD brains at varying Braak stages. They reported an association of ramified “non-activated” microglial cells with Aβ plaques and an association of dystrophic damaged, rather than functionally active, microglia with the various forms of tau pathology (14). On this basis the microglia could be considered as neuroprotective and if there is an age-related diminishment in this protective capacity the neurons will become vulnerable. A potential result of this would be the development of neurofibrillary tangle pathology. There have been a number of studies showing such an association between tangle distribution and activated microglia (7, 15, 16). In one of these studies the distribution of microglia in relation to that of neurofibrillary tangles was examined in AD and elderly control cases and it was found that microglia are most extensive in areas with significant tangle pathology (in AD and control cases). The conclusion drawn was that the regional distribution of microglia might provide the template for the development of the tangles (16).

Further evidence that microglia may play an active role in causing neuronal death, rather than reacting to it, comes from *in vivo* imaging studies in animals. Using two-photon imaging in transgenic mice expressing the *Cx3cr1* gene, tagged with green fluorescent protein, it has been shown that microglia are very mobile and are constantly remodelling their processes, presumably as part of their active monitoring role (17). When there is any perturbation of the parenchyma this remodelling becomes more focussed and the microglia move towards the damaged area of tissue. However, using this technique in a triple transgenic AD mouse model it has been shown that microglia are recruited early and not just after the death of neurons (18). Furthermore when the triple transgenics were crossed with *Cx3cr1* knockout mice the neuronal loss was prevented. Cx3cr1 is a chemokine receptor which binds to fractalkine and is important in neuron-microglia interactions.

While there is significant evidence that microglia can contribute to the initiation and/or progression of AD pathology it’s also clear that they can have beneficial effects. In animal models of AD it has been shown that impairment of microglial phagocytic activity accelerates pathology progression (19) whereas exogenous supplementation of microglia favours clearance of Aβ plaques (20). Similarly, post mortem follow up of patients who took

part in a clinical trial of Aβ peptide immunisation revealed evidence of extensive phagocytic clearance of Aβ from the cortex (21).

The basis for these apparently contradictory roles of microglia is that there is heterogeneity in the activation process. What defines a microglial phenotype and how the cell is going to react to a stimulus depends on the nature of that stimulus and what other factors are present locally. It is clear that there are alternatives to the classical activation pathway whereby microglia exposed to Aβ peptide secrete inflammatory cytokines. Based on work primarily on peripheral macrophages alternative activation pathways have been identified whereby microglia can be stimulated to secrete anti-inflammatory cytokines and trophic factors (22–24). Some of these alternative activation states of microglia in the brain have been observed in AD and mouse models of AD (25). It is this mixed functional phenotype of the microglia in the AD brain, which is still not well understood, that provides the biggest challenge in terms of possible therapeutic intervention. Is there a normal physiological balance between the alternative activation states that we need to try and correct in AD? Can individual microglia move between different activation states? Are the microglial cells in specific activated state at different stages of the disease and hence, is the timing of any intervention important? (26, 27).

## Parkinson's disease (PD)

As is seen in AD, there is a neuroinflammatory component to the pathology of PD. In the substantia nigra, the *locus classicus* of PD pathology, the loss of dopaminergic cells is associated with the presence of activated microglia cells (28–30). This specific association between differential susceptibility of cells in the substantia nigra and the number of reactive microglia is supported by rodent studies in which the inflammatory toxin, LPS, was injected in to different brain regions and the numbers of microglia found in the midbrain were significantly higher (31). Interferon-γ (IFN-γ) is increased in the plasma of patients with PD (32) and has been implicated in the development of nigrostriatal degeneration (33). Based on these observations IFN-γ deficient mice were treated with MPTP, which kills the dopaminergic cells in the substantia nigra, and it was observed that there were fewer microglial cells present and less dopaminergic cell loss in these animals than in the wild type animals. This would support the concept of a detrimental effect of microglial activation in the substantia nigra of PD patients. The inflammatory component of PD pathology has been extensively reviewed and one of the key potential pathological factors regarding microglia is that they express inducible nitric oxide synthase (iNOS) which can generate free radicals and potentially cause oxidative damage to dopaminergic cells (34).

While these various inflammatory mechanisms can be used to explain some of the dopamainergic cell death they don't directly address the toxic effects of the alpha-synuclein (αSN) aggregates that characterise PD pathology. αSN has been shown to promote microglia activation (35, 36) and more specifically the monomeric form is more effective than the aggregates in promoting phagocytosis (37). This is similar to the findings in AD where the oligomeric forms of the Aβ peptide are thought to be more toxic. Perhaps unsurprisingly much of the research focus has been on the substantia nigra in PD but with the advent of αSN antibodies it's become clear that there is a much wider, extra-nigral, distribution of αSN pathology throughout the brain in PD. It is these pathological αSN lesions that are probably responsible for many of the non-motor symptoms in PD and they are also associated with microglial activation and proliferation (38). In this respect there is a similar variety of microglial functional phenotype as is seen in AD (see Fig 2).

There is a similar discussion to that in AD as to whether microglial cells initiate or react to pathology in PD. More recently it has been suggested that astrocytes may have more of a

primary role and that microglia are reactive (39). More specifically αSN has been found to accumulate in astrocytes and this parallels the spread of pathology (40, 41). Via a mechanism that has yet to be determined this astrocytic accumulation of αSN is thought to initiate a microglial reaction. In support of this, astrocytic expression of mutated αSN has been shown to cause neurodegeneration in mice (42).

## Amyotrophic Lateral Sclerosis (ALS)

In ALS there is a complex interplay between microglia and T cells that modify the rate of disease progression in a way that is not seen in other neurodegenerative disorders (43). Microglial activation has been observed around motoneurons in the primary motor cortex, brainstem motor nuclei and in the ventral horn of the spinal cord (44, 45). Microglial activation has also been seen *in vivo* in ALS patients using the PK11195 ligand in PET imaging (46). Based largely on observations in animal models of ALS the microglial cells seem to have neuroprotective and neurotoxic roles, slowing and accelerating disease progression respectively (47). This was nicely illustrated in a recent study in a mutant superoxide dismutase (mSOD1) animal model where the microglial phenotype apparently changed during the course of the disease. The microglia isolated at disease onset had a neuroprotective phenotype whereas those isolated from end-stage disease animals had a classical neuroinflammatory phenotype (48). Earlier studies in mSOD1 where the mutant protein was expressed in the microglia showed an enhanced neurotoxicity of these cells compared to wild type microglia not expressing the mutant (49, 50). Conversely a possible neuroprotective role for microglia in ALS patients is supported by the observation of insulin growth factor II (IGF-II) in these cells in post mortem tissue samples (51).

## Summary

It appears that microglial cells have a role in the pathogenesis of AD, PD and ALS but their precise role appears to vary between these disorders. In AD there is evidence for a role in the initiation and progression of the disease. Alternatively, senescence and impaired function of the microglia may lead to loss of a neuroprotective function. In PD the microglial response does not seem to be quite so prolific and is perhaps more reactive and closely linked to astrocytic changes whereas in ALS the microglia expressing mutant protein seem to be directly toxic to motoneurons.

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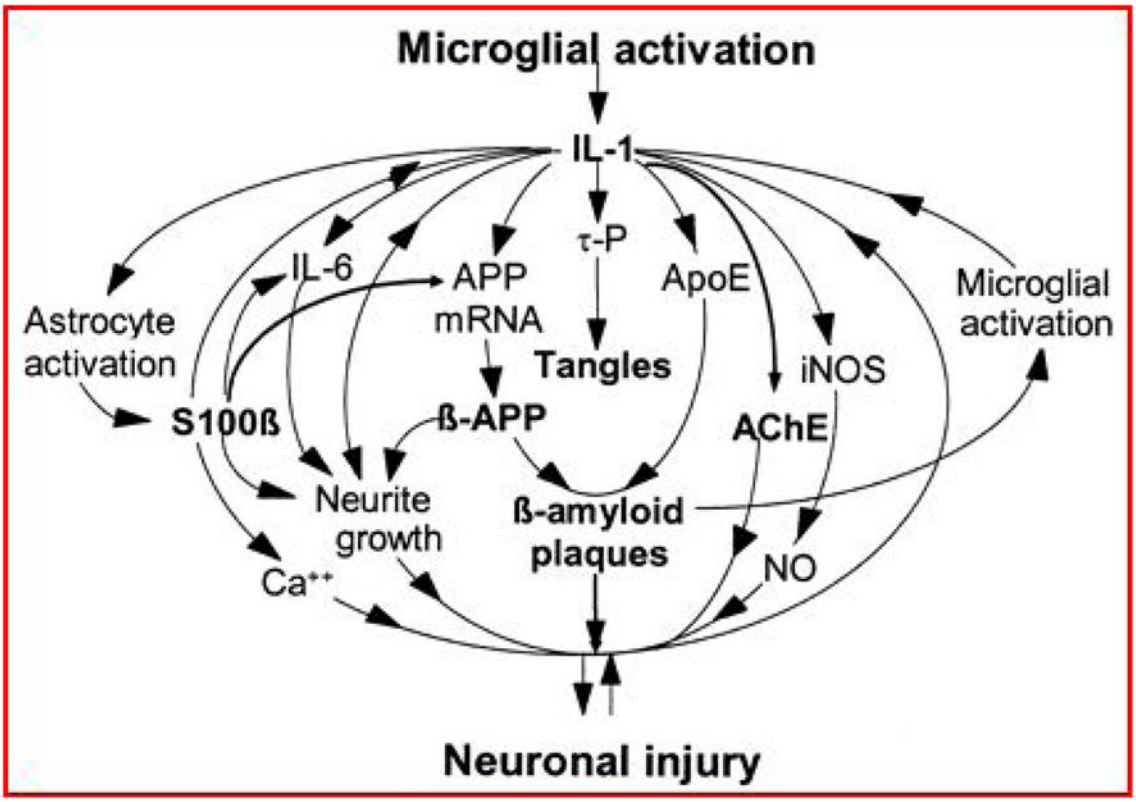
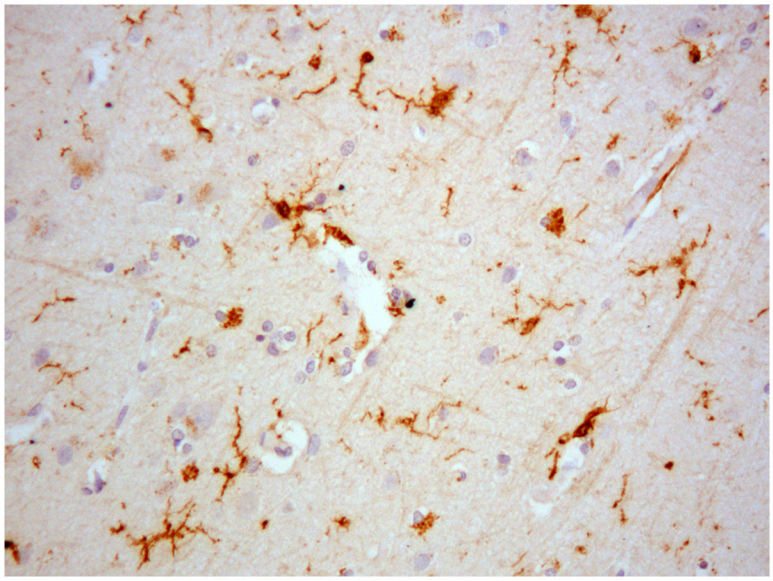
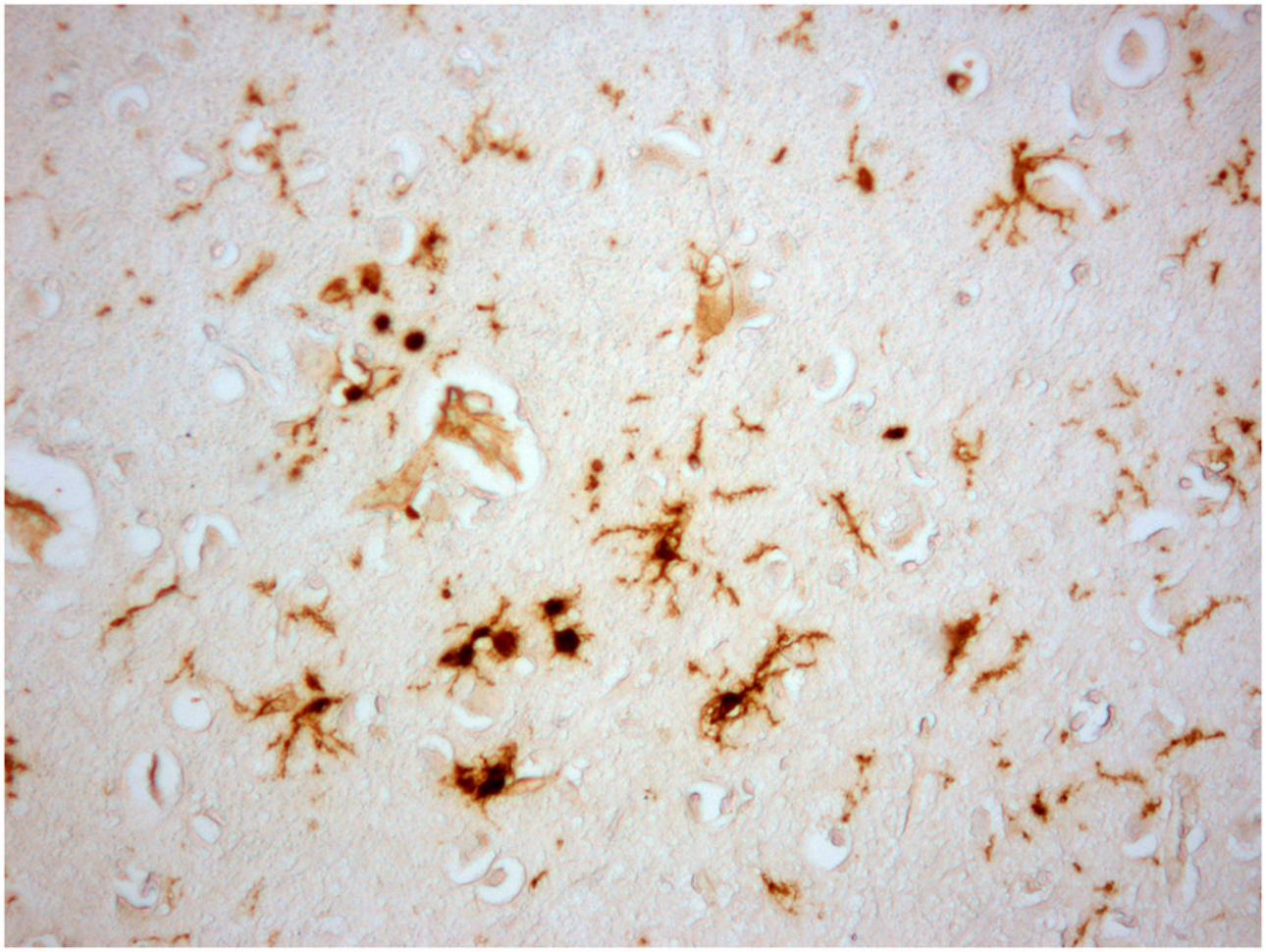



**Fig 1.**

The cytokine cycle [6] which postulates a key role for microglial activation and cytokine release in the formation of protein aggregate pathology and ultimately neuronal injury.





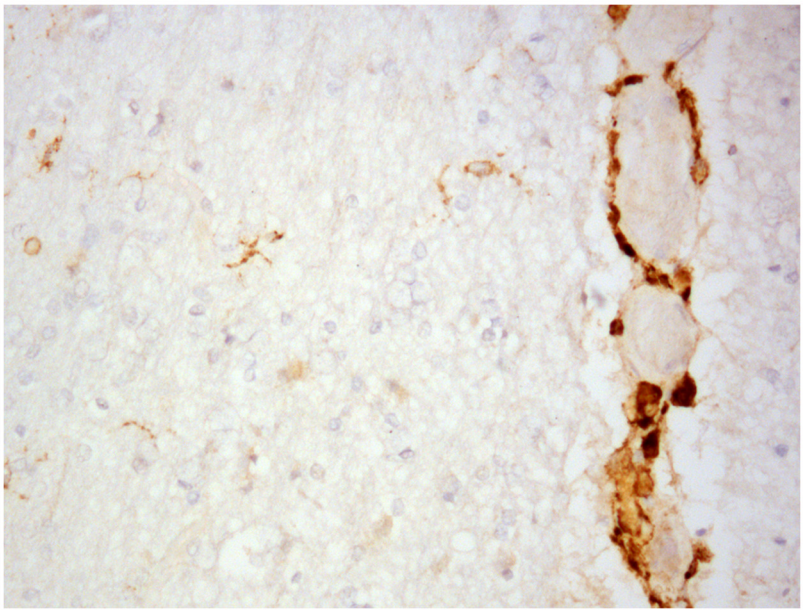


**Fig 2.**

Microglial cells in a Parkinson's disease brain demonstrating a variety of morphologies and displaying different phenotypic markers. A) Ionized calcium binding adaptor molecule 1 (iba1), a pan-microglial marker staining cells with multiple morphologies. B) Microglia with a more activated morphology, with retracted thicker processes immunostained with an antibody to CR3/43, an MHC II marker. C) Perivascular macrophages and some parenchymal microglial-like cells immunostained with CD163, a membrane-bound scavenger receptor.