Biochimica et Biophysica Acta 1802 (2010) 889–902

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Inflammation in transgenic mouse models of neurodegenerative disorders

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ARTICLE INFO

Article history:
Received 7 July 2009
Received in revised form 9 October 2009
Accepted 23 October 2009
Available online 31 October 2009

Keywords:
Transgenic mice
Alzheimer's disease
Parkinson's disease
Huntington's disease
Immune system
Microglia
Cytokines
Complement system

ABSTRACT

Much evidence is available that inflammation contributes to the development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease. Our review investigates how well current mouse models reflect this aspect of the pathogenesis.

Transgenic models of AD have been available for several years and are the most extensively studied. Modulation of cytokine levels, activation of microglia and, to a lesser extent, activation of the complement system have been reported. Mouse models of PD and HD so far show less evidence for the involvement of inflammation.

An increasing number of transgenic mouse strains is being created to model human neurodegenerative diseases. A perfect model should reflect all aspects of a disease. It is important to evaluate continuously the models for their match with the human disease and reevaluate them in light of new findings in human patients.

Although none of the transgenic mouse models recapitulates all aspects of the human disorder they represent, all models have provided valuable information on basic molecular pathways. In particular, the mouse models of Alzheimer disease have also led to the development of new therapeutic strategies such as vaccination and modulation of microglial activity.

1. Introduction

The perfect animal model of a human disorder should reflect (i) the symptoms, (ii) the lesions and (iii) the causes [1]. Here we will review how transgenic mouse models meet these criteria with special consideration of the inflammation hypothesis. We discuss the role and modulation of inflammatory processes in these models.

The inflammation hypothesis proposes that a chronic inflammatory response occurs in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), and that this response exacerbates the characteristic neurodegeneration. Several findings support the hypothesis for AD and to some extent for PD and HD: (i) markers of inflammation are elevated in postmortem brain tissue (gliosis, proinflammatory cytokines, complement activation); (ii) epidemiological studies indicate that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) lowers the risk of disease; (iii) DNA polymorphism of some cytokines and acute phase proteins modulates the risk; and (iv) animal and cell culture models show that modulation of inflammation is effective in curbing the disease process (reviewed in [2–4]). When involvement of inflammation in these disorders was first discovered, it was viewed solely as a detrimental factor. More recently it has been suggested that certain aspects of the immune response can play a positive role in regeneration and clearance of pathological aggregates, creating great interest in the possible modulation of immune responses in order to obtain beneficial effects [5–7].

2. Transgenic mouse models of Alzheimer's disease

In AD, a disturbance of beta amyloid protein (Aβ) metabolism leads to the formation of soluble oligomers and larger, insoluble aggregates. It is now thought that the oligomers themselves may be neurotoxic, causing synapse loss and neuronal degeneration, accompanied by aberrant tau phosphorylation and formation of neurofibrillary tangles (NFT). Transgenic mouse models of AD have been created by introducing to the mouse genome mutated forms of the human amyloid precursor protein (APP) or the presenilin 1 (PS1) gene found in familial AD cases (sporadic AD is not connected with such mutations). Introduction of wild-type forms of APP and PS1 as found in normals and non-familial AD cases does not result in mouse pathology. The mice expressing pathological human mutant proteins readily develop Aβ deposits, show behavioral deficits, and display some aberrant tau-phosphorylation, even though very little neuronal death occurs (for recent reviews see: [1,8,9]). Neurofibrillary tangles (one of the major pathological hallmarks of AD) are not found in these mouse strains. Different transgenic models with additional

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doi:10.1016/j.bbadis.2009.10.013

pathological tau mutations have been created to mimic this aspect of AD [10]. Even though these tau mutations cause other tauopathies, they are not associated with AD.

2.1. Complement activation in AD mouse models

The complement system is a major component of the body's immune defense. It is an ancient and highly conserved system which is a key component of the innate defense against microbes and other infections. It is also a key component of the adaptive immune system clearing antigen-antibody complexes. In addition, it is involved in clearance of damaged tissue and necrotic cells of the body itself. The complement pathways are cascades of proteins which are sequentially cleaved and terminally assembled. They can be activated via the classical pathway initiated by C1q binding, the alternative pathway, starting with activation of C3, or the lectin pathway. Full complement activation results in formation of the membrane attack complex (MAC or C5b-9) consisting of the assembly of the proteins C5b through C9. MAC inserts into membranes and lyses cells. The complement system is a potent mechanism and is tightly regulated by inhibitors such as C1 inhibitor, factor H and C4b-binding protein. Activation of the complement system results in opsonization of targets for phagocytosis, production of pro-inflammatory anaphylatoxins (C5a, C3a) and in lysis of cells. For a review of the complement system see [11].

Complement activation in AD was first described more than two decades ago (for review see [12,13]). This activation likely occurs as an attempt to clear toxic protein aggregates and debris of dying cells. Complement activation attracts microglia, promotes secretion of inflammatory cytokines and induces neuronal damage via MAC and free radicals, contributing to the pathogenesis of AD [3]. It has been demonstrated that Aβ is a powerful activator of complement. It binds to C1q [14,15], initiating the classical pathway of complement activation. Aβ also activates the alternative pathway by formation of complexes with activation products of C3 [16]. In AD complement is activated fully [17,18] and early [19] in the disease process. With the exception of C4b binding protein [20], expression of complement inhibitors is deficient and the complement system activation is not adequately controlled [19,21].

Markers of complement activation have also been detected in several AD mouse models. In a triple mutation model of cerebral amyloid angiopathy (SwDI; Dutch E693Q, Iowa D694N and Swedish K670N/M671L mutations), Fan et al. [22] described that mRNAs of the early complement components C1q and C3 were upregulated. C1q, C3, and C4 protein levels were also elevated in Western blots. In immunostaining, the complement proteins colocalized with fibrillary Aβ deposits and microglia. Matsuoka and colleagues [23] showed that mouse C1q strongly colocalized with fibrillary Aβ, and was also upregulated in some plaque-associated microglia in PS/APP mice. Failure to detect robust C1q binding to plaques in another report [24] may be due to differences between transgenic strains or the anti-C1q antibodies used. A more recent study found C1q deposition to increase with age in Tg2576 mice [25].

C1q knock-out mice (Q−/−) are not able to activate the classical complement pathway. Crossing this strain with Tg2576 or APP/PS1 mice reduced neuropathology as demonstrated by a decreased loss of the presynaptic marker synaptophysin and diminished glia activation, while the plaque load remained unchanged [26]. In the double-transgenic strain (APPQ−/−), Zhou and colleagues [25] reported reduced C4 expression and upregulated C3 expression, suggesting that components of the alternative complement pathway (C3b, C3a, or C5a) could have a neuroprotective function. However, a recent study showed that C5a may actually play a detrimental role [27]. Additional evidence for a neuroprotective function of C3 of the alternative pathway was provided by Maier et al. [28] who found that C3 deficiency increased Aβ plaque formation and neuronal loss in APP mice which were crossed with C3 knock-out mice. The phenotype of microglia was switched towards an increase in CD45 expressing cells.

Overexpression of the C3 inhibitor, soluble complement receptor-related protein y (sCrry), also caused a 2- to 3-fold increase in Aβ deposition and increased neuropathology in APP mice [29]. A different approach to complement modulation was used by Pillay and colleagues [30] by employing Vaccinia virus complement control protein (VCP), which inhibits both the classical and alternate complement pathways. It improved memory performance in APP/PS1 mice.

Although an activation of the complement system occurs in mouse models of AD, several studies have pointed out significant differences between the human and mouse systems (for reviews see [31,32]). It has been shown that mouse C1q binds to Aβ [23,26], but as Webster and colleagues [33] demonstrated binding was less efficient compared to the human form, resulting in a lower activation of the mouse complement complex in transgenic models compared with humans. Immunostaining of plaque-associated complement proteins was generally weaker in mice compared to AD [24](see Fig. 1). By using erythrocyte lysis assays Ong et al. [34] showed that mice have lower serum complement protein levels compared to humans and other species. Ebanks and colleagues [35] found that mouse complement C4 lacked C5 convertase activity, preventing complement activation via the classical pathway.

Taken together, these studies show that the complement system is activated in transgenic models of AD (for summary see Table 1). Complement protein expression is increased and associated with plaques and glial cells. While C1q deficiency reduces neuronal degeneration and improves learning, inhibition of the alternative pathway (C3) increases Aβ pathology and neuronal loss. Important differences between AD and mouse models are the lower expression levels of the complement proteins, and possibly reduced binding of C1q to Aβ as well as lack of late-stage complement activation [17]. These mouse models also fail to display extensive tau pathology and widespread neuronal death. Tau aggregates are, in addition to Aβ aggregates, possible activators of the complement system. Several approaches of modulating the complement system in transgenic mice have been shown to reduce neuropathology and/or Aβ load. It remains to be determined if these interventions can also be effective in human AD, particularly in early stages, before full-blown complement activation exacerbates the severe degeneration in end stage disease.

2.2. Microglial activation in AD mouse models

There is a plethora of evidence that activated microglia contribute to neurodegeneration in AD. Microglial cells are the immune effector cells in the CNS and are part of the mononuclear phagocytic system, expressing characteristic markers of phagocytes and immune cells, such as complement components and their receptors, major histocompatibility complex (MHC) glycoproteins, and scavenger receptors (for review see [36,37]). Once activated, microglia phagocytose targets, release cytokines and, if fully activated, discharge toxic free radicals [38–40]. In neurodegenerative disorders, such as AD, microglia fail to clear pathological protein aggregates and cellular debris and become chronically activated, continuously releasing neurotoxic substances and contributing to the pathogenesis [41]. It was long thought that microglia exist in either an activated or a resting state. More recently it has been proposed that microglia can be activated into either anti-inflammatory (alternative, adaptive) or pro-inflammatory (classical, chronic) states, having either beneficial (Aβ clearance, release of neurotrophic factors) or detrimental effects (release of pro-inflammatory cytokines, free radicals) [7,42].

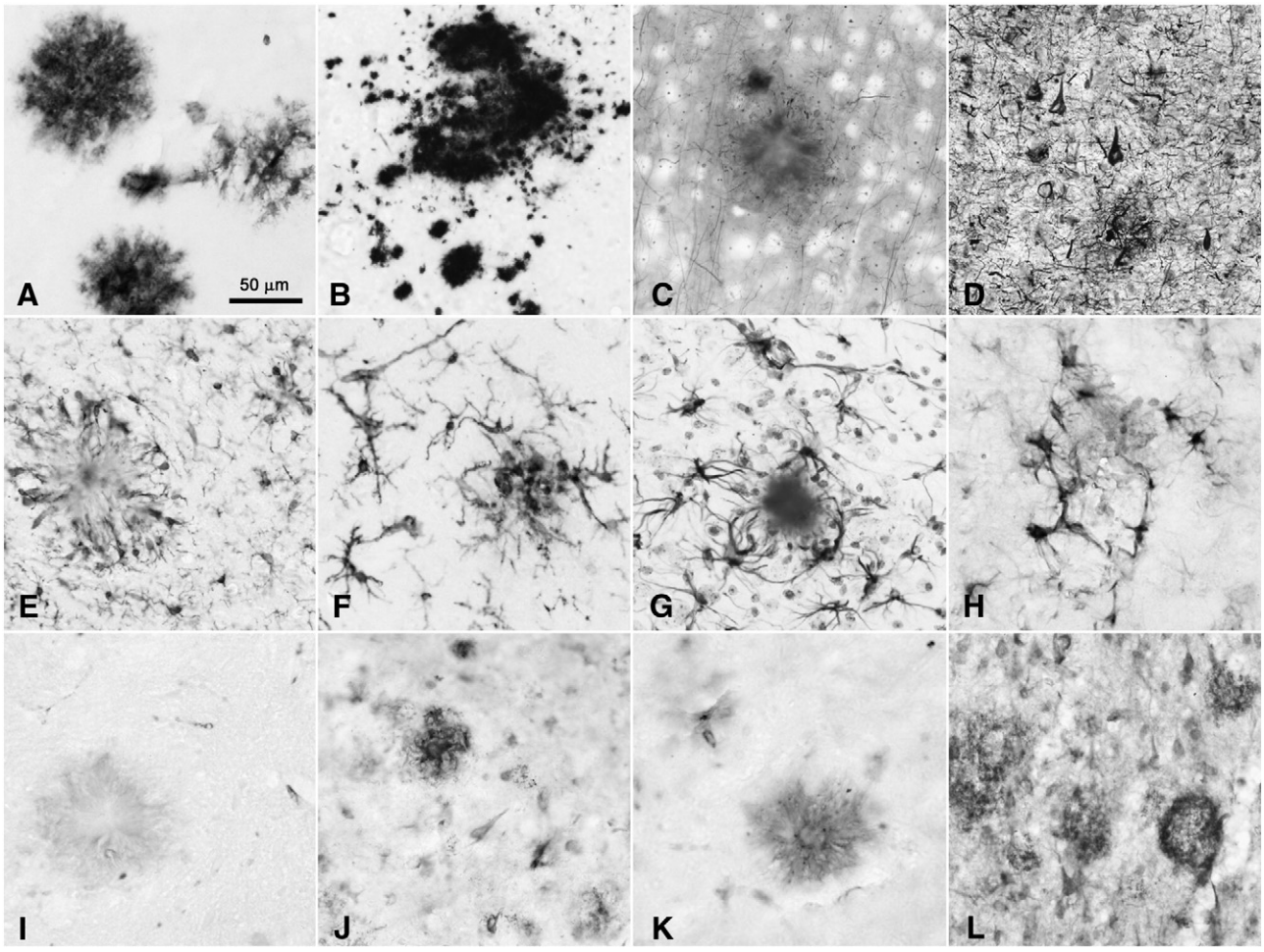

Fig. 1. Comparison of immunostaining and histology staining of the cortex of APP23 mice (A, C, E, G, I and K) and of a human AD case (B, D, F, H, K and L). (A) and (B) compare Aβ deposits. (C) and (D) compare Bielschowsky histology staining demonstrating only few dystrophic neurites associated with Aβ plaques in APP23 mice but dense fibrillary changes in the AD case. (E) and (F) compare immunostaining for microglial cells. The mouse tissue is stained with an antibody against Iba1 and the human tissue with an antibody against HLA-DR. (G) and (H) compare GFAP immunostaining for astrocytes (G is counterstained with Cresyl Violet, labeling all nuclei). (I) and (J) compare immunostaining of C1q of complement (note that C1q association with plaques in tg strains has been reported by [23,25]), and (K) and (L) compare immunostaining for C3 of complement. Calibration bar: 50 µm.

2.2.1. Microglia accumulate around Aβ deposits and are activated in mouse models

In transgenic mouse models, activated microglial cells accumulate in the vicinity of Aβ plaques, similarly to AD (Fig. 1). This has been shown in various strains including Tg2576 (Swedish), APP 22 (Swedish/London), APP 23 (Swedish), and TgCRND8 (Indiana/Swedish) [43–46]. While in other mouse models microglia are mainly associated with compact (dense core) plaques [47], in TgCRND8 mice, which develop diffuse and compact plaques earlier than other strains (at 9–10 weeks), microglia and astroglia were associated early on with both types of plaques [46]. Early activation of microglia stained with HLA-DR and CD11b was also reported in the PS19 model of tauopathy which carry the human tau P301S mutation. Microglial activation coincided with synaptic pathology, followed later by fibrillary tau pathology and astrogliosis [48]. Although Howlett and colleagues [9,49] found no up-regulation of microglial CD11b in TASTPM mice (double APP/PS1 transgenic), expression of Iba-1 was greatly increased, suggesting a change in activation state.

Recent advances in imaging have made it possible to observe individual cells in vivo over time. Using in vivo multiphoton microscopy Meyer-Luehmann and colleagues [50] demonstrated that plaques form within days in both Tg2576 and PS1/APP mice and that microglial cells aggregate around these newly formed plaques within 1 to 2 days, followed by dysmorphic changes to neurites. Despite the close association with microglia, the plaques were not cleared, but possibly restricted from growing larger. In a different *in-vivo* imaging study, it was observed that additional microglial cells continue to migrate to plaques, that their volume predicts changes in plaque size, and that the microglia closest to plaques phagocytose more actively [51].

Microglia in SwDI mice were found to express complement proteins C1q, C3, C4 [22]. Microglia expressing complement receptor-3 (CR3, CD11) and astroglia were detected in APP/PS1 (Tg2576/5.1PS1) transgenic mice as soon as the first Aβ deposits formed at 6 months, but MHC-II expression was not found until 12 months of age, coinciding with stabilization of fibrillary Aβ and suggesting a more severe state of inflammation and activation [52].

2.2.2. Modulation of states of microglial activity in transgenic mice

Several recent studies have focused on the regulation of microglial activity via their receptors. CD40–CD40 ligand (CD40L) suppression shifts microglia towards increased phagocytic activity ("anti-inflammatory state"). Tan and colleagues [53] crossed Tg2576 mice with CD40L deficient mice and reported decreased plaque loads and microgliosis [54]. Interruption of CD40–CD40L interaction in vaccinated PSAPP and Tg2576 mice increased Aβ clearance via increasing the phagocytotic activity of microglia, suggesting that CD40–CD40L acts as a molecular switch between pro- and anti-inflammatory states

Table 1
Summary of studies on inflammation in mouse models of AD.

Model	Experimental intervention	Inflammatory response	References
		COMPLEMENT	
SwDI		UP mRNA C1q, C3; UP Western C1q, C3, C4; colocal. complement w. fib Aβ and microglia	[22]
PS/APP		Colocal. C1q w. Aβ /MG	[23]
Tg2576		UP C1q deposition w. age	[25]
Tg2576	x C1q KO	DN glia activation, DN neurodegeneration, unchanged plaque load	[26]
Tg2576	x C1q KO	DN C4, UP C3	[25]
APP22	x C3 KO	UP plaque load, neuronal loss MG express CD45	[28]
APP22	x sCrry TG	UP Aβ deposition, UP neurodegeneration	[29]
APP/PS1	Vaccinia virus complement control protein	UP memory	[30]
Tg2576, 3xTg-AD	C5a receptor antagonist	DN Aβ deposition, neurodegeneration, gliosis, phospho tau, UP behavior	[27]
		MICROGLIA	
Tg2576		MG activation	[43]
APP 22		MG activation	[45]
APP 23		MG activation	[44]
TgCRND8		Early MG association with diffuse and compact Aβ	[46]
APP/PS1		UP Iba-1, unchanged CD11b in MG	[9,49]
PS19 (tau)		MG activation	[48]
APP/PS1 and Tg2576		MG aggregate near plaques and phagocytose	[50,51]
SwDI		MG express C1q, C3, C4	[22]
APP/PS1		MG express CR3 (CD11) at 6 mo and MHC-II at 12 mo	[52]
Tg2576	x CD40L deficient strain	DN microgliosis and Aβ load	[53,54]
PSAPP, Tg2576	x CD40 or neutralizing CD40L antibody, Active Vacc.	Up Aβ clearance, UP MG phagocytosis	[55]
PSAPP and Tg2576	infusion with human umbilical cord blood cells	UP MG phagocytosis via suppression of CD40–CD40L interaction	[56]
Tg2576	x CD40L/CD40 KO	DN tau phosphorylation	[57]
Tg2576	x CCR2 KO	DN MG recruitment to plaques, UP Aβ aggregation, memory impairment	[58]
APP/PS1	x TLR2 KO	DN MG recruitment to plaques, UP Aβ aggregation, memory impairment	[59]
APP/PS1	x LXR KO	UP Aβ load	[60]
Tg2576	LXR agonist	DN Aβ deposits, DN CD45+ MG, DN IL-6 mRNA	[61]
APP/PS1	M-CFS	UP number of MG, UP Aβ phagocytosis, DN Aβ deposits	[62]
Tg2576	Exercise	DN IL-1β Aβ, TNF-α, UP MHC-II	[63]
Tg2576	x C1q KO	DN MG activation, unchanged plaque load	[26], [25]
APP	x C3 KO	UP MG CD45, DN MG F4/80 and CD68	[28]
APP/PS1	Glatimer acetate vaccination	UP MG CD11c, UP IGF, Aβ clearance	[65]
Tg2576	LPS, intracerebral	UP MG activation, UP Aβ clearance	[66]
	Dexamethasone	Blocks activation	
SwDI	Minocycline	DN MHC-II MG, DN IL-6, UP memory, no change to Aβ deposition	[67]
APPswe	Aged mice UP Aβ	UP MG expression of pro-inflammatory genes	[68]
APP/PS1	Aged mice UP Aβ	UP MG TNF-α, iNOS	[69]
APP/PS1	Pass. Vaccine	Activation CD45+ MG, clearance of Aβ	[83]
PDAPP	Pass. Vaccine	MG migrate to plaques	[85]
APP23, Tg2576	DNA vaccines	UP phagocytosis, number of MG, DN Aβ burden	[88,89]
APP/PS1	Pass. Vaccine	UP number of MG, but no change in Aβ clearance	[90]
		CYTOKINES	
Tg2576		UP IFN-γ; IL-12 and IL-4 absent	[96]
Tg2576		UP IL-1β, TGF- β, IL-10, IL-6	[95]
Tg2576		UP IL-1 β, TGF- β, IL-6	[94]
Tg2576, PS1/APPsw		UP TNF-α, IL-6, IL-12p40, IL-1 β, IL-1 α, GM-CSF	[97]
3xTg-AD		UP TNF-α, MCP-1	[98]
3xTg-AD	dominant negative TNF inhibitor	DN Aβ deposition	[99]
APP23	x TNF-αR KO	DN Aβ deposition, neuronal loss	[100]
Tg2576	Exercise	DN TNF- α, IL-1 β, Aβ UP IFN-γ, MIP-1 α, CD40, MHC-II, CD11c	[63]
Tg2576	x IFN-γ R 1 KO	DN TNF-α, BACE1, Aβ plaques	[101]
APPswe	x TLR-4 KO	DN TNF-α, IL-1β, IL-10 and IL-17	[102]
APPswe/PS1	UP IL-1β	DN Aβ	[103]
hAPP	x TGF-β1 (AG)	DN Aβ	[104]
TGF-β1		UP Aβ (murine)	[105]
Tg2576	x CCL2 (MCP-1)	UP glial activation, Aβ deposition	[107]
APP/PS1	AAV-dominant-negative CCL2	DN glial activation, Aβ deposition	[107]

AG: astroglia; DN: downregulation, reduction; MG: microglia; MIP: macrophage inflammatory protein; PassVaccine: passive vaccination; UP: upregulation, increase, improvement; x crossbreeding.

of microglial activation[55]. Increased microglial phagocytosis was also shown in Tg2576 and PSAPP mice after infusion with human umbilical cord blood cells, via suppression of CD40–CD40L interaction [56]. CD40L or CD40 deficiency also reduced pathological tau phosphorylation in Tg2576 mice [57].

Impairment of microglia recruitment to plaques by inducing a deficiency of CCR2, a microglial chemokine receptor [58], or the innate immune receptor toll-like receptor 2 (TLR2, [59]) increased Aβ aggregation and accelerated memory impairment, indicating that microglial chemotaxis is important in controlling Aβ deposition.

Liver x receptor (LXR) plays a dual role in controlling cholesterol homeostasis, while inhibiting inflammation. Loss of LXR in APP/PS1 mice leads to increased plaque load. In cell culture, LXR activation reduced the microglial inflammatory response to

fibrillary Aβ and enhanced microglial phagocytosis [60]. Treatment of Tg2576 mice with the LXR agonist GW3965, reduced Aβ deposits by half, and was accompanied by reduction in the number of CD45+ microglia as well as interleukin (IL)-6 mRNA expression [61]. The authors suggest that LXR acts via increased expression of lipidated ApoE.

Microglial activity can also be altered by modification of cytokine levels. Treatment of APP/PS1 mice with macrophage colony-stimulating factor (M-CSF) increased the number of microglial cells, as well as their phagocytosis of Aβ and reduced the number of Aβ deposits [62]. Nichol and colleagues [63] found that exercise induced a shift from pro-inflammatory to anti-inflammatory microglial activation in Tg2576 mice. Exercise resulted in reduced expression of the pro-inflammatory cytokines IL-1β and tumor necrosis factor (TNF)-α, increased MHC-II levels (indicating a shift to an antigen-presenting state), and induced a trend towards reduction in levels of aggregated Aβ.

As reviewed earlier in this article, there is good evidence for an activation of the complement system in AD mouse models. Alterations in the level of complement components also modulate microglial activation. Microglial accumulation, C4 levels and neurodegeneration were reduced in C1q deficient Tg2576 and APP/PS1 mice, while C3 levels were increased and Aβ load remained unchanged [25,26]. Extrinsic C1q can shift microglia into a pro-inflammatory activation state, as demonstrated recently in wildtype rat cell culture [64]. In a different set of experiments Maier et al. [28] showed that reducing levels of C3 led to increased microglia/macrophage CD45 levels while F4/80 and CD68 showed a trend toward reduction, suggesting a switch in phenotype of microglia.

Butovsky and colleagues [65] showed that T-cell-based immunization of APP/PS1 mice with glatimer acetate caused a phenotype switch in microglia inducing CD11c and insulin-like growth factor 1 expression as well as increased clearance of Aβ. This was also accompanied by increased neurogenesis.

Intracerebral injections of lipopolysaccharide (LPS) induced neuroinflammation associated with clearance of Aβ and microglial activation. Dexamethasone inhibited microglial activation and Aβ clearance [66].

Minocycline is a tetracycline with anti-inflammatory properties and reduces microglial activation. Although minocycline treatment did not alter Aβ deposition in SwDI mice, it reduced the number of MHC-II microglia and IL-6 expression as well as improving learning performance [67]. The studies of minocycline treatment and C1q deficiency show that the harmful effects of microglia can be ameliorated in mouse models independently of Aβ levels.

Aβ itself can influence the balance between pro- and anti-inflammatory activation. It drives microglia towards a pro-inflammatory state. While microglia of wild-type mice subjected to traumatic brain injury predominantly produce anti-inflammatory factors, microglia in APPswe mice have increased expression of pro-inflammatory genes [68]. Jimenez and colleagues [69] reported that in 6-month-old APP/PS1 mice, microglia are TNF-α negative and phagocytose Aβ in accordance with an anti-inflammatory phenotype, while microglia of 18-month-old mice have switched to a pro-inflammatory phenotype with increased TNF-α and inducible nitric oxide synthase (iNOS) expression. The authors suggest that soluble oligomeric Aβ, which had increased 10-fold by 18 months, may be responsible for this switch. This phenotypic switch may be the murine equivalent of "microglial senescence", leading to deficiency in phagocytosis and immune defense in aged human brains [70] or "inflammaging" [71], a chronic up-regulation of the pro-inflammatory state associated with aging.

2.2.3. Resident brain microglia vs. peripheral, bone-marrow derived cells

An interesting question is whether infiltrating peripheral macrophages enter the brain and whether they take part in clearance of Aβ. It has been shown that in whole-body irradiated mice, peripheral macrophages cross the blood-brain barrier and differentiate into CD11c positive microglia. Such infiltrated cells are more efficient as phagocytes than the resident cells [72,73]. Considerable infiltration of peripheral macrophages and accumulation near vessels and plaques was induced when transforming growth factor (TGF)-β-Smad2/3 signaling was interrupted in immune cells of Tg2576 mice, accompanied with a substantial reduction of Aβ deposits and improved learning [74]. The potential of bone-marrow derived cells for Aβ clearance was also demonstrated by Butovsky and colleagues [75], who specifically ablated these cells by irradiation in APP/PS1 chimeric mice. The number of CD11c+ cells in brain was reduced and Aβ deposition increased. It is still a point of debate as to whether peripheral recruitment can occur without damage of the blood-brain-barrier, since much of the data are derived from experiments using whole-body irradiation [72,75]. A different approach was used by Ajami and colleagues [76] who created parabiotic mice with peripheral blood chimerism in which one of the chimeric partners expressed GFP in hematopoietic cells. When microgliosis was induced in the GFP-negative partner, none of the microglial cells was GFP-positive, suggesting that the microgliosis resulted from expansion of the local brain microglial pool.

2.2.4. Microglia are involved in vaccination-mediated clearance of Aβ

Both active and passive Aβ based vaccination protocols have been used successfully in AD mouse models to reduce the Aβ burden and to improve behavioral functions (for reviews see [77–79]). Encouraged by such positive results, a clinical trial in human patients was initiated, but was hampered by unwanted side effects, such as meningoencephalitis, stroke and even death [80,81]. Subsequent clinical trials are aimed at avoidance of inflammation, complement activation and inappropriate T-cell responses.

Several distinct mechanisms for vaccination results have been proposed but we include only studies with relevance to microglial activation and phagocytosis in this review.

It has been proposed that one of the effects of Aβ vaccination is a shift in the state of microglia towards a phenotype with increased phagocytotic activity and limited production of inflammatory cytokines [82]. Wilcock and colleagues [83] reported activation of CD45+ microglia after intracranial injection of anti-Aβ antibodies. Anti-inflammatory drugs reduced microglial activation and inhibited fibrillary Aβ clearance. This suggests that microglial activation is necessary for clearance of compact deposits. The same authors showed also that microglial activation (upregulated CD45) was transient after repeated vaccination of APP/PS1 mice with Aβ [84].

Using in vivo two-photon microscopy imaging in PDAPP mice with GFP labeled microglia, Koenigsknecht-Talboo and colleagues [85] showed that microglia migrate to Aβ plaques within 3 days after systemic administration of an anti-Aβ antibody (m3D6). Microglia did not react to a different antibody which recognizes only soluble Aβ (mHJ5) or to Fab fragments of m3D6. This indicates that antibodies against different Aβ epitopes have differing effects on microglia activation. Similar effects were also shown by Bard et al. and Gray et al. [86,87] who found that antibodies against the Aβ N-terminus activated phagocytosis, while C-terminal antibodies acted by peripheral sequestration of Aβ.

Aβ DNA vaccines were used as an alternate approach for immunotherapy and they have been shown to work effectively in mouse models. Okura and colleagues [88] reported that increased phagocytotic activity and numbers of microglia were the main drivers of Aβ clearance in their model (APP23), while inflammatory cytokine TNF-α expression remained unchanged. Mouri and coworkers [89] used Aβ cDNA in an oral vaccination paradigm in Tg2576 mice and reported reduction in Aβ burden without lymphocytic infiltration.

Although most studies show involvement of microglial activation in vaccination-induced Aβ clearance, others suggest that microglia have only a limited role [90]. The number of microglial cells associated with plaques significantly increased when the anti-Aβ antibody 10D5 was directly applied into the brain of APP/PS1 mice and was further increased by IFN-γ. Inhibition of microglia with anti-Mac1-saporin or minocycline reduced the number of microglia. Effects of microglial inhibition or activation on Aβ clearance, in addition to 10D5 effects, were limited.

In summary (see also Table 1), these studies demonstrate that in transgenic AD mouse models, microglia are activated, accumulate around Aβ deposits, and are involved in their clearance (although one study only shows a limited role [90]). It will be very interesting to see if further studies on modulating microglial activity towards alternate, anti-inflammatory states can lead to an improved clearance of plaques and/or reduced neurodegeneration. It will also be important to search for possible differences between mouse and human microglial activation, such as NOS production and microglial senescence. In contrast to human microglia which do not produce measurable amounts of NOS, murine microglia produce large quantities when subjected to the same type of stimulation [91].

2.3. Cytokines in AD mouse models

Up- or down-regulation of the expression of various pro- and anti-inflammatory cytokines has been widely reported in AD patients (for reviews see: [7,92,93]). Similar changes in cytokine expression have been shown in transgenic mouse models of AD. The cytokines IFN-γ, IL-12, TNF-α, IL-6, IL-1β, IL-1α, TGF-β, and IL-10, monocyte chemoattractant protein (MCP)-1 and granulocyte-macrophage (GM)-CSF were reported to be up-regulated in various transgenic mouse models (Tg2576, TgAPPsw, PS1/APPsw, 3xTg-AD), while IL-4 was found to be down-regulated [94–98].

In addition, experimental manipulation of the cytokine system has been shown to affect the AD type pathology in these models. Disruption of the soluble TNF-α signaling with dominant negative TNF inhibitors (DN-TNFs) in the 3xTg-AD (APP/PS1/tau) model prevents intraneuronal Aβ accumulation [99]. Deletion of the TNF-α receptor TNFR1 in APP23 mice resulted in reduced plaque formation and limited neuronal loss [100]. Exercise was shown to reduce TNF-α and IL-1β in Tg2576 mice to wild-type levels, accompanied by an increase in IFN-γ, macrophage inflammatory protein (MIP)-1α, CD40, MHC-II, CD11c and reduced Aβ levels [63].

Suppression of IFN-γ signaling in Tg2576 mice via IFN-γ receptor 1 knockout reduced Aβ plaque load and gliosis [101]. The same authors showed that in glial cell cultures TNF-α and BACE1 expression was reduced in mutants, suggesting that this pathway is involved in Aβ formation. Microglial production of TNF-α, IL-1β, IL-10 and IL-17 is up-regulated in APPswe mice, but this up-regulation was blocked by knock-out of the TLR-4 gene [102]. Shaftel and colleagues [103] demonstrated that in APPswe/PS1 mice, local overexpression of IL-1β resulted in an inflammatory response and led to a reduction in Aβ deposition, possibly through enhanced microglial Aβ degradation. A moderate increase in astroglial TGF-β1 expression resulted in a reduction of Aβ deposition in hAPP mice (K670M/N671L and V717F) [104]. These findings seem inconsistent with the reported increased Aβ production in TGF-β1 transgenic mice (not transgenic for APP) [105]. Over-expression of CCL2 (MCP-1) in double transgenic Tg2576 mice increased glial activation and Aβ deposition [106], while gene delivery of a dominant-negative CCL2 mutant reduced gliosis and Aβ deposition in APP/PS1 mice [107].

In summary, inflammatory cytokines levels in transgenic mouse models reflect similar changes in AD. Their modulation regulates microglia activity in these models. These studies are summarized in Table 1. It will be interesting to see if this can be translated into a useful therapeutic strategy in humans.

2.4. Efficiency of NSAIDs in AD mouse models

Evidence of chronic inflammation in the brain of AD patients, including upregulation of inflammatory cytokines, over-activation of microglia, and neurotoxic effects from the activated glia, suggests that NSAIDs may be useful in the treatment and prevention of AD. In addition to the pathological evidence for activation of the immune system, the majority of epidemiological studies have demonstrated that long-term exposure to certain NSAIDs reduces the risk of AD in humans. The large Rotterdam study demonstrated that long-term use of ibuprofen (2 years and longer) reduced the relative risk of developing AD to 0.2 (95% CI 0.05–0.83) [108]. Incidence of AD was also reduced in users of NSAIDs (ibuprofen, naproxen and indomethacin) in the Baltimore longitudinal study of aging [109]. These and other epidemiological studies are reviewed in [110]. Although some newer studies found no benefits of NSAIDs, another recent study using records of the Veterans Affairs Health Care System showed that long-term NSAID use protected against AD [111].

With such epidemiological rationale, several trials in transgenic mouse models of AD have been conducted to assess the effectiveness of NSAIDs. Ibuprofen, the most commonly used NSAID in humans, was successfully utilized in the majority of transgenic studies. Feeding 10-month-old Tg2576 mice with chow mixed with ibuprofen for 6 months reduced the number and area of Aβ plaques, as well as IL-1β and glial fibrillary acidic protein levels [112]. Yan et al. [113] reported a similar reduction of plaque load (60%) in Tg2576 when ibuprofen treatment was started at 11 months of age. But they found no effect of pioglitazone (a peroxisome proliferator-activated receptors (PPAR) γ agonist). In double-transgenic mice (APP/PS1), which develop plaques at an earlier age, Jantzen et al. [114] found that a nitric oxide-releasing derivative of flurbiprofen (NCX-2216) reduced the Aβ load dramatically, accompanied by an increase in the number of MHC-II expressing microglia. Ibuprofen reduced the Aβ load moderately, and celecoxib (a cyclooxygenase (COX)-2-selective NSAID) had no effect. A different nitric oxide-releasing derivative of flurbiprofen (HCT 1026) also reduced the Aβ load and microglial activation near plaques [115].

R-flurbiprofen, which is not a COX inhibitor, was found to be effective in improving spatial learning deficits in Tg2576 if administered to younger mice [116]. If the drug was used after plaque development ensued, the plaque load was reduced but the learning deficit was not ameliorated. When treating 10-month-old APP V171I transgenic mice with pioglitazone (at a higher dose than [113]) and ibuprofen for only 7 days, Heneka et al. [117] found a reduced number of activated microglia and reactive astrocytes, decreased expression of COX-2, iNOS and BACE1, and reduction of Aβ deposits and soluble Aβ42. Also, in the Tg2576 mouse model, Morihara et al.[118] reported that ibuprofen reduced IL-1β and the pro-amyloidogenic α1-antichymotrypsin (ACT) expression. They suggested that ibuprofen reduced the Aβ burden via this pathway. In a recent study on triple transgenic mice (APPswe, PS1M146V, tauP301L), ibuprofen reduced intraneuronal oligomeric Aβ, cognitive deficits, and hyperphosphorylated tau immunoreactivity [119]. But when ibuprofen was given to 3-month-old Tg2576 mice for a very short duration (4 days), no effect on Aβ levels was observed [120]. Indomethacin and a lecithin derivative (DP-155) were shown to be effective in reducing Aβ levels in Tg2576 mice [121–123]. Drugs which inhibit COX-2 did not reduce Aβ burden or even increased Aβ levels in mouse models [114,122,124].

The proposed mechanisms of action for NSAIDs include reduction of inflammation via COX inhibition [125,126] or inhibition of cytokine expression (IL-1β, α1-ACT, [118]). In addition, certain NSAIDs have been shown at high concentration to reduce Aβ production by modulation of γ-secretase activity [127]. Some also act as agonists of PPARγ and by modulation of Rho-GTPase (reviewed in [128]).

Despite the epidemiological evidence and successful trials with NSAIDs in transgenic mice, the outcomes of clinical trials in humans have been disappointing and have, in some cases, been accompanied by cardiovascular or gastrointestinal side effects. Several COX-2-selective NSAIDs (Nimesulide, Celecoxib, Rofecoxib) and non-selective NSAIDs (indomethacin, diclofenac, naproxen, ibuprofen) have been used in trials, but benefits were either very small or absent (for review see [110,128]).

3. Transgenic mouse models of Parkinson's disease

The 1988 report describing reactive microglia within the substantia nigra of PD patients was the first line of evidence to support the involvement of the immune system in PD [129]. Since then there have been numerous studies showing that inflammatory processes play an important role in the pathogenesis of PD, and several recent reviews have summarized the current state of our understanding of neuroinflammatory processes in PD [4,130–132]. Similarly to AD, the evidence stems from observations in human postmortem tissue of reactive microglia and astrocytes in the affected areas. Such findings were supported by genetic studies identifying correlations between polymorphisms of genes associated with inflammatory responses and the risk of PD. They were further supported by epidemiological data showing protective effects of chronic use of anti-inflammatory drugs and by functional animal studies showing that activation of the inflammatory response in the central nervous system may lead to selective loss of dopaminergic neurons and that anti-inflammatory treatments ameliorate neuronal and behavioural deficits observed in these animals.

Additional support for the inflammatory hypothesis in the case of PD comes from the investigation of an accidental human model of the disease. In 1983 Langston et al. [133] reported that drug addicts who consumed a synthetic product containing the previously undiscovered neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed symptoms that were very similar to idiopathic PD. A dissimilarity was noted in the pathological examination at autopsy since these patients did not develop Lewy bodies. Nevertheless, there was a selective loss of dopaminergic neurons and continued presence of activated microglia. In one case, this sign of inflammation was seen as late as 16 years after the exposure to the agent [134]. These observations were supported by later studies on MPTP-treated monkeys that showed both microglial and astroglial reactions up to 14 years after the experimental treatment [135,136]. The presence of reactive immune cells years after the initial toxic insult indicates that inflammatory processes in these cases, and possibly also in idiopathic PD, may evolve into self-sustaining mechanisms that are damaging to selective groups of neurons. A number of functional animal models of PD that use various toxins (e.g. 6-OH-dopamine, MPTP, rotenone) or exogenous immune mediators (e.g. LPS) have demonstrated robust activation of neuroimmune mechanisms that are accompanied by neuronal death in the substantia nigra. Furthermore, several of these models rely on immune activation of glial cells as the trigger of selective loss of dopaminergic neurons (reviewed in [41,131,137]). In transgenic animal models of PD, the identification of inflammatory mechanisms has proven to be more challenging. In similarity to AD, transgenic animal models of PD have been created based on knowledge of gene mutations associated with the human disease. They include α-synuclein (Asyn), DJ-1, LRRK2, Parkin, PINK1 and UCH-L1 [138–141]. Thus far transgenic PD models have been created in three different species: mice, as well as *Drosophila melanogaster* and *Caenorhabditis elegans*. Only in the latter two species has the incorporation of Asyn mutations resulted in a consistent loss of dopaminergic neurons. This illustrates that genetic manipulation alone may not be sufficient to trigger the pathogenesis of PD and that additional environmental factors are needed [137]. Even though the genetically modified animals display certain pathophysiological and behavioural characteristics of PD, there have been very few reports describing neuroimmune responses associated with the genetic manipulations. A scarcity of pertinent information does not rule out the possibility that immune responses are evoked by genetic manipulations. Future experiments in transgenic animals may establish such correlations. Below we review the evidence obtained thus far from the various groups of transgenic animal models of PD.

3.1. Alpha-synuclein transgenic mouse models

This is the most studied group of animals, perhaps due to the fact that alpha-synuclein (Asyn, PARK 1) was the first gene to be linked to PD. Asyn has also become the most studied PD-associated protein. Three different mutations (A30P, A53T and E46K) as well as genomic duplication and triplication of a locus containing the Asyn gene have been linked to familial forms of PD [142–145]. The first Asyn transgenic mice were created by Masliah and colleagues [146] by expressing wild-type human Asyn in neuronal cells under the regulatory control of the platelet-derived growth factor-b (PDGF-b) promoter. This resulted in progressive accumulation of Asyn and ubiquitin-immunoreactive inclusions in neurons in the neocortex, hippocampus and substantia nigra. Although loss of dopaminergic terminals in the basal ganglia and motor impairments were observed, there was no substantial decrease in the number of dopaminergic neurons and no glial activation was reported [146]. Since then, pan-neuronal expression of Asyn has been achieved by using PDGF-b, Thy1 or prion protein promoters. In contrast the tyrosine hydroxylase (TH) promoter has been used to restrict Asyn expression to catecholaminergic neurons.

Even though some of the transgenic models mimic certain stages or features of human PD, none of them display the full pathological cascade of PD (reviewed in [147,148]). While neurodegeneration is absent in some cases, it is non-specific or of late onset in others. Similarly, the evidence of immune system involvement has not been consistent and depends on the type of Asyn and the promoter used.

Thy1 is another promoter that has been used in addition to PDGF-b to achieve broad expression of Asyn in mouse neurons. The Thy1 transgenic mouse lines have a wide range of phenotypes with different patterns of Asyn expression [147]. Activated microglia associated with Asyn inclusions have been observed in these mice [138]. However this upregulation was not confirmed in the same mice after paraquat injection, which may have been due to the fact that microglial activation occurs concomitant to neuronal death and is not detectable 2 weeks after the onset of neuronal degeneration [149]. Lewy-like pathological changes in neurons were reported in mice expressing the Thy1-driven A53T mutant form of human Asyn. Astrocytic gliosis and microglial activation accompanied motor neuron pathology, which was also seen in other affected brain regions [150].

Giasson and colleagues [151] reported that pan-neuronal overexpression of A53T Asyn leads to significant astrogliosis in the spinal cord, which was interpreted as being consistent with neuronal injury. These mice displayed motor impairments although no significant loss of motor neurons was observed. A more severe phenotype of A53T Asyn mice was described by Lee et al. [152] who reported adult-onset neurodegeneration leading to progressive motor dysfunction and eventual death of the animals. A prominent astroglial reaction was observed in areas affected by neurodegenerative changes. Interestingly, mice expressing the wild-type or A30P variant of Asyn did not develop such pathology [152]. The above two studies used the mouse prion protein promoter which generally leads to high levels of Asyn protein expression. Despite this fact, not all mice expressing A53T, even under the control of the prion promoter, displayed a glial reaction. Negative results have also been reported [153].

High levels of A30P Asyn expression in the Tg5093 mouse line was associated with a progressive motor disorder characterized by

rigidity, dystonia, gait impairment, and tremor. Even though these mice did not exhibit specific deterioration of the nigrostriatal dopaminergic neurons, they did display neuropathological features including age-related central nervous system astrocytosis and microgliosis. Gliosis was evident in the hippocampal formation at the age of 7–8 months in heterozygote mice and at 4 months in the homozygote mice [154].

In a more recent study, Su et al. [155] characterized inflammatory responses in mice expressing human wild-type Asyn under control of the rat TH promoter. Asyn expressing (SynWT+/+) animals exhibited a significant increase in the number of activated microglia in the substantia nigra at 1 month compared to age-matched control animals. They also had significantly higher levels of expression of the pro-inflammatory cytokine tumor necrosis factor (TNF)-α. Similarly, expression of truncated human Asyn(1–120), driven by the rat TH promoter, led to the formation of pathological inclusions in the substantia nigra; even though no significant cell loss was observed, an increase in microglial cells was evident [156]. A lack of microgliosis has also been reported in mice expressing a truncated (1-130) form of Asyn with the A53T mutation [157].

Transgenic mice with oligodendrocyte-specific expression of wild-type Asyn were created to model multiple system atrophy (MSA) since Asyn-positive glial inclusions are a major histopathological hallmark of idiopathic MSA [158]. These mice showed early and progressive microglial activation in the substantia nigra pars compacta (SNc), which was associated with increased expression of iNOS and loss of dopaminergic neurons. Suppression of microglial activation by minocycline protected dopaminergic SNc neurons [158]. Transgenic mice overexpressing human Asyn have also been used to perform functional animal experiments by using various toxins and immune mediators to trigger neurodegeneration. For example, Gao et al. [159] studied the effects of bacterial LPS injection in mice that expressed human wild-type or mutant A53T Asyn in the absence of murine Asyn (Asyn-null background). Stereotaxic injection of LPS into the substantia nigra caused a similar inflammatory reaction in all animals studied. However, loss of dopaminergic neurons and aggregates of Asyn were observed in mice overexpressing wild-type and mutant Asyn but not in Asyn-null control mice. Furthermore, ex vivo glial cultures or mixed neuron/glial cultures from transgenic animals overexpressing or lacking Asyn have been used to demonstrate differences in microglial phenotype and their ability to produce pro-inflammatory and toxic species [159,160]. Thus microglia from Asyn knock-out animals displayed a reactive phenotype and increased cytokine secretion, but impaired phagocytic ability [160]. This indicates that Asyn plays a major role in regulating the microglial activation state. Human Asyn overexpressing mice were also used to study the effects of immunization with Asyn. Since immunization has been shown to reduce the amyloid burden and reduce the pathology in a number of AD transgenic mouse lines, Masliah et al. [161] vaccinated human Asyn overexpressing transgenic mice with human Asyn. In mice that produced high affinity antibodies against Asyn there was a decreased accumulation of Asyn aggregates and reduced neurodegeneration. Even though vaccination did not induce a significant glial reaction, these experiments clearly demonstrate involvement of the immune system in regulating Asyn aggregation and its associated neurodegenerative pathology.

In summary, due to the various Asyn forms, as well as different promoters and strains of animal used, there have been significant inconsistencies between various studies. It appears that glial reactions typically accompany neuronal cell death, if and when it occurs. However, several reports have described glial activation in the absence of significant neuronal death, which may indicate that Asyn is a signaling molecule released not only from dying neurons, but also from neurons that are functionally compromised or are just simply overexpressing Asyn. Support for this hypothesis comes from a study demonstrating that neurons overexpressing Asyn secrete high concentrations of Asyn which are capable of activating microglia [155], and from in vitro observations that extracellular Asyn can be recycled by neurons and is an effective pro-inflammatory stimulant of both microglia and astrocytes [162–166]. Alternatively, the formation of neuronal inclusions, the development of neuronal deficits, and neuroimmune responses, may not be linked in a causal chain.

3.2. DJ-1, Parkin and PINK transgenic mouse models

Mutations in DJ-1, PARK and PINK genes produce rare inherited forms of PD. DJ-1 at the PARK7 locus has been linked to multiple cellular processes including oxidative stress responses. At least three different lines of DJ-1 knockout mice have been created, which show decreased motor functions without clear loss of dopaminergic neurons [139,167–169]. None of these studies reported inflammatory responses in DJ-1 knockout mice.

PINK1 (PARK6) is believed to play an important role in mitochondrial function, while Parkin (PARK2) is important in protein targeting for proteosomal degradation. PINK1-defficient and Parkin (PARK2) knockout mice do not exhibit loss of dopaminergic neurons and alterations in inflammatory markers have not been reported [139,170–178]. Recently, Frank-Cannon et al. [170] reported that long-term intraperitoneal administration of LPS induced neuroinflammation, which was accompanied by fine motor deficits and loss of dopaminergic neurons in Parkin-deficient (parkin−/−) mice, but not in wild-type animals. Meanwhile Thomas et al. [179] reported that nigrostriatal dopaminergic neurons in Parkin knockout mice did not show increased susceptibility to the parkinsonian neurotoxin, MPTP, which was administered in various doses.

There are a number of other transgenic mouse models that resemble human PD that still have not been characterized with regard to immune system involvement. One example are MitoPark mice, which were created by conditional knockout of the gene for mitochondrial transcription factor A (Tfam) in dopaminergic neurons. These mice have reduced mitochondrial DNA (mtDNA) expression and respiratory chain deficiency in midbrain DA neurons. This leads to adult onset formation of intraneuronal Asyn negative inclusions, dopaminergic cell death, and associated progressive impairment of motor function [180].

Other transgenic mouse models involve genes that do not have identified mutations associated with PD, but which nevertheless may be involved in the pathogenesis of this disease. Thus, the naturally occurring murine weaver mutant (gene symbol, wv) carries a mutation in the gene encoding the G-protein which inwardly rectifies the potassium channel Girk2. It has been reported that in these mice the degeneration of midbrain dopaminergic neurons, unlike other types of neurons, is mediated via neuroinflammatory mechanisms [181].

Mallajosyula et al. [182] reported the creation of inducible monoamine oxidase B (MAO-B) transgenic mice. Astrocytic MAO-B levels were specifically induced in adult animals, which caused selective and progressive loss of dopaminergic neurons in the substantia nigra. Since local microglial activation was observed within the substantia nigra in addition to global astrogliosis, these mice may provide a new model for the investigation of the neuroinflammatory features of PD.

Transgenic mice deficient in various key signaling molecules have been widely used to investigate the role of specific molecular pathways in neuroinflammatory processes associated with PD pathology. Examples include mice deficient in MAPK-activated protein kinase 2 (MK2) [183], complement C3 [184], protease-activated receptor 1 (PAR1) [185], IL-1α/β [186], MCP-1/CC chemokine ligand 2 (Mcp-1/Ccl2) [187], (TNF)-α receptors R1 and R2 [188] and prostaglandin E_2 receptor subtype 2 (EP2) [189].

Transgenic models of PD have also been created by using invertebrates, namely *C. elegans* and Drosophila. While these species

may offer certain advantages, such as the absence of endogenous Asyn which allows for the study of this protein in naïve organisms [190], the obvious disadvantage in using any fly or worm model is the potential risk that a critical factor in the pathology of the diseases is specific to mammals in general or humans in particular [191]. Immune reactions may be an example of a mammal-specific mechanism, which could explain why we were unable to identify any publications describing glial or other immune activation in the two invertebrate models of PD.

4. Transgenic mouse models of Huntington's disease

Huntington's disease is a hereditary polyglutamine disorder caused by extension of the triplet repeat region of the huntingtin (htt) gene. HD is characterized by severe atrophy of the striatum, where up to 95% of the medium spiny neurons degenerate, as well as by the presence of intracellular and intranuclear htt inclusions, and by reactive gliosis.

Evidence for involvement of inflammation in the pathogenesis of HD includes reports on activation of the complement system, increased microglial activity and up-regulation of inflammatory cytokines. Singhrao and colleagues [192] found complement activation and increased mRNA levels for complement proteins and regulators (C1q C chain, C1r, C4, C3, C1 inhibitor, clusterin, membrane cofactor protein, decay accelerating factor, CD59) in HD brain tissue. Increased protein expression of complement components C7 and C9, complement inhibitor clusterin and acute phase protein α-2-macroglobulin was shown in HD plasma and cerebrospinal fluid [193]. Activated microglia expressing HLA-DR were reported in affected areas in HD [194]. These microglial cells were found in close association with degenerating neurons [195]. The peripheral benzodiazepine receptor is selectively expressed by brain microglia. Increased binding of its ligand PK11195 has been described in postmortem HD putamen and frontal cortex [196]. Using PK11195 for positron emission tomography (PET) imaging, increased microglial activation was demonstrated in HD patients and in presymptomatic carriers of the mutated htt gene, indicating that microglial activation is an early event in HD pathogenesis [197,198]. Microglial activation correlated inversely with raclopride binding, a marker of striatal cell function [199].

Data on microglial activation in HD mouse models are relatively sparse. In both HD patients and R6/2 mice, expression of ferritin in microglia is increased and the microglial cells appear dystrophic [200]. But unlike the human HD cases, microglial size and density is reduced with age in R6/2 mice [201].

Upregulation of inflammatory and anti-inflammatory cytokines has been reported in the plasma (IL-6, IL-8, IL-4, IL-10, TNF-α) and striatum (IL-6, IL-8 and TNF-α) of HD patients [193,202]. Interestingly, IL-6 plasma levels were found to be increased in presymptomatic HD mutation carriers 16 years prior to the predicted onset of the disease, suggesting that inflammatory changes commence very early in the disease process [202]. HD monocytes showed increased IL-6 expression when activated by LPS and IFN-γ. R6/2 microglia and YAC128 macrophages were similarly hyperactivated and protein expression of IL-6, IL-10, IL-1β or IL-12p70 was increased in R6/2, Hdh 150Q/150Q, and to a lesser extent in YAC128 mouse models. Less severe and more localized pathology was also observed in the YAC128 model (for review see [203]). In contrast to these studies, Godavarthi and colleagues [204] found no differences in cytokine expression (MCP-1, IL-6, IL-10, TNF-α, interferon-γ, IL-12) and microglia numbers in 12-week-old R6/2 mice, at an age when these mice show severe symptoms.

The anti-inflammatory tetracycline minocycline has been shown to improve behavioral and neuropathological deficits in R6/2 mice [205,206] and was also protective in an excitotoxic rat model of HD [207]. In a different excitotoxic model of HD (3-nitropropionic acid) treatment with C5a receptor antagonists reduced neuropathology, behavioural and motor deficits [208].

Abnormalities in the kynurenic acid pathway are an interesting aspect of HD pathology. Quinolinic acid and 3-hydroxykynurenine are neurotoxic metabolites that are elevated in HD and in the R6/2, Hdh 150Q/150Q and YAC128 mouse models. The kynurenine pathway is

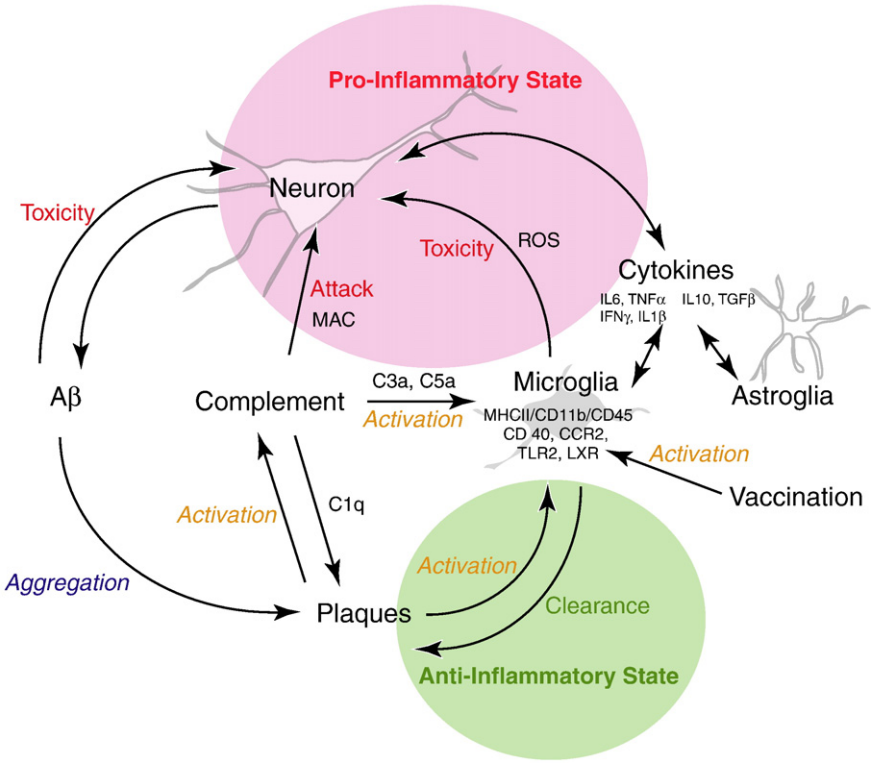

Fig. 2. Possible mechanism of inflammatory response in mouse models of AD and interactions between Aβ, microglia and the complement system.

mainly localized in glial cells, and it is possible that activation of microglia and astroglia may result in production of these excitotoxic metabolites before morphological markers of glial activation are apparent [209–211]. The data on activation of the inflammatory system in transgenic HD mouse models are sparse and contradictory, possibly due to considerable differences in the pathology between different transgenic strains, but also due to the paucity of studies. However, data in HD patients show that the inflammatory system is activated very early and thus may be an important therapeutic target.

5. Summary

As stated in the introduction, the perfect animal model of a human disease should reflect the symptoms, lesions and causes of the disease [1]. Our review explored how transgenic mouse models of AD, PD and HD matched these requirements in the particular area of neuroinflammation. Possible mechanisms involving inflammatory responses in transgenic mouse models are shown in Fig. 2.

Mouse models of AD have been available for a number of years and have been studied widely (for recent reviews comparing mouse models and AD in general see: [1,8,9]). These transgenic mice develop symptoms comparable to AD (memory and behavioral deficits). They build up Aβ deposits, one of the hallmarks of AD, but lack two others; NFTs and overt neuronal death. Since APP and PS1 mutations do not cause sporadic AD (the majority of AD cases), models with these mutations reflect the cause of disease only for the subset of familial cases. Evidence is readily available that Aβ deposition in AD mouse models is accompanied by glial accumulation and activation, and, to variable degrees, modulation of the levels of inflammatory cytokines and complement activation. This inflammatory response is incomplete and less severe compared to AD.

There are several possible explanations: (i) neurodegenerative diseases in humans take many years or even decades to develop; mice may simply not get old enough to develop full-blown inflammation; (ii) in most models human genes are introduced and human proteins are expressed. Interactions with the mouse proteome may not reflect the situation in humans. (iii) Different mechanisms of repair and compensation may exist in long-lived organisms such as humans, and interspecies differences in the complement system have been reported [34,35].

Similarly to AD, only a fraction of PD cases is caused by mutations. These mutations have been used to create mouse models. Compared with AD transgenic models, the available PD models show less behavioral deficits and pathological changes. Only little evidence for activation of the immune system is available. This may in part be due to the fact that these models have been developed recently and only a few studies have been conducted to investigate the involvement of inflammation in the disease process.

Since HD is a hereditary disorder, models created using genes of extended triplet repeats mirror the cause of the disease in humans. Introduction of segments or the complete HD gene causes a range of pathology from wide-spread, non-specific degeneration to mild disease [203]. Again only little and conflicting information on the involvement of inflammation in these mice can be found in the literature.

The seeming lack of inflammatory changes in PD and HD mouse models may be due to (i) the fact that the aggregated proteins in AD are deposited extracellularly, while in HD (and in some models of PD), pathological proteins aggregate intracellularly; (ii) that inflammatory processes may play a lesser role in the mouse models and/or in human PD and HD; or (iii) the current lack of studies focused on the involvement of inflammation in these models.

In conclusion, transgenic models have been proven to be useful tools in the exploration of molecular mechanisms of neurodegenerative disorders and in the discovery of potential therapeutic strategies. Particularly in AD these transgenic models represent an improvement over previous toxic or lesion models. Especially interesting are data in the field of in-vivo multi photon imaging, differential microglial activation and the promising results of vaccination studies. The last example also demonstrates the importance of careful scrutiny when translating results from mouse models into clinical application.

Like most models, the available transgenic mouse strains are imperfect models of human neurodegenerative diseases. However, further studies will lead to a continuously improving match with human disorders for the development of useful therapeutic strategies. Careful comparison with data from human pathology and studies on other organisms, such as dogs or non-human primates [212] will be the most useful additions to mouse models. The recent report describing creation of the first transgenic nonhuman primate line [213] will hopefully encourage further efforts into the development of new transgenic animal models of neurodegenerative disease that more closely resemble human pathology, including neuroimmune responses.

Acknowledgements

This research was supported by the Jack Brown and Family AD Research Foundation, the Pacific Alzheimer Research Foundation and the Natural Sciences and Engineering Research Council of Canada.

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