Published in final edited form as:

Acta Neuropathol. 2011 June ; 121(6): 675–693. doi:10.1007/s00401-011-0833-z.

Glial dysfunction in the pathogenesis of α -synucleinopathies: emerging concepts

Lisa Fellner,

Division of Clinical Neurobiology, Department of Neurology, Innsbruck Medical University,
Anichstrasse 35, 6020 Innsbruck, Austria

Kurt A. Jellinger,

Institute of Clinical Neurobiology, Kenyongasse 18, 1070 Vienna, Austria

Gregor K. Wenning, and

Division of Clinical Neurobiology, Department of Neurology, Innsbruck Medical University,
Anichstrasse 35, 6020 Innsbruck, Austria

Nadia Stefanova

Division of Clinical Neurobiology, Department of Neurology, Innsbruck Medical University,
Anichstrasse 35, 6020 Innsbruck, Austria

Abstract

Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) are adult onset neurodegenerative disorders characterised by prominent intracellular α -synuclein aggregates (α -synucleinopathies). The glial contribution to neurodegeneration in α -synucleinopathies was largely underestimated until recently. However, brains of PD and DLB patients exhibit not only neuronal inclusions such as Lewy bodies or Lewy neurites but also glial α -synuclein aggregates. Accumulating experimental evidence in PD models suggests that astrogliosis and microgliosis act as important mediators of neurodegeneration playing a pivotal role in both disease initiation and progression. In MSA, oligodendrocytes are intriguingly affected by aberrant cytoplasmic accumulation of α -synuclein (glial cytoplasmic inclusions, Papp-Lantos bodies). Converging evidence from human postmortem studies and transgenic MSA models suggests that oligodendroglial dysfunction both triggers and exacerbates neuronal degeneration. This review summarises the wide range of responsibilities of astroglia, microglia and oligodendroglia in the healthy brain and the changes in glial function associated with ageing. We then provide a critical analysis of the role of glia in α -synucleinopathies including putative mechanisms promoting a chronically diseased glial microenvironment which can lead to detrimental neuronal changes, including cell loss. Finally, major therapeutic strategies targeting glial pathology in α -synucleinopathies as well as current pitfalls for disease-modification in clinical trials are discussed.

Keywords

α -Synuclein; Microglia; Astroglia; Oligodendroglia; Neurodegeneration; Parkinson's disease; Multiple system atrophy

α -Synucleinopathies: general characterisation

α -Synucleinopathies are neurodegenerative diseases characterised by misfolded, hyperphosphorylated and fibrillar α -synuclein-positive cytoplasmic inclusions in the central nervous system (CNS) [17, 51, 211].

α -Synuclein is a protein with 140 amino acids that belongs to a family encoded by three distinct genes for α -, β - and γ -synuclein. In normal brain, α -synuclein is enriched in presynaptic terminals, especially in the neocortex, hippocampus, striatum, thalamus and cerebellum [101, 161]. The normal function of α -synuclein is poorly understood. The absence of α -synuclein expression in knock-out mice is associated with striatal dopamine-dependent dysfunction [1]. α -Synuclein interacts with presynaptic membranes and may regulate synaptic vesicle pools [44]. A recent study of $\alpha\beta\gamma$ -synuclein triple knockout mice demonstrated the fundamental role of synucleins in the control of presynaptic terminal size and synaptic structure. Its deletion causes alterations in synaptic transmission, age-dependent neuronal dysfunction and diminished survival [81]. α -Synuclein may directly bind to mitochondrial membranes leading to mitochondrial fragmentation and neuronal cell death [154]. α -Synuclein can also function as a molecular chaperone, important for the folding and re-folding of synaptic proteins [39].

α -Synucleinopathies include Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Their pathological hallmarks are α -synuclein-positive depositions in neurons [Lewy bodies (LBs) and Lewy neurites (LNs)] in PD and DLB, and α -synuclein-positive glial cytoplasmic inclusions (GCIs) in oligodendrocytes in MSA. These inclusions are widely accepted as diagnostic hallmark lesions of α -synucleinopathies [11, 168, 212, 241]. Genetic studies have suggested the causal role of α -synuclein in neurodegenerative diseases [174, 202, 263]. SNCA gene duplications and triplications, as well as three pathogenic point mutations (A53T, A30P, and E46K) have been associated with genetic variants of PD [159, 174, 205, 262], and common SNCA variants influence disease risk of PD [56]. Recent studies confirmed the association between PD and both SNCA SNPs (single nucleotide polymorphisms) and the H1 haplotype of MAPT (microtubule-associated protein tau) [59]. In MSA, familial disease appears rare [209, 257], and up to now mutations have not been detected in the entire coding region of the α -synuclein gene of pathologically confirmed MSA cases [167]. However, candidate SNP studies have demonstrated a significant association between polymorphisms within the SNCA locus and the risk of developing MSA [3, 197]. Post-translational modifications of α -synuclein, including nitration, glycosylation, phosphorylation and ubiquitination are commonly described in relation to pathological accumulation of the protein and may contribute to the pathogenesis of PD, DLB and MSA [6, 73, 74, 239]. Furthermore, the detection of α -synuclein in human cerebrospinal fluid and blood plasma has suggested a possible role of extracellular α -synuclein in neurodegeneration [58, 124, 152]. Finally,

prion-like cell-to-cell transmission of α -synuclein has been proposed which may provide a novel insight in disease progression mechanisms [50, 86, 126].

Parallel to α -synuclein accumulation, α -synucleinopathies are characterised by selective neuronal loss in specific brain regions. In PD, dopaminergic neurons in substantia nigra pars compacta (SNpc) and dopaminergic terminals in the striatum are commonly affected [64, 104, 194]. In addition, PD also shows prominent extranigral pathology affecting the mesocortical dopaminergic system, the noradrenergic system with damage to the locus coeruleus, the serotonergic system with involvement of the dorsal raphe nucleus, the cholinergic system involving the nucleus basalis of Meynert and Westphal–Edinger nucleus, the centre–median parafascicular thalamic system, and many limbic structures including the amygdala [104, 105]. MSA has two major clinical subtypes. Cerebellar predominant MSA (MSA-C) presents with gait ataxia reflecting olivopontocerebellar atrophy, while Parkinson-predominant MSA (MSA-P) is characterised by levodopa-unresponsive parkinsonism reflecting striatonigral degeneration [75]. Both motor subtypes feature progressive autonomic failure due to degeneration in autonomic brainstem centres, intermediolateral cell columns and Onuf's nucleus in the spinal cord [73, 166, 254].

Attempts to stage the neuropathology of PD, DLB and MSA have been made reflecting the possible initiation and progression of these disorders in association with α -synuclein pathology. According to Braak's staging in PD, LB pathology may first affect lower brainstem nuclei, including the dorsal motor nucleus of the vagus, the lower raphe nuclei, the locus coeruleus and the olfactory system (Braak stages 1–2). Then, the pathology can progress and lead to changes in SNpc, intralaminar thalamic nuclei, hippocampal CA2 and amygdala (Braak stages 3–4). Ultimately, involvement of the neocortex (cingulate, temporal, frontal and parietal cortex) may occur (Braak stages 5–6) [21–23]. However, the Braak staging scheme has also been contested for multiple reasons including the unclear pathogenic versus protective role of α -synuclein inclusions and the lack of clear correlations with neuronal loss and clinical course [30, 35, 106, 171]. Grading of MSA neuropathology has been proposed by Jellinger and colleagues, based on semiquantitative analysis of brain atrophy, neuronal loss, astrogliosis and GCI pathology in striatum, globus pallidus, SNpc, pontine basis, cerebellum, and inferior olives [108]. Ozawa and colleagues further demonstrated significant correlation between the frequency of GCIs and the severity of neuronal cell loss, both associated with the disease duration, supporting the presumptive major role of oligodendroglial pathology in MSA [166, 253].

Glial pathology is a common finding in α -synucleinopathies and may play a key role in the neurodegenerative process [84]. Neuropathological and in vivo imaging data suggest a role of microgliosis in α -synucleinopathies [71, 72, 100, 137, 164]. In an experimental study aggregated α -synuclein appeared to activate microglia and further, to promote dopaminergic neurodegeneration [263]. The production of reactive oxygen species (ROS) and proinflammatory cytokines by activated microglia are linked to disease progression and neuronal cell death in mouse models of MSA and PD [182, 183, 218, 256]. Furthermore, reactive astrogliosis has been demonstrated in α -synucleinopathies and α -synuclein-positive inclusions in astroglia and oligodendroglia have been described in PD [24, 166, 240, 247]. Chemical signals from astrocytes affect microglia and therefore may play a fundamental

mediator role in neurodegeneration [43, 231]. Finally, oligodendrocytes have a significant role in the pathogenesis of MSA, because α -synuclein aggregates predominantly in this cell type may lead to neuronal loss, reactive gliosis, iron deposition and myelin degeneration [142, 253]. In this review, we summarise the multiple physiological roles of glia, the effects of ageing on glial function and discuss the role of glia in α -synucleinopathies as well as the involvement of glial cells in the mechanisms of disease progression. Major therapeutic strategies targeting glial pathology in α -synucleinopathies as well as current pitfalls for disease-modification in clinical trials are discussed.

The multiple roles of glial cells in the CNS and their interactions

Glial cells represent around 90% of all cells in the human brain. Astroglia and oligodendroglia are of ectodermal origin, and are often referred to as “macroglial cells”, while microglia are of mesodermal origin [76].

Microglia and the general concept of microgliosis

The first detailed description of microglial cells, as cells of mesodermal origin with the ability to enter the brain was provided in 1919 by Del Rio Hortega. He depicted microglia as process-bearing cells and demonstrated that these cells could switch to an activated and phagocytic state after injury [47]. Microglia represent around 10% of the total glial cell population in the brain and are evenly distributed throughout the CNS [123]. In addition, they are the most crucial factor of innate immunity in the CNS [224]. Microglia play a major role in injury and disease, including neurodegeneration, stroke and brain tumours [223–225]. In the past, different activity states of microglia, resting (quiescent) or activated, were proposed (Fig. 1). In 2005, Nimmerjahn et al. [157] showed with in vivo two-photon imaging that microglia never rest, but constantly scan their microenvironment with their protrusions for intruders or injury. Microglia can respond to different stimuli through various receptors, e.g. receptors for inflammatory stimuli, complement fragments, adhesion molecules and immunoglobulins [178], and directly contact neuronal synapses [250].

With the activation of microglia through injury or disease, their morphology changes and they undergo functional transformations. Activated microglia change the movement of their processes from undirected to targeted towards the injured site [157]. Further, microglia respond to activating stimuli through expression of neurotrophic factors or the release of pro- and anti-inflammatory cytokines [244]. Major histocompatibility complex II (MHCII) and inducible nitric oxide (iNOS) up-regulation can be detected in activated microglia [90, 138]. When activated, because of certain immunological stimuli or injury, microglia can serve diverse beneficial functions to neuron survival, e.g. clearance of damaged or dead cells [47]. Further, they may promote neuron survival through the release of anti-inflammatory or trophic factors [244] and also through the ability to protect already injured sites [157]. Microglia can provide a physical barrier for the protection of the neighbouring healthy tissue [93]. Trophic factors that are crucial for the viability of neurons include brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) can be released by microglia [77]. The release of anti-inflammatory cytokines, such as transforming growth factor β (TGF- β) and interleukin 10 (IL-10) has also been described [103, 113, 132]. The activation of microglia can lead to an altered expression of cell surface markers, an

increased process retraction with change to an amoeboid morphology, a higher proliferative capacity and migration to injured sites [136].

It is suggested that microglia can become over-activated under specific circumstances, which mostly lead to a chronic microglial activation as observed in different chronic CNS diseases. This up-regulation or accumulation of microglia in the CNS has been termed microgliosis. Microglial over-activation can lead to the release of deleterious and neurotoxic factors which facilitate chronic inflammation of the brain and further, neuronal dysfunction and death can develop [176]. These include pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF- α) and IL-1 β [7, 34, 45, 57, 175, 233] which may be directly toxic to neurons [45, 133, 175]. Furthermore, microglial production of large amounts of superoxide radicals, e.g. ROS and nitric oxide (NO), may contribute to the damage associated with chronic brain inflammation [145, 175, 233].

The involvement of microglial activation in neurodegenerative diseases is unequivocal [80]. However, it is evident that microglia can have both neuroprotective and neurotoxic effects. A question that has to be answered is how do microglia switch from supporting neuronal function to a form where the cells become autoaggressive effector cells that affect neurons and lead to neurodegeneration [224]. In summary, microglial activation is complex, context dependent and further studies are needed to clearly define the beneficial versus deleterious role of microglia in the CNS.

Astroglia: structure and function

Astrocytes are the most numerous glial cell type in the CNS, and represent about one-third of the brain mass [112]. Astroglia show two types of morphology: (1) protoplasmic astrocytes populating the grey matter [32], and (2) fibrous astrocytes populating the white matter [91]. Protoplasmic astrocytes are important in wrapping synapses and neuronal cell bodies. In contrast, the fibrous type wraps oligodendroglial cells and nodes of Ranvier [208]. Their bodies are shaped irregularly and they have leaflet-like processes [204]. Astroglia show an even and non-overlapping spread throughout the whole CNS being responsible for many different essential functions in the healthy brain. Both subtypes establish extensive contacts with blood vessels and are therefore, important for energy as well as nutrient-support of neurons [78, 118]. Astroglial cells form interconnections by gap junctions [48] and regulate the activity of large synaptic sets by covering many synapses with their leaflet shaped processes [83]. Astrocytes are involved in the maintenance of the blood–brain barrier [204] and the regulation of blood flow [37, 118]. Furthermore, astroglia are important in the control of extracellular homeostasis of water, ions and neurotransmitters to optimise the interstitial space for synaptic transmission. Astroglia support synaptic transmission as part of the most frequent CNS synapse—the tripartite synapse. Astroglia can sense transmitter release from the neuronal terminal and modulate/control synaptogenesis and plasticity [63] and the potency of the synapse [8, 91, 245]. One function of astroglial cells is the control of the extracellular K⁺ concentration through local K⁺ uptake, thus acting as buffer of extracellular K⁺ [119]. Control of water homeostasis through aquaporin (AQP) channels, mainly AQP4, is also an important astroglial task [5]. Another major function is the uptake of glutamate by astrocytes. They can maintain a low concentration of glutamate in the

extracellular space through the uptake by high affinity glutamate transporters (GLT1 and GLAST1 subtypes), which are enriched in astroglial processes. This uptake plays a crucial role in neurotransmitter clearance and in the prevention from reaching excitotoxic levels [180, 189].

The general concept of astrogliosis

In response to various stimuli, astroglia, similar to microglia, change their morphology to a reactive form (reactive astrogliosis). Astrogliosis is widely accepted as pathological hallmark of diseased CNS tissue. Thereby, astroglia reply to all forms of CNS insults, such as infections, trauma, ischemia and neurodegenerative diseases. This includes changes in morphology and in the molecular expression pattern [255]. Their cell bodies get enlarged with thick processes and increased immunoreactivity to glial fibrillary acidic protein (GFAP) at the injured site, compared to non-reactive astroglia [255] (Fig. 2). Astrogliosis is associated with cellular proliferation, scar formation and the production and release of trophic factors which can have neuroprotective functions [31, 200]. Only in severe cases, scar formation can develop. The glial scar is formed by astroglial processes which are oriented within a single plane. It incorporates newly proliferated cells and separates healthy from lesioned or injured tissue. Thereby, the processes can overlap in ways that do not occur in healthy tissue [31, 92]. During scar formation, astroglia can interact with other cell types, such as fibromeningeal and other glial cells (NG2-positive glia), and those structural changes can be long-lasting [28, 92]. Another feature of astroglial cells is the interaction with microglial cells. In vitro, microglia can attach to GFAP-positive astroglia and display a more resting state than microglia cultured alone [231]. Bianco et al. [18] showed that ATP, derived from astroglia, induces the release of IL-1 β by microglial cells which indicates a role of astrocytes in neuroinflammation. In turn, other studies have shown the impact of microglial activation on astrogliosis. Pro-inflammatory factors released by activated microglia can trigger astrogliosis [12, 85, 186]. It is suggested that in disease both cell types get activated by diverse stimuli and further influence each other.

The definition of reactive astrogliosis lacks uniformity among authors. Different types or categories of severity and intensity have been described. Sofroniew et al. suggest that astrogliosis is a finely graduated continuum of progressive changes (cellular and gene expression) and is regulated by specific mechanisms that can alter the nature and degree of these changes. Furthermore, it is proposed that astroglial changes can involve a gain and loss of function which may be beneficial or detrimental for the surrounding tissue [207]. Others propose two different types: anisomorphic and isomorphic astrogliosis. Anisomorphic astrogliosis includes changes, such as cellular hypertrophy, astroglial proliferation and increased production of GFAP, vimentin and nestin [61, 128, 162]. This response arises after major tissue damaging injuries and astroglia are able to enhance tissue damage through the release of pro-inflammatory cytokines, e.g. the production of TNF α [156] and ROS or NO. Moreover, this glial response can result in glial scar formation, as described above. The isomorphic astrogliosis is a less severe response to mostly mild brain insults. It is characterised by morphological changes of astroglia, such as nuclear hypertrophy and stellar shape. GFAP expression is more transient and not so prominent. Besides, astroglia enhance the production of antioxidants, cytosolic proteins, soluble trophic and growth factors which

are important for the recovery from tissue damage, beneficial for neuronal and glial survival and homeostasis. The isomorphic astrogliosis is considered the more common astroglial response in neurodegenerative diseases. It can adopt a premorbid cytoarchitecture over time, unlike anisomorphic astrogliosis which forms a permanent glial scar [41, 128, 178].

To summarise, astroglia are important for the maintenance of homeostasis and synaptic function in the healthy brain. Astroglia, similar to microglia, can have a beneficial function in the diseased or injured brain via the production of growth and trophic factors [41, 128]. However, they can also be neurotoxic, and enhance tissue damage when releasing ROS, NO and inflammatory cytokines [49, 151, 156]. Astrocytes present with a range of various responses to brain insults and therefore may provide a potential therapeutic target in CNS disease [84].

Oligodendroglia and oligodendroglial dysfunction

In the adult brain, oligodendrocytes display a heterogeneous population of glial cells with various morphologies, states of maturation and of functional activity [13]. Four different subtypes (I–IV) have been described. Oligodendroglia types I and II myelinate especially numerous small diameter axons, whereas type III myelinates only a small amount of axons with large diameters. Type IV is responsible for the myelination of individual axons with large diameter by opposing its cell body directly to the axon [29, 33]. However, oligodendroglia can also be classified in myelinating cells especially located in the white matter and non-myelinating cells located in the grey matter and around non-myelinated axons [13, 84]. All of them originate from oligodendrocyte progenitor cells (OPCs). Oligodendroglial cells derive from progenitor cells that express the membrane marker neuron glia 2 (NG2) chondroitin sulfate proteoglycan, ganglioside GD3, and platelet-derived growth factor- α (PDGF- α) receptor [79, 148]. Newly formed oligodendroglia then migrate along gradients and when reaching their destination, the differentiation to fully functioning cells begins [148]. Mature oligodendroglia are characterised by the expression of a range of myelin-associated markers (Fig. 3) [25]. The major function of oligodendroglia is the production and formation of myelin sheaths to assure the fast saltatory conduction of the action potential as well as the maintenance and restoration of myelin sheaths. Furthermore, they play an important role in the development, maintenance and regeneration of axons [13, 155].

In contrast to microglia and astroglia, which respond to pathological stress by reactive gliosis, as described above, oligodendrocytes are characterised by increased vulnerability which leads to major cellular dysfunction, demyelination and often cell death.

Oligodendroglial cells are highly susceptible to oxidative damage, because of their high metabolic rate with toxic by-products, their increased requirement for ATP, the high intracellular iron and low concentrations of the antioxidative glutathione [110, 237]. High oligodendroglial iron levels are very important in the production of myelin [238]; however, they are related to enhanced free radical formation and lipid peroxidation. The accumulation of intracellular hydrogen peroxide is further increased, because of the low levels of glutathione in oligodendrocytes [148]. Oligodendroglia are also vulnerable to excitotoxic damage and effects of cytokines [131, 143, 264]. Glutamate and cytokines (e.g. TNF- α)

released by activated microglia can cause oligodendroglial dysfunction and oligodendroglial apoptosis [53, 109]. LPS may trigger TLR4-mediated signalling by JNK (c-Jun-amino-terminal kinase) phosphorylation in oligodendrocytes [234] as well as induction of neuronal NOS (nNOS) in OPCs resulting in extensive demyelination [260].

In conclusion, the main role of oligodendroglia in the CNS is associated with the formation, maintenance, and restoration of myelin sheaths and the maintenance of normal axonal function, related to the support of neuronal survival. Multiple factors relevant to the specific properties of oligodendroglia, their environment and interactions with neighbouring cells may compromise the normal function of oligodendrocytes and lead to neurodegeneration.

Glial changes in normal ageing

Age is an important factor that increases the risk of neurodegenerative diseases. α -Synucleinopathies show increasing incidence and prevalence in the elderly population. PD is the most common neurodegenerative movement disorder affecting about 3% of the general population over the age of 65 [54]. In MSA, mean age at onset of first reported symptom is 52–57 years [163, 199], with age-adjusted prevalence of 4.4 new cases per 100,000 year⁻¹ [198]. DLB accounts for up to 20% of all elderly cases of dementia coming to autopsy [146, 147].

To date, different reports evidence that microglia show morphological and phenotypic changes in the course of ageing. Morphological alterations of senescent microglia of the human cerebral cortex of non-demented individuals have been described [226]. The dystrophic microglia are characterised by deramification, spheroid formation, shortened and twisted cytoplasmic processes, and fragmentation of processes [226]. A decrease of total number of microglial cells in the hippocampal field CA1 was shown in 50- to 59-week-old mice [89]. Furthermore, telomere shortening, a sign of cellular senescence, was demonstrated in rat microglia over time in vitro [66], as well as in vivo in rat cerebellum and cerebral cortex [65]. Senescent microglia show an increase of immunophenotypic expression, including MHCII [201]. Aged brains feature an increase of IL-1 positive microglia [42] and up-regulation of inflammatory cytokines, such as IL-6 and TNF- α [160]. These reports indicate that microglial cells undergo profound changes during the ageing process and this could contribute to an increased inflammatory response in the brain. Enhanced inflammation may further lead to the progression of neurodegenerative diseases, although a direct correlation between activated microglia and neurodegeneration in human neurodegenerative disorders may be difficult to demonstrate. Age-related loss of microglia [89] may contribute to limitation of the beneficial effects which microglia exert including diminished phagocytosis and reduced trophic support.

Abnormal astroglial inclusions are common in neurodegenerative disease, but also during the ageing process of healthy elderly. Astroglial tau-inclusions have been reported in the subpial, subependymal and perivascular brain regions of healthy elderly [99]. It is suggested that damaged mitochondria are responsible for the formation of peroxidase-positive inclusions and this can lead to failure in astrocytic ATP-dependent processes. It is hypothesised that brain areas with astroglial inclusion pathology may be prone to oxidative

injury [195]. However, mature, old and senescent astrocytes retain their antioxidant capacity in comparison to neonatal murine astroglial cells in cell culture [129]. Ageing-prone astrocytes, cultured from senescence-accelerated mice, show a larger degree of gliosis than normal astrocytes, after amyloid- β and tau treatment. Besides gliosis, ageing-prone astroglia show a decrease in the ability to support co-cultured neurons, in comparison to normal astroglial cells [134]. Changes in oxidative stress, tau phosphorylation and glutamate uptake of senescence-accelerated murine astrocytes have been observed consistent with reduced neuroprotective capacity in the ageing brain [70]. Recently, further evidence in favour of deficient neuroprotection in senescence-accelerated mice was reported. These mice showed a defect in the cytokine-mediated neuroprotectivity of glial cells after excitotoxic hippocampal injury [87]. In conclusion, changes in ageing astroglial cells occur and these changes can lead to a decrease in neuroprotection and further, they may accelerate neurodegeneration or glial degeneration [43].

Oligodendroglial changes caused by normal ageing mainly concern alterations in myelin dynamics, repair and maintenance, but also changes in total number of oligodendroglial cells. Age-dependent decline of oligodendrocytic fibres in the mouse hippocampal field CA1 has been observed [89]. In an age-accelerated mouse a decrease of myelin basic protein (MBP) and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP), used as oligodendrocyte markers, was shown in the hippocampal CA1 in comparison to an ageing-resistant mouse strain [232]. In contrast, no change of total number of oligodendroglial cells in the human principle inferior olivary nucleus during normal ageing was observed [122]. A disruption of myelin sheath, caused by pro-inflammatory cytokines or by inappropriate protein maintenance within the oligodendroglial cells, has been demonstrated in the ageing rat [117, 229] and monkey [172, 206]. A similar disruption of myelin integrity was also reported in the ageing human brain [4]. The total length of myelinated fibres in a Danish population showed there was a decrease of 10% of total length of myelinated fibres per decade and a decline of 45% across lifetime [140].

In conclusion, ageing may be an important factor which compromises the normal glial function and predisposes to occurrence or mediates the progression of late onset neurodegenerative disorders like α -synucleinopathies.

Microgliosis in α -synucleinopathies

All α -synucleinopathies feature microglial activation. In PD, reactive microglia assemble close to LBs [71, 72, 137, 144, 164]. In MSA patients, microglial activation has been detected using [^{11}C](R)-PK11195 PET imaging [71]. Ishizawa et al. [100] reported an up-regulation of activated microglia in motor-related structures, such as cerebellar input, extrapyramidal motor, and pyramidal motor structures, often associated to GCI pathology. In DLB, a positive correlation between LBs and microglial activation in different brain regions has been demonstrated [137]. The different roles/phases of microglial activation in PD were recently discussed in relation to the disease initiation and progression [84]. It was suggested that microglia are activated by astroglial signals or extracellular α -synuclein before a loss of neurons in the SNpc occurs [84, 227]. Recent evidence suggests that microglial glucocorticoid receptors (GR) may play a role in the regulation of dopaminergic

neurodegeneration in parkinsonism [188]. Furthermore, it is considered that microglia in the progression phase of PD display phagocytic features [84, 144, 150]. Various experimental models support the role of α -synuclein and its modified forms as potent activators of microglia [10, 115, 183, 228]. Enhanced dose-dependent release of pro-inflammatory molecules was reported upon α -synuclein treatment of primary microglial cells in vitro [115, 228]. Interestingly, PD-linked mutant forms of α -synuclein (A30P, E46K and A53T) caused increased microglial activation and release of pro-inflammatory cytokines (e.g. IL-6, IL-10) and chemokines (RANTES, MCP-1) as compared to wild type α -synuclein [187]. Aggregated and nitrated α -synuclein induced inflammatory response and neuronal cell death in mesencephalic neuron-microglia co-cultures [182, 263]. α -Synuclein-induced dopaminergic neurotoxicity mediated by microglial cells was associated with activation of NADPH oxidase and ROS production, suggesting that oxidative stress induced by microglia may play a pivotal role in PD pathogenesis [263]. Exposure of microglia to nitrated α -synuclein leads to the secretion of inflammatory, regulatory, redox-active enzymes and cytoskeletal proteins in vitro [115, 183]. Monomeric α -synuclein, but not β - or γ -synuclein, was shown to increase microglial phagocytosis in a dose- and time-dependent manner, while microglial phagocytosis was inhibited when adding aggregated α -synuclein to cell culture [170]. Interestingly, the half-life of α -synuclein in microglia amounts up to 4 h, which is less than half compared to astrocytic and neuronal degradation of internalised α -synuclein [125].

The effects of α -synuclein on microglial activation have been further confirmed in in vivo models of α -synucleinopathies. Mice over-expressing wild type α -synuclein under control of a rat tyrosine hydroxylase promoter present early microglial activation [228] and the over-expression of mutant human α -synuclein (A53T and A30P homozygous double-mutants) may enhance this process [227]. Moreover, it was demonstrated that microglia may feature different roles during disease progression in a rat PD model with rAAV-based overexpression of α -synuclein in midbrain [192]. Four different types of microglial morphology were reported upon α -synuclein over-expression. Furthermore, microglial cell numbers in the SNpc correlated with the level of α -synuclein expression in the rat midbrain. α -Synuclein-induced activation of microglia in the absence of dopaminergic cell death was early and transient, while in the presence of dopaminergic cell death, α -synuclein-induced microglial activation was delayed and long-lasting [192]. α -Synuclein alone triggered microglial activation and stimulation of the adaptive immunity in a PD mouse model with rAAV-based overexpression of human α -synuclein [236]. Proteolipid protein (PLP)- α -synuclein mice, presenting a transgenic model of MSA with oligodendroglial overexpression of α -synuclein, developed chronic region-specific and age-dependent microgliosis correlating with progressive neuronal loss in SNpc. The early microglial activation in SNpc of MSA mice was associated with increased expression of iNOS [218]. Early suppression of microglial activation and iNOS expression led to protection of nigral dopaminergic neurons, supporting the role of microglial activation in disease pathogenesis.

The response of microglia to various stimuli depends on different receptors displayed on the cell surface. The pattern-recognition receptors (PRR) Toll-like receptor 2 and 4 (TLR2 and TLR4) have been identified to play a crucial role in microglial activation [96, 130]. Their function is the identification of conserved structural motifs on a wide array of pathogens (pathogen-associated molecular patterns, PAMPs) [2]. TLRs also recognise a wide number

of endogenous molecules, which include misfolded proteins, a hallmark feature of neurodegenerative diseases. An up-regulation of TLR2 was identified in an α -synuclein PD/DLB mouse model, although in DLB human postmortem brains no up-regulation was detected [127]. It has been suggested that the differences in the expression of TLR2 between the α -synuclein mouse models and the human disease may reflect higher disease dynamics in animal models [127]. TLR4 up-regulation with NF- κ B nuclear translocation was detected in human MSA and in a transgenic α -synuclein mouse model of MSA [218]. Further analysis of the role of microglial TLR4 expression in the PLP- α -synuclein mouse model of MSA indicated its contribution to microglial phagocytosis and clearance of α -synuclein [220].

To summarise, microglia seem to play a fundamental role in the recognition and clearance of α -synuclein in α -synucleinopathies. However, microglial role in these diseases may also be fatal, because of their over-activation and release of pro-inflammatory cytokines and ROS after α -synuclein recognition [263]. This can lead to a progressive loss of neurons in the diseased brain.

Astrogliosis in α -synucleinopathies

In PD, minimal astrogliosis has been demonstrated [95, 150, 246] as compared to extensive reactive astrogliosis in MSA [166]. However, recent evidence suggests a prominent role of astrogliosis in PD pathogenesis [55]. Furthermore, in PD astroglial cells may feature abnormal α -synuclein inclusion pathology, in contrast to MSA suggesting a different pattern of reactive astrogliosis in these disorders [24, 166, 247]. It appears that astroglial cells are important for the secretion of neurotrophic factors in these diseases [116]. In contrast to beneficial functions, astroglia may also contribute to the production of pro-inflammatory agents. In PD brains, inflammatory response was shown to be mediated by astroglial cells positive for inter-cellular adhesion molecule 1 (ICAM-1) attracting reactive microglia expressing the counter receptor lymphocyte function-associated antigen 1 (LFA-1). In PD postmortem tissue, activated astrocytes displayed enhanced levels of IFN- γ receptor, suggesting that astrocytes activated through IFN- γ may mediate a toxic effect on neighbouring neurons [88]. Myeloperoxidase (MPO), a key enzyme associated with oxidative stress during inflammation, has been found up-regulated in the ventral midbrain astroglia of human PD, suggesting a possible role of astrogliosis in the oxidative insult in PD [40]. Experimental data further strengthen the postmortem evidence on the role of astroglia in the pathogenesis of α -synucleinopathies. Klegeris et al. [114] found enhanced levels of IL-6 and ICAM-1 in astrocytic cell cultures after α -synuclein activation. However, experimental studies also provide evidence for the production and release of neurotrophic factors by astroglia. Human postmortem data showed astroglial BDNF production, while cell culture experiments demonstrated the secretion of glial cell-line-derived neurotrophic factor (GDNF) under the conditions of oxidative stress [190]. Astroglial GDNF and antioxidant GSH can be important neuroprotectors in PD-like neurodegeneration [193]. Jakel et al. [102] demonstrated the neuroprotective function of the astroglial factor Nrf-2. Nrf-2, a NF-E2-related factor, can bind to an antioxidant response element and therefore induces antioxidant enzymes with neuroprotective capacity.

α -Synuclein released from neuronal cells can be endocytosed by astrocytes [126]. This α -synuclein transfer is time-dependent and results in the formation of glial inclusions sharing some common features with LBs. α -Synuclein neuron-to-astroglia transfer further leads to changes in gene expression in astroglia related to drastic increases in TNF α and CXCL1 levels that may mediate enhanced neuroinflammatory response and neurodegeneration [126]. Moreover, selectively expressed mutant A53T α -synuclein in astroglial cells in α -synuclein inducible transgenic mice induced a rapidly progressive paralysis, supposedly resulting from widespread astrogliosis, and midbrain dopaminergic neuron and spinal cord motor neuron degeneration [82]. The transgenic overexpression of mutated α -synuclein has been further associated with mitochondrial damage in astroglia and a defective release of soluble factors supporting neuronal differentiation, which may represent an alternative pathogenic pathway of α -synuclein-related neurodegeneration mediated by astroglia [196].

Halliday and Stevens [84] have recently speculated that astrocytes may play a crucial role in the initiation of PD. They presumed that, if α -synuclein deposition is a primary event in the pathogenesis of PD, protoplasmic astrocytes are the first to respond by the accumulation of non-fibrillar α -synuclein in their cytoplasm, however, not undergoing changes typical for a classical reactive astrogliosis as seen in MSA. It is speculated that the pathogenic role of protoplasmic astroglia in PD, independent from a typical reactive response, may be related to interactions of α -synuclein with other proteins including β -synuclein and astrocytic neurotrophic factors. Next, astroglial dysfunction is proposed to mediate late disease progression by the expression of inflammatory molecules and recruitment of reactive microglia [84]. In summary, astroglial cells appear to play a dual role in PD and maybe other α -synucleinopathies. On one hand, there is the production and release of pro-inflammatory cytokines and chemokines and on the other hand, astroglia can provide neurotrophic factors, which may support the survival of neighbouring neurons. Although differences in the histopathology of reactive astrogliosis in MSA versus PD have been observed as mentioned above, there is still insufficient data on the specific facets of astroglial response related to MSA, postulating the need of future studies to identify possible functional differences. Further analyses need to be accomplished to fully understand the specific roles of astroglial cells in α -synucleinopathies, the timing of reactive astrogliosis in these disorders and the relation to normal ageing deficits.

Oligodendroglia in α -synucleinopathies

There is currently no evidence suggesting that oligodendrocytes participate in the initiation of PD [84], whereas there is some association with the distribution of pathology, particularly in MSA [165, 253].

Filamentous α -synuclein inclusions have been reported in non-myelinating oligodendroglia in clinically overt PD cases [36, 247] suggesting a late secondary involvement. Further oligodendroglial involvement in PD and DLB has been evidenced by the presence of complement-activated oligodendrocytes in the SN of PD cases and in some brain regions of DLB cases [258, 259]. α -Synuclein-affected neurons may show lack or decrease of axon myelination suggesting oligodendroglial involvement [20, 21]. However, oligodendroglial pathology does not seem to be a leading factor in the pathogenesis of PD/DLB.

In contrast, oligodendroglial α -synuclein inclusions (GCI) are the pathological hallmark lesion in MSA and may represent a primary injury [252, 253]. GCI or Papp-Lantos inclusions were first described in 1989 by Papp et al. [168]. They can be triangular, sickle, half-moon, oval or conical shaped. In 1998 α -synuclein was found to be the main component of GCI [211, 249]. Further components of GCI are ubiquitin and a large number of multifunctional proteins, such as leucine-rich repeat serine/threonine-protein LRRK2, heat shock proteins, microtubule-associated protein tau, prion disease-linked 14-3-3 protein among others [253]. Their distribution in the CNS is extensive: GCI occur in the pons, medulla, putamen, SN, cerebellum and preganglionic autonomic structures [17, 107, 158, 169]. The formation of α -synuclein aggregation in oligodendroglia has not been completely elucidated, but two hypotheses exist: (1) selective up-regulation of α -synuclein expression and impaired ability to degrade α -synuclein in oligodendroglial cells could lead to oligodendroglial accumulation [153, 184] or (2) active uptake of α -synuclein by oligodendroglia of protein released by neighbouring neurons may lead to dislocated abnormal accumulation of the protein in diseased oligodendrocytes [248].

Expression of α -synuclein has been shown during the early phases of maturation in rat oligodendrocytes in vitro [184], and in vivo a low level of α -synuclein in astroglial and oligodendroglial cells has been suggested [153]. However, no α -synuclein mRNA expression has been detected in oligodendroglia of human control and MSA brains [149, 165].

The second hypothesis has become increasingly relevant in light of the recent findings on cell-to-cell propagation of α -synuclein [50, 86, 126]. α -Synuclein is released in culture media of neural cells overexpressing the protein, experimentally confirming its release in the extracellular space [60, 86]. Yet, the hypothesis of cell-to-cell transfer of α -synuclein specifically to oligodendroglia has not been proven in any in vivo graft experiment to date [86, 214].

Cytoplasmic α -synuclein aggregates may significantly affect the normal functions and viability of oligodendrocytes. In vitro evidence has indicated that overexpression of α -synuclein in glial cells leads to increased susceptibility to oxidative stress and TNF- α [215, 219]. Oligodendroglial cells overexpressing α -synuclein show decreased adhesion to fibronectin, relating the oligodendroglial cytotoxicity of α -synuclein to altered cell–extracellular matrix interactions [242]. In a recent in vitro study, the role of α -synuclein and tau protein in oligodendroglia was examined [185]. The formation of inclusion bodies with aggregated α -synuclein, tau and α B-crystallin under oxidative stress was demonstrated. However, in the absence of α -synuclein, no aggregation of tau could be found under the same conditions, suggesting a primary role for α -synuclein as proaggregatory protein in oligodendrocytes [185]. p25 α also known as tubulin polymerisation promoting protein (TPPP) is an oligodendroglia-specific phosphoprotein functionally linked to myelination [230]. After phosphorylation of p25 α its binding-affinity to microtubule decreases [97]. Interestingly, p25 α was shown to induce α -synuclein aggregation in vitro [131]. Moreover, in MSA p25 α was found to co-localise with α -synuclein-positive GCI. Oligodendroglial cells within affected fibre tracts in MSA show abnormal redistribution and accumulation of p25 α in the cell soma in contrast to the normal distribution in a thin perinuclear cytoplasmic

sheet, as well as in the surrounding myelin. The dislocation of oligodendroglial p25 α in MSA may represent early oligodendroglial pathology preceding GCI formation [210]. The experimental coexpression of human α -synuclein and p25 α in a rat oligodendroglial cell line resulted in a disorganisation of the microtubular cytoskeleton and induction of apoptosis [121]. The response was dependent on Ser 129 phosphorylation of α -synuclein. Its inhibition abrogated the formation of phosphorylated α -synuclein oligomers, microtubule retraction and apoptosis [121].

Transgenic mouse models with overexpression of α -synuclein in oligodendroglial cells, using selective oligodendroglial promoters have been major contributors to evidence the role of oligodendroglial α -synucleinopathy [221]. This approach has reproduced the hyperphosphorylation and insolubility of human α -synuclein aggregates [111]. Mouse models have provided further evidence that neurodegeneration may be promoted by the accumulation of α -synuclein in oligodendrocytes, either through mitochondrial dysfunction, myelin disruption which causes axonal degeneration, or through inducing microglial activation [203, 218, 261]. In the PLP- α -synuclein mouse model, overexpression of human α -synuclein in oligodendroglia leads to progressive degeneration of brain areas, such as SNpc, locus coeruleus, nucleus ambiguus, pedunculopontine tegmental nucleus, laterodorsal tegmental nucleus and Onuf's nucleus [217, 222]. In a recent study, it was demonstrated that the neurodegeneration in the MBP- α -synuclein mouse model is associated with altered expression of neurotrophic factors, especially GDNF released from oligodendroglial cells [243] providing a new insight in the possible pathogenic mechanisms of oligodendroglial α -synucleinopathy.

In summary, oligodendroglial cells may play a major part in the pathogenesis of MSA and rather a secondary role in other α -synucleinopathies. To date the origin of α -synuclein in MSA oligodendroglia is not clear; however, the pathogenic role of α -synuclein-positive GCIs is beyond question.

Glial dysfunction and therapeutic target definition in α -synucleinopathies

The impact of glia has been increasingly recognised in α -synucleinopathies. Therefore, possible therapeutic targets to regulate glial responses in α -synucleinopathies are of high interest. However, up to date, the origin and progression of glial dysfunction in α -synucleinopathies remain, to a great extent, unclear. The insufficient knowledge on the chronology of gliosis and on understanding the patterns of glial dysfunction in α -synucleinopathies, like in other neurodegenerative disorders, may be a main reason for the divergence between pre-clinical neuroprotection data and the limited success in a clinical setting.

Neuroinflammatory responses of activated glia related to up-regulation of pro-inflammatory mediators and pathways have been of interest in α -synucleinopathies like in other neurodegenerative disorders with reactive gliosis. Early studies indicated that non-steroidal anti-inflammatory drugs (NSAIDs) might protect against toxin-induced dopaminergic lesions in rodents [9, 62, 235]. Furthermore, NSAIDs, such as ibuprofen, indomethacin, aspirin and ketoprofen, were shown to inhibit the formation of α -synuclein fibrils in vitro in

a dose-dependent manner as well as destabilise pre-formed α -synuclein fibrils [94]. Inhibitors of iNOS and NADPH oxidase were found neuroprotective in transgenic models of PD featuring overexpression of A53T mutant or wild type α -synuclein and LPS-induced microglial activation [68, 69]. An interesting strategy to suppress the activation of glial cells and their inflammatory properties is the targeting of peroxisome proliferator-activated receptor γ pathway (PPAR γ) achieved with the PPAR γ agonist pioglitazone [179]. In the MPTP mouse model, pioglitazone crossed the blood–brain barrier, attenuated MPTP induced micro- and astroglial activation and partially prevented dopaminergic cell loss [26, 46]. Pioglitazone was also effective to decrease microglial activation and protect dopaminergic neurons in rats after intrastriatal LPS injection which normally leads to inflammation-induced neurodegeneration [98]. Myeloperoxidase (MPO), a key enzyme which is involved in the production of ROS has been shown up-regulated in both experimental and human PD and MSA associated with gliosis accompanying the neurodegeneration [40, 213]. Suppression of MPO activity by genetic ablation [40] or pharmacological inhibition [213] in experimental models of PD and MSA proved efficient to protect against neurodegeneration and α -synuclein aggregation, associated with reduced oxidative and nitrative stress. As aforementioned, TLR4 may play an important role in microglial activation related to α -synucleinopathies. Therefore, therapeutic implications to control TLR4 activation are of great interest in α -synucleinopathies. Naloxone, an opioid receptor antagonist and effector of TLR4 mediated up-regulation of TNF α , NO and IL-1 β [120], provoked a reduction of dopaminergic neurodegeneration in the SNpc of PD models [135]. However, recent observations in TLR4 knock-out mice with α -synucleinopathy suggest that in addition to mediating pro-inflammatory microglial response, TLR4 may be crucial in the microglial clearance of pathogenic α -synuclein, thus postulating caution in the use of TLR4 blockers in these disorders [220].

The experimental evidence on anti-neuroinflammatory strategies still need appropriate translation as a therapeutic approach in α -synucleinopathies under clinical conditions. While to date the successful experimental treatments in animal models of α -synucleinopathies have aimed primarily at early detrimental glial changes to provide neuroprotection, in patients with longer standing α -synuclein disease, downstream glial events should be considered. This is one of the issues which may cause the divergence between the outcomes of pre-clinical and clinical studies.

Epidemiological studies suggested possible neuroprotection by anti-inflammatory medication (NSAIDs), related to reduced risk of PD [67]; however, this hypothesis could not be confirmed by a recent study using data of PD cases and controls from the UK primary care [14], and by meta-analysis of observational studies evaluating NSAID use and the risk of PD [173, 191]. To date there has been no clinical trial confirming unequivocally disease-modification through anti-inflammatory treatment. A prime example for an anti-inflammatory drug which has gone through pre-clinical studies and clinical trials in α -synucleinopathies is minocycline. Minocycline is a tetracycline antibiotic that crosses the blood–brain barrier and has anti-inflammatory along with its anti-apoptotic activity [251]. This drug has proven at least partial neuroprotective efficacy in various experimental models of PD and MSA [38, 216, 218, 256]. However, clinical trials in PD and MSA had inconsistent outcomes regarding the disease-modifying potential of minocycline therapy [52,

177]. Interestingly, in a prospective, randomised, double-blind clinical trial of minocycline in MSA, microglial activation was significantly reduced after 24 weeks therapy as shown by [¹¹C](R)-PK11195 PET, but no clinical effect on symptom severity could be achieved probably due to the late start of the therapy [52].

Immunomodulation has been an alternative approach proposed to target glial dysfunction in α -synucleinopathies. Adaptive T cell-mediated immunity may play a part in the modulation of neuroinflammatory response in α -synucleinopathies. CD8⁺ and CD4⁺ T cells were shown to invade the PD brain. Experimental data suggested that T cell-mediated dopaminergic toxicity was mainly controlled by CD4⁺ T cells in a FAS-dependent way [27]. Although these data need further confirmation, they suggest a possible rationale for targeting adaptive immunity in PD which may involve developing vaccines for antigens that promote cell-mediated anti-inflammatory responses. In support of this strategy, preclinical studies showed that adoptive transfer of copolymer-1 immune cells leads to T cell accumulation within SNpc, suppression of microglial activation, and increased local expression of astrocyte-associated GDNF [16, 181]. Alternatively, the adoptive transfer of T cells from mice immunised with nitrated α -synuclein resulted in a robust neuroinflammatory response with accelerated dopaminergic cell loss [15]. The immunisation approach has been further evaluated in experiments applying transgenic mice overexpressing human α -synuclein. Active immunisation with recombinant α -synuclein in this mouse model of PD induced the production of antibodies against human α -synuclein and resulted in modulation of microglial and astroglial response, reduction of the inclusion pathology and neuroprotection [141]. Immunomodulatory strategies await clinical confirmation and approval in α -synucleinopathies.

Neurotrophic factor delivery and modulation is considered a further major candidate therapeutic strategy in α -synucleinopathies. Glial dysfunction in these disorders may directly relate to the reduction of trophic support. For example, in a transgenic mouse model of MSA, GDNF reduction was directly associated with α -synuclein inclusion pathology in oligodendroglia and intracerebroventricular infusion of GDNF ameliorated neurodegeneration [243]. Alternatively, glial reactivity, typical for the neurodegenerating brain in α -synucleinopathies, may be used as a tool to supply targeted delivery of trophic factors and provide neuroprotection. The adoptive transfer of CD3-activated regulatory T cells to MPTP-intoxicated mice triggered protection of the nigrostriatal system and modulation of microglial responses, associated with up-regulation of astrocyte-derived GDNF [181]. Further, microglial activation following MPTP intoxication has been successfully used to confer neuroprotection by targeted experimental brain delivery of GDNF through genetically modified macrophages [19]. However, AAV gene delivery of neurturin, a structural and functional analogue of GDNF, in the putamen of PD patients failed to improve the motor performance from baseline to 12 months versus placebo [139].

In summary, based on the wide range of pre-clinical experimental data, glial dysfunction seems to be a prominent target for disease-modification in α -synucleinopathies. Unfortunately, clinical translation of these strategies is still lacking success due to many undefined variables associated with temporal and spatial initiation and progression of glial

pathology, regulatory mechanisms as well as definition of the transitional border between beneficial and detrimental properties of glia in α -synucleinopathies.

Conclusion

The pathological cascade of α -synucleinopathies includes a variety of important aspects (Fig. 4). The aggregation of α -synuclein is obviously a very prominent factor which may lead to degeneration accompanied by gliosis. Microgliosis and astrogliosis are two common mechanisms that may play an important modulatory role in these neurodegenerative diseases. Microglial cells may react to α -synuclein stimulus by phagocytosis and release of neurotrophic factors and exert beneficial neuroprotective effects. However, progression of pathology in α -synucleinopathies may lead to an over-activation of microglia which results in a pro-inflammatory response and increased oxidative and nitrative stress, all leading to enhanced neurodegeneration. Astroglial cells in α -synucleinopathies may be activated by either α -synuclein or activated microglia. Astroglia in PD but not in MSA can incorporate α -synuclein which may trigger a pro-inflammatory response and accelerate neurodegeneration and disease progression in a disease-specific manner. However, the release of neurotrophic factors by astroglia can be an advantage to inhibit disease progression and is of high interest for the development of neuroprotective strategies. Oligodendroglial pathology is prominent in MSA suggesting different pathogenic mechanisms as compared to PD and DLB. Primary oligodendroglial pathology is supposed to precede α -synuclein accumulation in GCIs and this oligodendroglial dysfunction is probably the major contributor to the MSA pathogenic cascade involving dysmyelination, disturbed oligodendroglial trophic support, and secondary reactive gliosis which altogether accelerate the rapid progression of MSA. Finally, α -synucleinopathies are diseases with late-onset and therefore, ageing plays a prominent role in their development and progression. The age-dependent decrease of glial cell numbers and the change of phenotype of glia over time can be devastating and may have a negative impact on the beneficial functions of glial cells in α -synucleinopathies. Glial cells provide potential therapeutic targets in neurodegenerative diseases with α -synuclein inclusion pathology posing a major challenge for successful translation into clinical trials in the future.

Acknowledgments

This review was supported by grants of the Austrian Science Funds (FWF) P19989-B05 and SFB F44-B19.

References

1. Abeliovich A, Schmitz Y, Farinas I, et al. Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron*. 2000; 25:239–252. [PubMed: 10707987]
2. Akira S. Toll-like receptors and innate immunity. *Adv Immunol*. 2001; 78:1–56. [PubMed: 11432202]
3. Al-Chalabi A, Durr A, Wood NW, et al. Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. *PLoS One*. 2009; 4:e7114. [PubMed: 19771175]
4. Albert M. Neuropsychological and neurophysiological changes in healthy adult humans across the age range. *Neurobiol Aging*. 1993; 14:623–625. [PubMed: 8295666]

5. Amiry-Moghaddam M, Otsuka T, Hurn PD, et al. An alpha-syntrophin-dependent pool of AQP4 in astroglial end-feet confers bidirectional water flow between blood and brain. *Proc Natl Acad Sci USA*. 2003; 100:2106–2111. [PubMed: 12578959]
6. Anderson JP, Walker DE, Goldstein JM, et al. Phosphorylation of Ser-129 is the dominant pathological modification of alpha-synuclein in familial and sporadic Lewy body disease. *J Biol Chem*. 2006; 281:29739–29752. [PubMed: 16847063]
7. Appel K, Honegger P, Gebicke-Haerter PJ. Expression of interleukin-3 and tumor necrosis factor-beta mRNAs in cultured microglia. *J Neuroimmunol*. 1995; 60:83–91. [PubMed: 7642751]
8. Araque A, Parpura V, Sanzgiri RP, Haydon PG. Tripartite synapses: glia, the unacknowledged partner. *Trends Neurosci*. 1999; 22:208–215. [PubMed: 10322493]
9. Aubin N, Curet O, Deffois A, Carter C. Aspirin and salicylate protect against MPTP-induced dopamine depletion in mice. *J Neurochem*. 1998; 71:1635–1642. [PubMed: 9751197]
10. Austin SA, Floden AM, Murphy EJ, Combs CK. Alpha-synuclein expression modulates microglial activation phenotype. *J Neurosci*. 2006; 26:10558–10563. [PubMed: 17035541]
11. Baba M, Nakajo S, Tu PH, et al. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am J Pathol*. 1998; 152:879–884. [PubMed: 9546347]
12. Balasingam V, Dickson K, Brade A, Yong VW. Astrocyte reactivity in neonatal mice: apparent dependence on the presence of reactive microglia/macrophages. *Glia*. 1996; 18:11–26. [PubMed: 8891688]
13. Baumann N, Pham-Dinh D. Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiol Rev*. 2001; 81:871–927. [PubMed: 11274346]
14. Becker C, Jick SS, Meier CR. NSAID use and risk of Parkinson disease: a population-based case-control study. *Eur J Neurol*. 2011; 10.1111/j.1468-1331.2011.03399.x
15. Benner EJ, Banerjee R, Reynolds AD, et al. Nitrated alpha-synuclein immunity accelerates degeneration of nigral dopaminergic neurons. *PLoS One*. 2008; 3:e1376. [PubMed: 18167537]
16. Benner EJ, Mosley RL, Destache CJ, et al. Therapeutic immunization protects dopaminergic neurons in a mouse model of Parkinson's disease. *Proc Natl Acad Sci USA*. 2004; 101:9435–9440. [PubMed: 15197276]
17. Beyer K, Ariza A. Protein aggregation mechanisms in synucleinopathies: commonalities and differences. *J Neuropathol Exp Neurol*. 2007; 66:965–974. [PubMed: 17984679]
18. Bianco F, Pravettoni E, Colombo A, et al. Astrocyte-derived ATP induces vesicle shedding and IL-1 beta release from microglia. *J Immunol*. 2005; 174:7268–7277. [PubMed: 15905573]
19. Biju K, Zhou Q, Li G, et al. Macrophage-mediated GDNF delivery protects against dopaminergic neurodegeneration: a therapeutic strategy for Parkinson's disease. *Mol Ther*. 2010; 18:1536–1544. [PubMed: 20531393]
20. Braak H, Del Tredici K. Poor and protracted myelination as a contributory factor to neurodegenerative disorders. *Neurobiol Aging*. 2004; 25:19–23. [PubMed: 14675725]
21. Braak H, Del Tredici K. Neuroanatomy and pathology of sporadic Parkinson's disease. *Adv Anat Embryol Cell Biol*. 2009; 201:1–119. [PubMed: 19230552]
22. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol*. 2002; 249(Suppl 3):III/1–III/5.
23. Braak H, Rub U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm*. 2003; 110:517–536. [PubMed: 12721813]
24. Braak H, Sastre M, Del Tredici K. Development of alpha-synuclein immunoreactive astrocytes in the forebrain parallels stages of intraneuronal pathology in sporadic Parkinson's disease. *Acta Neuropathol*. 2007; 114:231–241. [PubMed: 17576580]
25. Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. *Acta Neuropathol*. 2010; 119:37–53. [PubMed: 19847447]
26. Breidert T, Callebert J, Heneka MT, Landreth G, Launay JM, Hirsch EC. Protective action of the peroxisome proliferator-activated receptor-gamma agonist pioglitazone in a mouse model of Parkinson's disease. *J Neurochem*. 2002; 82:615–624. [PubMed: 12153485]

27. Brochard V, Combadiere B, Prigent A, et al. Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J Clin Invest.* 2009; 119:182–192. [PubMed: 19104149]
28. Bundesen LQ, Scheel TA, Bregman BS, Kromer LF. Ephrin-B2 and EphB2 regulation of astrocyte-meningeal fibroblast interactions in response to spinal cord lesions in adult rats. *J Neurosci.* 2003; 23:7789–7800. [PubMed: 12944508]
29. Bunge RP. Glial cells and the central myelin sheath. *Physiol Rev.* 1968; 48:197–251. [PubMed: 4866614]
30. Burke RE, Dauer WT, Vonsattel JP. A critical evaluation of the Braak staging scheme for Parkinson's disease. *Ann Neurol.* 2008; 64:485–491. [PubMed: 19067353]
31. Bush TG, Puvanachandra N, Horner CH, et al. Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. *Neuron.* 1999; 23:297–308. [PubMed: 10399936]
32. Bushong EA, Martone ME, Ellisman MH. Maturation of astrocyte morphology and the establishment of astrocyte domains during postnatal hippocampal development. *Int J Dev Neurosci.* 2004; 22:73–86. [PubMed: 15036382]
33. Butt AM, Ibrahim M, Berry M. Axon-myelin sheath relations of oligodendrocyte unit phenotypes in the adult rat anterior medullary velum. *J Neurocytol.* 1998; 27:259–269. [PubMed: 10640184]
34. Buttini M, Boddeke H. Peripheral lipopolysaccharide stimulation induces interleukin-1 beta messenger RNA in rat brain microglial cells. *Neuroscience.* 1995; 65:523–530. [PubMed: 7777165]
35. Calne DB, Mizuno Y. The neuromythology of Parkinson's disease. *Parkinsonism Relat Disord.* 2004; 10:319–322. [PubMed: 15196512]
36. Campbell BC, McLean CA, Culvenor JG, et al. The solubility of alpha-synuclein in multiple system atrophy differs from that of dementia with Lewy bodies and Parkinson's disease. *J Neurochem.* 2001; 76:87–96. [PubMed: 11145981]
37. Carmignoto G, Gomez-Gonzalo M. The contribution of astrocyte signalling to neurovascular coupling. *Brain Res Rev.* 2010; 63:138–148. [PubMed: 19948187]
38. Casarejos MJ, Menendez J, Solano RM, Rodriguez-Navarro JA, Garcia de Yébenes J, Mena MA. Susceptibility to rotenone is increased in neurons from parkin null mice and is reduced by minocycline. *J Neurochem.* 2006; 97:934–946. [PubMed: 16573651]
39. Chandra S, Gallardo G, Fernandez-Chacon R, Schluter OM, Sudhof TC. Alpha-synuclein cooperates with CSPalpha in preventing neurodegeneration. *Cell.* 2005; 123:383–396. [PubMed: 16269331]
40. Choi DK, Pennathur S, Perier C, et al. Ablation of the inflammatory enzyme myeloperoxidase mitigates features of Parkinson's disease in mice. *J Neurosci.* 2005; 25:6594–6600. [PubMed: 16014720]
41. Ciccarelli R, Ballerini P, Sabatino G, et al. Involvement of astrocytes in purine-mediated reparative processes in the brain. *Int J Dev Neurosci.* 2001; 19:395–414. [PubMed: 11378300]
42. Conde JR, Streit WJ. Microglia in the aging brain. *J Neuropathol Exp Neurol.* 2006; 65:199–203. [PubMed: 16651881]
43. Croisier E, Graeber MB. Glial degeneration and reactive gliosis in alpha-synucleinopathies: the emerging concept of primary gliodegeneration. *Acta Neuropathol.* 2006; 112:517–530. [PubMed: 16896905]
44. de Silva HR, Khan NL, Wood NW. The genetics of Parkinson's disease. *Curr Opin Genet Dev.* 2000; 10:292–298. [PubMed: 10826990]
45. Dean JM, Wang X, Kaindl AM, et al. Microglial MyD88 signaling regulates acute neuronal toxicity of LPS-stimulated microglia in vitro. *Brain Behav Immun.* 2010; 24:776–783. [PubMed: 19903519]
46. Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB. Protection by pioglitazone in the MPTP model of Parkinson's disease correlates with I kappa B alpha induction and block of NF kappa B and iNOS activation. *J Neurochem.* 2004; 88:494–501. [PubMed: 14690537]
47. del Rio-Hortega, P. Microglia. In: Penfield, W., editor. *Cytology and cellular pathology of the nervous system.* Hoeber PB; New York: 1932. p. 483-534.

48. Dermietzel R, Gao Y, Scemes E, et al. Connexin43 null mice reveal that astrocytes express multiple connexins. *Brain Res Brain Res Rev.* 2000; 32:45–56. [PubMed: 10751656]
49. Deshpande M, Zheng J, Borgmann K, et al. Role of activated astrocytes in neuronal damage: potential links to HIV-1-associated dementia. *Neurotox Res.* 2005; 7:183–192. [PubMed: 15897153]
50. Desplats P, Lee HJ, Bae EJ, et al. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci USA.* 2009; 106:13010–13015. [PubMed: 19651612]
51. Dickson DW, Lin W, Liu WK, Yen SH. Multiple system atrophy: a sporadic synucleinopathy. *Brain Pathol.* 1999; 9:721–732. [PubMed: 10517510]
52. Dodel R, Spottke A, Gerhard A, et al. Minocycline 1-year therapy in multiple-system-atrophy: effect on clinical symptoms and [(11)C] (R)-PK11195 PET (MEMSA-trial). *Mov Disord.* 2010; 25:97–107. [PubMed: 20014118]
53. Domercq M, Sanchez-Gomez MV, Sherwin C, Etzebarria E, Fern R, Matute C. System xc- and glutamate transporter inhibition mediates microglial toxicity to oligodendrocytes. *J Immunol.* 2007; 178:6549–6556. [PubMed: 17475885]
54. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology.* 2007; 68:384–386. [PubMed: 17082464]
55. Durrenberger PF, Filiou MD, Moran LB, et al. DnaJB6 is present in the core of Lewy bodies and is highly up-regulated in parkinsonian astrocytes. *J Neurosci Res.* 2009; 87:238–245. [PubMed: 18711724]
56. Edwards TL, Scott WK, Almonte C, et al. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. *Ann Hum Genet.* 2010; 74:97–109. [PubMed: 20070850]
57. Eklind S, Hagberg H, Wang X, et al. Effect of lipopolysaccharide on global gene expression in the immature rat brain. *Pediatr Res.* 2006; 60:161–168. [PubMed: 16864697]
58. El-Agnaf OM, Salem SA, Paleologou KE, et al. Alpha-synuclein implicated in Parkinson's disease is present in extra-cellular biological fluids, including human plasma. *FASEB J.* 2003; 17:1945–1947. [PubMed: 14519670]
59. Elbaz A, Ross OA, Ioannidis JP, et al. Independent and joint effects of the MAPT and SNCA genes in Parkinson disease. *Ann Neurol.* 2010; 69:778–792. [PubMed: 21391235]
60. Emmanouilidou E, Melachroinou K, Roumeliotis T, et al. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. *J Neurosci.* 2010; 30:6838–6851. [PubMed: 20484626]
61. Escartin C, Bonvento G. Targeted activation of astrocytes: a potential neuroprotective strategy. *Mol Neurobiol.* 2008; 38:231–241. [PubMed: 18931960]
62. Esposito E, Di Matteo V, Benigno A, Pierucci M, Crescimanno G, Di Giovanni G. Non-steroidal anti-inflammatory drugs in Parkinson's disease. *Exp Neurol.* 2007; 205:295–312. [PubMed: 17433296]
63. Faissner A, Pyka M, Geissler M, et al. Contributions of astrocytes to synapse formation and maturation—potential functions of the perisynaptic extracellular matrix. *Brain Res Rev.* 2010; 63:26–38. [PubMed: 20096729]
64. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain.* 1991; 114(Pt 5):2283–2301. [PubMed: 1933245]
65. Flanary BE, Streit WJ. Telomeres shorten with age in rat cerebellum and cortex in vivo. *J Anti Aging Med.* 2003; 6:299–308. [PubMed: 15142431]
66. Flanary BE, Streit WJ. Progressive telomere shortening occurs in cultured rat microglia, but not astrocytes. *Glia.* 2004; 45:75–88. [PubMed: 14648548]
67. Gagne JJ, Power MC. Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. *Neurology.* 2010; 74:995–1002. [PubMed: 20308684]
68. Gao HM, Kotzbauer PT, Uryu K, Leight S, Trojanowski JQ, Lee VM. Neuroinflammation and oxidation/nitration of alpha-synuclein linked to dopaminergic neurodegeneration. *J Neurosci.* 2008; 28:7687–7698. [PubMed: 18650345]

69. Gao HM, Zhou H, Zhang F, Wilson BC, Kam W, Hong JS. HMGB1 acts on microglia Mac1 to mediate chronic neuroinflammation that drives progressive neurodegeneration. *J Neurosci.* 2011; 31:1081–1092. [PubMed: 21248133]
70. Garcia-Matas S, Gutierrez-Cuesta J, Coto-Montes A, et al. Dysfunction of astrocytes in senescence-accelerated mice SAMP8 reduces their neuroprotective capacity. *Aging Cell.* 2008; 7:630–640. [PubMed: 18616637]
71. Gerhard A, Banati RB, Goerres GB, et al. [11C](R)-PK11195 PET imaging of microglial activation in multiple system atrophy. *Neurology.* 2003; 61:686–689. [PubMed: 12963764]
72. Gerhard A, Pavese N, Hotton G, et al. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Dis.* 2006; 21:404–412. [PubMed: 16182554]
73. Geser, F.; Jellinger, K.A.; Köllensperger, M.; Stefanova, N.; Wenning, G.K. Multiple system atrophy. Etiology, pathology, and pathogenesis. In: Schapira, AHV.; Lang, AET.; Fahn, S., editors. *Movement disorders 4.* Elsevier; Saunders: 2010. p. 321-339.
74. Giasson BI, Duda JE, Murray IV, et al. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. *Science.* 2000; 290:985–989. [PubMed: 11062131]
75. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci.* 1999; 163:94–98. [PubMed: 10223419]
76. Ginhoux F, Greter M, Leboeuf M, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science.* 2010; 330:841–845. [PubMed: 20966214]
77. Glanzer JG, Enose Y, Wang T, et al. Genomic and proteomic microglial profiling: pathways for neuroprotective inflammatory responses following nerve fragment clearance and activation. *J Neurochem.* 2007; 102:627–645. [PubMed: 17442053]
78. Golgi, C. *Opera Omnia.* Hoepli; Milano: 1903.
79. Gonzalez-Perez O, Alvarez-Buylla A. Oligodendrogenesis in the subventricular zone and the role of epidermal growth factor. *Brain Res Rev.* 2011
80. Graeber MB, Streit WJ. Microglia: biology and pathology. *Acta Neuropathol.* 2010; 119:89–105. [PubMed: 20012873]
81. Greden-Harrison B, Polydoro M, Morimoto-Tomita M, et al. alphasynuclein triple knockout mice reveal age-dependent neuronal dysfunction. *Proc Natl Acad Sci USA.* 2010; 107:19573–19578. [PubMed: 20974939]
82. Gu XL, Long CX, Sun L, Xie C, Lin X, Cai H. Astrocytic expression of Parkinson's disease-related A53T alpha-synuclein causes neurodegeneration in mice. *Mol Brain.* 2010; 3:12. [PubMed: 20409326]
83. Halassa MM, Fellin T, Takano H, Dong JH, Haydon PG. Synaptic islands defined by the territory of a single astrocyte. *J Neurosci.* 2007; 27:6473–6477. [PubMed: 17567808]
84. Halliday GM, Stevens CH. Glia: initiators and progressors of pathology in Parkinson's disease. *Mov Disord.* 2011; 26:6–17. [PubMed: 21322014]
85. Hanisch UK. Microglia as a source and target of cytokines. *Glia.* 2002; 40:140–155. [PubMed: 12379902]
86. Hansen C, Angot E, Bergstrom AL, et al. alpha-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. *J Clin Invest.* 2011; 121:715–725. [PubMed: 21245577]
87. Hasegawa-Ishii S, Takei S, Inaba M, et al. Defects in cytokine-mediated neuroprotective glial responses to excitotoxic hippocampal injury in senescence-accelerated mouse. *Brain Behav Immun.* 2010; 25:83–100. [PubMed: 20804842]
88. Hashioka S, Klegeris A, Schwab C, McGeer PL. Interferon-gamma-dependent cytotoxic activation of human astrocytes and astrocytoma cells. *Neurobiol Aging.* 2009; 30:1924–1935. [PubMed: 18375019]
89. Hayakawa N, Kato H, Araki T. Age-related changes of astrocytes, oligodendrocytes and microglia in the mouse hippocampal CA1 sector. *Mech Ageing Dev.* 2007; 128:311–316. [PubMed: 17350671]

90. Hayes GM, Woodroffe MN, Cuzner ML. Microglia are the major cell type expressing MHC class II in human white matter. *J Neurol Sci.* 1987; 80:25–37. [PubMed: 3302117]
91. Heneka MT, Rodriguez JJ, Verkhratsky A. Neuroglia in neurodegeneration. *Brain Res Rev.* 2010; 63:189–211. [PubMed: 19944719]
92. Herrmann JE, Imura T, Song B, et al. STAT3 is a critical regulator of astrogliosis and scar formation after spinal cord injury. *J Neurosci.* 2008; 28:7231–7243. [PubMed: 18614693]
93. Hines DJ, Hines RM, Mulligan SJ, Macvicar BA. Microglia processes block the spread of damage in the brain and require functional chloride channels. *Glia.* 2009; 57:1610–1618. [PubMed: 19382211]
94. Hirohata M, Ono K, Morinaga A, Yamada M. Non-steroidal anti-inflammatory drugs have potent anti-fibrillogenic and fibril-destabilizing effects for alpha-synuclein fibrils in vitro. *Neuropharmacology.* 2008; 54:620–627. [PubMed: 18164319]
95. Hirsch EC, Hunot S, Hartmann A. Neuroinflammatory processes in Parkinson's disease. *Parkinsonism Relat Disord.* 2005; 11(Suppl 1):S9–S15. [PubMed: 15885630]
96. Hirschfeld M, Ma Y, Weis JH, Vogel SN, Weis JJ. Cutting edge: repurification of lipopolysaccharide eliminates signaling through both human and murine toll-like receptor 2. *J Immunol.* 2000; 165:618–622. [PubMed: 10878331]
97. Hlavanda E, Klement E, Kokai E, et al. Phosphorylation blocks the activity of tubulin polymerization-promoting protein (TPPP): identification of sites targeted by different kinases. *J Biol Chem.* 2007; 282:29531–29539. [PubMed: 17693641]
98. Hunter RL, Dragicevic N, Seifert K, et al. Inflammation induces mitochondrial dysfunction and dopaminergic neurodegeneration in the nigrostriatal system. *J Neurochem.* 2007; 100:1375–1386. [PubMed: 17254027]
99. Ikeda K, Akiyama H, Kondo H, et al. Thorn-shaped astrocytes: possibly secondarily induced tau-positive glial fibrillary tangles. *Acta Neuropathol.* 1995; 90:620–625. [PubMed: 8615083]
100. Ishizawa K, Komori T, Sasaki S, Arai N, Mizutani T, Hirose T. Microglial activation parallels system degeneration in multiple system atrophy. *J Neuropathol Exp Neurol.* 2004; 63:43–52. [PubMed: 14748560]
101. Iwai A, Masliah E, Yoshimoto M, et al. The precursor protein of non-A beta component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron.* 1995; 14:467–475. [PubMed: 7857654]
102. Jakel RJ, Townsend JA, Kraft AD, Johnson JA. Nrf2-mediated protection against 6-hydroxydopamine. *Brain Res.* 2007; 1144:192–201. [PubMed: 17336276]
103. Jander S, Pohl J, D'Urso D, Gillen C, Stoll G. Time course and cellular localization of interleukin-10 mRNA and protein expression in autoimmune inflammation of the rat central nervous system. *Am J Pathol.* 1998; 152:975–982. [PubMed: 9546358]
104. Jellinger KA. Neuropathological spectrum of synucleinopathies. *Mov Disord.* 2003; 18(Suppl 6):S2–S12. [PubMed: 14502650]
105. Jellinger KA. Lewy body disorders. In: Youdim, MBH.; Riederer, P.; Mandel, SA.; Battistin, L.; Lajtha, A., editors. *Degenerative diseases of the nervous system.* Springer; New York: 2007. p. 267–343.
106. Jellinger KA. A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. *Biochim Biophys Acta.* 2009; 1792:730–740. [PubMed: 18718530]
107. Jellinger KA, Lantos PL. Papp-Lantos inclusions and the pathogenesis of multiple system atrophy: an update. *Acta Neuropathol.* 2010; 119:657–667. [PubMed: 20309568]
108. Jellinger KA, Seppi K, Wenning GK. Grading of neuropathology in multiple system atrophy: proposal for a novel scale. *Mov Disord.* 2005; 20(Suppl 12):S29–S36. [PubMed: 16092088]
109. Jurewicz A, Matysiak M, Tybor K, Kilianek L, Raine CS, Selmaj K. Tumour necrosis factor-induced death of adult human oligodendrocytes is mediated by apoptosis inducing factor. *Brain.* 2005; 128:2675–2688. [PubMed: 16219674]
110. Juurlink BH. Response of glial cells to ischemia: roles of reactive oxygen species and glutathione. *Neurosci Biobehav Rev.* 1997; 21:151–166. [PubMed: 9062938]
111. Kahle PJ, Neumann M, Ozmen L, et al. Hyperphosphorylation and insolubility of alpha-synuclein in transgenic mouse oligodendrocytes. *EMBO Rep.* 2002; 3:583–588. [PubMed: 12034752]

112. Kandel, ER. Principles of neural science. Elsevier; New York: 1991. Nerve cell and behavior; p. 18-32.
113. Kiefer R, Schweitzer T, Jung S, Toyka KV, Hartung HP. Sequential expression of transforming growth factor-beta1 by T-cells, macrophages, and microglia in rat spinal cord during autoimmune inflammation. *J Neuropathol Exp Neurol*. 1998; 57:385–395. [PubMed: 9596409]
114. Klegeris A, Giasson BI, Zhang H, Maguire J, Pelech S, McGeer PL. Alpha-synuclein and its disease-causing mutants induce ICAM-1 and IL-6 in human astrocytes and astrocytoma cells. *FASEB J*. 2006; 20:2000–2008. [PubMed: 17012252]
115. Klegeris A, Pelech S, Giasson BI, et al. Alpha-synuclein activates stress signaling protein kinases in THP-1 cells and microglia. *Neurobiol Aging*. 2008; 29:739–752. [PubMed: 17166628]
116. Knott C, Stern G, Kingsbury A, Welcher AA, Wilkin GP. Elevated glial brain-derived neurotrophic factor in Parkinson's diseased nigra. *Parkinsonism Relat Disord*. 2002; 8:329–341. [PubMed: 15177062]
117. Knox CA, Kokmen E, Dyck PJ. Morphometric alteration of rat myelinated fibers with aging. *J Neuropathol Exp Neurol*. 1989; 48:119–139. [PubMed: 2921612]
118. Koehler RC, Roman RJ, Harder DR. Astrocytes and the regulation of cerebral blood flow. *Trends Neurosci*. 2009; 32:160–169. [PubMed: 19162338]
119. Kofuji P, Newman EA. Potassium buffering in the central nervous system. *Neuroscience*. 2004; 129:1045–1056. [PubMed: 15561419]
120. Kong LY, McMillian MK, Hudson PM, Jin L, Hong JS. Inhibition of lipopolysaccharide-induced nitric oxide and cytokine production by ultralow concentrations of dynorphins in mixed glia cultures. *J Pharmacol Exp Ther*. 1997; 280:61–66. [PubMed: 8996182]
121. Kragh CL, Lund LB, Febraro F, et al. {alpha}-Synuclein aggregation and Ser-129 phosphorylation-dependent cell death in oligodendroglial cells. *J Biol Chem*. 2009; 284:10211–10222. [PubMed: 19203998]
122. Lasn H, Winblad B, Bogdanovic N. Neuroglia in the inferior olivary nucleus during normal aging and Alzheimer's disease. *J Cell Mol Med*. 2006; 10:145–156. [PubMed: 16563227]
123. Lawson LJ, Perry VH, Dri P, Gordon S. Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience*. 1990; 39:151–170. [PubMed: 2089275]
124. Lee HJ, Patel S, Lee SJ. Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. *J Neurosci*. 2005; 25:6016–6024. [PubMed: 15976091]
125. Lee HJ, Suk JE, Bae EJ, Lee SJ. Clearance and deposition of extracellular alpha-synuclein aggregates in microglia. *Biochem Biophys Res Commun*. 2008; 372:423–428. [PubMed: 18492487]
126. Lee HJ, Suk JE, Patrick C, et al. Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. *J Biol Chem*. 2010; 285:9262–9272. [PubMed: 20071342]
127. Letiembre M, Liu Y, Walter S, et al. Screening of innate immune receptors in neurodegenerative diseases: a similar pattern. *Neurobiol Aging*. 2009; 30:759–768. [PubMed: 17905482]
128. Liberto CM, Albrecht PJ, Herx LM, Yong VW, Levison SW. Pro-regenerative properties of cytokine-activated astrocytes. *J Neurochem*. 2004; 89:1092–1100. [PubMed: 15147501]
129. Liddell JR, Robinson SR, Dringen R, Bishop GM. Astrocytes retain their antioxidant capacity into advanced old age. *Glia*. 2010; 58:1500–1509. [PubMed: 20648641]
130. Lien E, Means TK, Heine H, et al. Toll-like receptor 4 imparts ligand-specific recognition of bacterial lipopolysaccharide. *J Clin Invest*. 2000; 105:497–504. [PubMed: 10683379]
131. Lindersson E, Lundvig D, Petersen C, et al. p25alpha Stimulates alpha-synuclein aggregation and is co-localized with aggregated alpha-synuclein in alpha-synucleinopathies. *J Biol Chem*. 2005; 280:5703–5715. [PubMed: 15590652]
132. Liu JS, Amaral TD, Brosnan CF, Lee SC. IFNs are critical regulators of IL-1 receptor antagonist and IL-1 expression in human microglia. *J Immunol*. 1998; 161:1989–1996. [PubMed: 9712071]
133. Long-Smith CM, Collins L, Toulouse A, Sullivan AM, Nolan YM. Interleukin-1beta contributes to dopaminergic neuronal death induced by lipopolysaccharide-stimulated rat glia in vitro. *J Neuroimmunol*. 2010; 226:20–26. [PubMed: 20605229]

134. Lu L, Mak YT, Fang M, Yew DT. The difference in gliosis induced by beta-amyloid and Tau treatments in astrocyte cultures derived from senescence accelerated and normal mouse strains. *Biogerontology*. 2009; 10:695–710. [PubMed: 19221889]
135. Lu X, Bing G, Hagg T. Naloxone prevents microglia-induced degeneration of dopaminergic substantia nigra neurons in adult rats. *Neuroscience*. 2000; 97:285–291. [PubMed: 10799760]
136. Lynch MA. The multifaceted profile of activated microglia. *Mol Neurobiol*. 2009; 40:139–156. [PubMed: 19629762]
137. Mackenzie IR. Activated microglia in dementia with Lewy bodies. *Neurology*. 2000; 55:132–134. [PubMed: 10891923]
138. Maehlen J, Olsson T, Zachau A, Klareskog L, Kristensson K. Local enhancement of major histocompatibility complex (MHC) class I and II expression and cell infiltration in experimental allergic encephalomyelitis around axotomized motor neurons. *J Neuroimmunol*. 1989; 23:125–132. [PubMed: 2786005]
139. Marks WJ Jr, Bartus RT, Siffert J, et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol*. 2010; 9:1164–1172. [PubMed: 20970382]
140. Marner L, Nyengaard JR, Tang Y, Pakkenberg B. Marked loss of myelinated nerve fibers in the human brain with age. *J Comp Neurol*. 2003; 462:144–152. [PubMed: 12794739]
141. Masliah E, Rockenstein E, Adame A, et al. Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease. *Neuron*. 2005; 46:857–868. [PubMed: 15953415]
142. Matsuo A, Akiguchi I, Lee GC, McGeer EG, McGeer PL, Kimura J. Myelin degeneration in multiple system atrophy detected by unique antibodies. *Am J Pathol*. 1998; 153:735–744. [PubMed: 9736024]
143. Matute C, Alberdi E, Domercq M, et al. Excitotoxic damage to white matter. *J Anat*. 2007; 210:693–702. [PubMed: 17504270]
144. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology*. 1988; 38:1285–1291. [PubMed: 3399080]
145. McGeer PL, McGeer EG. Glial reactions in Parkinson's disease. *Mov Disord*. 2008; 23:474–483. [PubMed: 18044695]
146. McKeith IG, Burn DJ, Ballard CG, et al. Dementia with Lewy bodies. *Semin Clin Neuropsychiatry*. 2003; 8:46–57. [PubMed: 12567332]
147. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996; 47:1113–1124. [PubMed: 8909416]
148. McTigue DM, Tripathi RB. The life, death, and replacement of oligodendrocytes in the adult CNS. *J Neurochem*. 2008; 107:1–19. [PubMed: 18643793]
149. Miller DW, Johnson JM, Solano SM, Hollingsworth ZR, Standaert DG, Young AB. Absence of alpha-synuclein mRNA expression in normal and multiple system atrophy oligodendroglia. *J Neural Transm*. 2005; 112:1613–1624. [PubMed: 16284907]
150. Mirza B, Hadberg H, Thomsen P, Moos T. The absence of reactive astrogliosis is indicative of a unique inflammatory process in Parkinson's disease. *Neuroscience*. 2000; 95:425–432. [PubMed: 10658622]
151. Mizuno T, Kuno R, Nitta A, et al. Protective effects of nicergoline against neuronal cell death induced by activated microglia and astrocytes. *Brain Res*. 2005; 1066:78–85. [PubMed: 16325157]
152. Mollenhauer B, Locascio JJ, Schulz-Schaeffer W, Sixel-Doring F, Trenkwalder C, Schlossmacher MG. alpha-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. *Lancet Neurol*. 2011; 10:230–240. [PubMed: 21317042]
153. Mori F, Tanji K, Yoshimoto M, Takahashi H, Wakabayashi K. Demonstration of alpha-synuclein immunoreactivity in neuronal and glial cytoplasm in normal human brain tissue using proteinase K and formic acid pretreatment. *Exp Neurol*. 2002; 176:98–104. [PubMed: 12093086]
154. Nakamura K, Nemani VM, Azarbal F, et al. Direct membrane association drives mitochondrial fission by the Parkinson disease-associated protein {alpha}-synuclein. *J Biol Chem*. 2011

155. Nave KA, Trapp BD. Axon-glia signaling and the glial support of axon function. *Annu Rev Neurosci.* 2008; 31:535–561. [PubMed: 18558866]
156. Neumann H, Schweigreiter R, Yamashita T, Rosenkranz K, Wekerle H, Barde YA. Tumor necrosis factor inhibits neurite outgrowth and branching of hippocampal neurons by a rho-dependent mechanism. *J Neurosci.* 2002; 22:854–862. [PubMed: 11826115]
157. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science.* 2005; 308:1314–1318. [PubMed: 15831717]
158. Nishie M, Mori F, Fujiwara H, et al. Accumulation of phosphorylated alpha-synuclein in the brain and peripheral ganglia of patients with multiple system atrophy. *Acta Neuropathol.* 2004; 107:292–298. [PubMed: 14722716]
159. Nishioka K, Hayashi S, Farrer MJ, et al. Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. *Ann Neurol.* 2006; 59:298–309. [PubMed: 16358335]
160. Njie EG, Boelen E, Stassen FR, Steinbusch HW, Borchelt DR, Streit WJ. Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. *Neurobiol Aging.* 2010 (in press, corrected proof).
161. Norris EH, Giasson BI, Lee VM. Alpha-synuclein: normal function and role in neurodegenerative diseases. *Curr Top Dev Biol.* 2004; 60:17–54. [PubMed: 15094295]
162. Norton WT, Aquino DA, Hozumi I, Chiu FC, Brosnan CF. Quantitative aspects of reactive gliosis: a review. *Neurochem Res.* 1992; 17:877–885. [PubMed: 1407275]
163. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain.* 2008; 131:1362–1372. [PubMed: 18385183]
164. Orr CF, Rowe DB, Mizuno Y, Mori H, Halliday GM. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. *Brain.* 2005; 128:2665–2674. [PubMed: 16219675]
165. Ozawa T, Okuizumi K, Ikeuchi T, Wakabayashi K, Takahashi H, Tsuji S. Analysis of the expression level of alpha-synuclein mRNA using postmortem brain samples from pathologically confirmed cases of multiple system atrophy. *Acta Neuropathol.* 2001; 102:188–190. [PubMed: 11563635]
166. Ozawa T, Paviour D, Quinn NP, et al. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. *Brain.* 2004; 127:2657–2671. [PubMed: 15509623]
167. Ozawa T, Takano H, Onodera O, et al. No mutation in the entire coding region of the alpha-synuclein gene in pathologically confirmed cases of multiple system atrophy. *Neurosci Lett.* 1999; 270:110–112. [PubMed: 10462110]
168. Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). *J Neurol Sci.* 1989; 94:79–100. [PubMed: 2559165]
169. Papp MI, Lantos PL. The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. *Brain.* 1994; 117(Pt 2):235–243. [PubMed: 8186951]
170. Park JY, Paik SR, Jou I, Park SM. Microglial phagocytosis is enhanced by monomeric alpha-synuclein, not aggregated alpha-synuclein: implications for Parkinson's disease. *Glia.* 2008; 56:1215–1223. [PubMed: 18449945]
171. Parkkinen L, Kauppinen T, Pirttilä T, Autere JM, Alafuzoff I. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Ann Neurol.* 2005; 57:82–91. [PubMed: 15562510]
172. Peters A. Structural changes in the normally aging cerebral cortex of primates. *Prog Brain Res.* 2002; 136:455–465. [PubMed: 12143402]
173. Polazzi E, Monti B. Microglia and neuroprotection: from in vitro studies to therapeutic applications. *Prog Neurobiol.* 2010; 92:293–315. [PubMed: 20609379]
174. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science.* 1997; 276:2045–2047. [PubMed: 9197268]
175. Qian L, Flood PM. Microglial cells and Parkinson's disease. *Immunol Res.* 2008; 41:155–164. [PubMed: 18512160]

176. Qian L, Flood PM, Hong JS. Neuroinflammation is a key player in Parkinson's disease and a prime target for therapy. *J Neural Transm.* 2010; 117:971–979. [PubMed: 20571837]
177. Racette B. A pilot clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. *Clin Neuropharmacol.* 2008; 31:141–150. [PubMed: 18520981]
178. Raivich G, Bohatschek M, Kloss CU, Werner A, Jones LL, Kreutzberg GW. Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. *Brain Res Brain Res Rev.* 1999; 30:77–105. [PubMed: 10407127]
179. Randy LH, Guoying B. Agonism of peroxisome proliferator receptor-gamma may have therapeutic potential for neuroinflammation and Parkinson's disease. *Curr Neuropharmacol.* 2007; 5:35–46. [PubMed: 18615152]
180. Rauen T, Taylor WR, Kuhlbrodt K, Wiessner M. High-affinity glutamate transporters in the rat retina: a major role of the glial glutamate transporter GLAST-1 in transmitter clearance. *Cell Tissue Res.* 1998; 291:19–31. [PubMed: 9394040]
181. Reynolds AD, Banerjee R, Liu J, Gendelman HE, Mosley RL. Neuroprotective activities of CD4+ CD25+ regulatory T cells in an animal model of Parkinson's disease. *J Leukoc Biol.* 2007; 82:1083–1094. [PubMed: 17675560]
182. Reynolds AD, Glanzer JG, Kadiu I, et al. Nitrated alpha-synuclein-activated microglial profiling for Parkinson's disease. *J Neurochem.* 2008; 104:1504–1525. [PubMed: 18036154]
183. Reynolds AD, Kadiu I, Garg SK, et al. Nitrated alpha-synuclein and microglial neuroregulatory activities. *J Neuroimmune Pharmacol.* 2008; 3:59–74. [PubMed: 18202920]
184. Richter-Landsberg C, Gorath M, Trojanowski JQ, Lee VM. alpha-synuclein is developmentally expressed in cultured rat brain oligodendrocytes. *J Neurosci Res.* 2000; 62:9–14. [PubMed: 11002283]
185. Riedel M, Goldbaum O, Richter-Landsberg C. alpha-Synuclein promotes the recruitment of tau to protein inclusions in oligodendroglial cells: effects of oxidative and proteolytic stress. *J Mol Neurosci.* 2009; 39:226–234. [PubMed: 19266322]
186. Rohl C, Lucius R, Sievers J. The effect of activated microglia on astrogliosis parameters in astrocyte cultures. *Brain Res.* 2007; 1129:43–52. [PubMed: 17169340]
187. Roodveldt C, Labrador-Garrido A, Gonzalez-Rey E, et al. Glial innate immunity generated by non-aggregated alpha-synuclein in mouse: differences between wild-type and Parkinson's disease-linked mutants. *PLoS One.* 2010; 5:e13481. [PubMed: 21048992]
188. Ros-Bernal F, Hunot S, Herrero MT, et al. Microglial glucocorticoid receptors play a pivotal role in regulating dopaminergic neurodegeneration in parkinsonism. *Proc Natl Acad Sci USA.* 2011; 108:6632–6637. [PubMed: 21467220]
189. Rothstein JD, Dykes-Hoberg M, Pardo CA, et al. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron.* 1996; 16:675–686. [PubMed: 8785064]
190. Saavedra A, Baltazar G, Santos P, Carvalho CM, Duarte EP. Selective injury to dopaminergic neurons up-regulates GDNF in substantia nigra postnatal cell cultures: role of neuron-glia crosstalk. *Neurobiol Dis.* 2006; 23:533–542. [PubMed: 16766196]
191. Samii A, Etminan M, Wiens MO, Jafari S. NSAID use and the risk of Parkinson's disease: systematic review and meta-analysis of observational studies. *Drugs Aging.* 2009; 26:769–779. [PubMed: 19728750]
192. Sanchez-Guajardo V, Febbraro F, Kirik D, Romero-Ramos M. Microglia acquire distinct activation profiles depending on the degree of alpha-synuclein neuropathology in a rAAV based model of Parkinson's disease. *PLoS One.* 2010; 5:e8784. [PubMed: 20098715]
193. Sandhu JK, Gardaneh M, Iwasio R, et al. Astrocyte-secreted GDNF and glutathione antioxidant system protect neurons against 6OHDA cytotoxicity. *Neurobiol Dis.* 2009; 33:405–414. [PubMed: 19118631]
194. Savitt JM, Dawson VL, Dawson TM. Diagnosis and treatment of Parkinson disease: molecules to medicine. *J Clin Invest.* 2006; 116:1744–1754. [PubMed: 16823471]
195. Schipper HM. Brain iron deposition and the free radical-mitochondrial theory of ageing. *Ageing Res Rev.* 2004; 3:265–301. [PubMed: 15231237]

196. Schmidt S, Linnartz B, Mendritzki S, et al. Genetic mouse models for Parkinson's disease display severe pathology in glial cell mitochondria. *Hum Mol Genet.* 2011; 20:1197–1211. [PubMed: 21212098]
197. Scholz SW, Houlden H, Schulte C, et al. SNCA variants are associated with increased risk for multiple system atrophy. *Ann Neurol.* 2009; 65:610–614. [PubMed: 19475667]
198. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet.* 1999; 354:1771–1775. [PubMed: 10577638]
199. Schrag A, Wenning GK, Quinn N, Ben-Shlomo Y. Survival in multiple system atrophy. *Mov Disord.* 2008; 23:294–296. [PubMed: 18044727]
200. Schwartz JP, Nishiyama N. Neurotrophic factor gene expression in astrocytes during development and following injury. *Brain Res Bull.* 1994; 35:403–407. [PubMed: 7532097]
201. Sheffield LG, Berman NE. Microglial expression of MHC class II increases in normal aging of nonhuman primates. *Neurobiol Aging.* 1998; 19:47–55. [PubMed: 9562503]
202. Shimura H, Schlossmacher MG, Hattori N, et al. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. *Science.* 2001; 293:263–269. [PubMed: 11431533]
203. Shults CW, Rockenstein E, Crews L, et al. Neurological and neurodegenerative alterations in a transgenic mouse model expressing human alpha-synuclein under oligodendrocyte promoter: implications for multiple system atrophy. *J Neurosci.* 2005; 25:10689–10699. [PubMed: 16291942]
204. Simard M, Nedergaard M. The neurobiology of glia in the context of water and ion homeostasis. *Neuroscience.* 2004; 129:877–896. [PubMed: 15561405]
205. Singleton AB, Farrer M, Johnson J, et al. alpha-Synuclein locus triplication causes Parkinson's disease. *Science.* 2003; 302:841. [PubMed: 14593171]
206. Sloane JA, Hinman JD, Lubonia M, Hollander W, Abraham CR. Age-dependent myelin degeneration and proteolysis of oligodendrocyte proteins is associated with the activation of calpain-1 in the rhesus monkey. *J Neurochem.* 2003; 84:157–168. [PubMed: 12485412]
207. Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. *Trends Neurosci.* 2009; 32:638–647. [PubMed: 19782411]
208. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol.* 2010; 119:7–35. [PubMed: 20012068]
209. Soma H, Yabe I, Takei A, Fujiki N, Yanagihara T, Sasaki H. Heredity in multiple system atrophy. *J Neurol Sci.* 2006; 240:107–110. [PubMed: 16307759]
210. Song YJ, Lundvig DM, Huang Y, et al. p25alpha relocates in oligodendroglia from myelin to cytoplasmic inclusions in multiple system atrophy. *Am J Pathol.* 2007; 171:1291–1303. [PubMed: 17823288]
211. Spillantini MG, Crowther RA, Jakes R, Cairns NJ, Lantos PL, Goedert M. Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. *Neurosci Lett.* 1998; 251:205–208. [PubMed: 9726379]
212. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature.* 1997; 388:839–840. [PubMed: 9278044]
213. Stefanova N, Eriksson H, Georgievska B, Poewe W, Wenning GK. Myeloperoxidase inhibition ameliorates multiple system atrophy-like degeneration in a transgenic mouse model. *Mov Disord.* 2010; 25(Suppl. 3):625.
214. Stefanova N, Hainzer M, Stemberger S, et al. Striatal transplantation for multiple system atrophy —are grafts affected by alpha-synucleinopathy? *Exp Neurol.* 2009; 219:368–371. [PubMed: 19460374]
215. Stefanova N, Klimaschewski L, Poewe W, Wenning GK, Reindl M. Glial cell death induced by overexpression of alpha-synuclein. *J Neurosci Res.* 2001; 65:432–438. [PubMed: 11536327]
216. Stefanova N, Mitschnigg M, Ghorayeb I, et al. Failure of neuronal protection by inhibition of glial activation in a rat model of striatonigral degeneration. *J Neurosci Res.* 2004; 78:87–91. [PubMed: 15372496]

217. Stefanova N, Reindl M, Neumann M, et al. Oxidative stress in transgenic mice with oligodendroglial alpha-synuclein overexpression replicates the characteristic neuropathology of multiple system atrophy. *Am J Pathol.* 2005; 166:869–876. [PubMed: 15743798]
218. Stefanova N, Reindl M, Neumann M, Kahle PJ, Poewe W, Wenning GK. Microglial activation mediates neurodegeneration related to oligodendroglial alpha-synucleinopathy: implications for multiple system atrophy. *Mov Disord.* 2007; 22:2196–2203. [PubMed: 17853477]
219. Stefanova N, Schanda K, Klimaschewski L, Poewe W, Wenning GK, Reindl M. Tumor necrosis factor-alpha-induced cell death in U373 cells overexpressing alpha-synuclein. *J Neurosci Res.* 2003; 73:334–340. [PubMed: 12868067]
220. Stefanova N, Stemberger S, Fellner L, et al. Disturbance of innate immunity linked to toll-like receptor 4 promotes neurodegeneration in a transgenic alpha-synucleinopathy model. *Mov Disord.* 2010; 25(Suppl. 2):210–211.
221. Stefanova N, Tison F, Reindl M, Poewe W, Wenning GK. Animal models of multiple system atrophy. *Trends Neurosci.* 2005; 28:501–506. [PubMed: 16043239]
222. Stemberger S, Poewe W, Wenning GK, Stefanova N. Targeted overexpression of human alpha-synuclein in oligodendroglia induces lesions linked to MSA-like progressive autonomic failure. *Exp Neurol.* 2010; 224:459–464. [PubMed: 20493840]
223. Stoll G, Jander S. The role of microglia and macrophages in the pathophysiology of the CNS. *Prog Neurobiol.* 1999; 58:233–247. [PubMed: 10341362]
224. Streit WJ. Microglia as neuroprotective, immunocompetent cells of the CNS. *Glia.* 2002; 40:133–139. [PubMed: 12379901]
225. Streit WJ. Microglia and Alzheimer's disease pathogenesis. *J Neurosci Res.* 2004; 77:1–8. [PubMed: 15197750]
226. Streit WJ, Sammons NW, Kuhns AJ, Sparks DL. Dystrophic microglia in the aging human brain. *Glia.* 2004; 45:208–212. [PubMed: 14730714]
227. Su X, Federoff HJ, Maguire-Zeiss KA. Mutant alpha-synuclein overexpression mediates early proinflammatory activity. *Neurotox Res.* 2009; 16:238–254. [PubMed: 19526281]
228. Su X, Maguire-Zeiss KA, Giuliano R, Prifti L, Venkatesh K, Federoff HJ. Synuclein activates microglia in a model of Parkinson's disease. *Neurobiol Aging.* 2008; 29:1690–1701. [PubMed: 17537546]
229. Sugiyama I, Tanaka K, Akita M, Yoshida K, Kawase T, Asou H. Ultrastructural analysis of the paranodal junction of myelinated fibers in 31-month-old-rats. *J Neurosci Res.* 2002; 70:309–317. [PubMed: 12391590]
230. Takahashi M, Tomizawa K, Fujita SC, Sato K, Uchida T, Imahori K. A brain-specific protein p25 is localized and associated with oligodendrocytes, neuropil, and fiber-like structures of the CA3 hippocampal region in the rat brain. *J Neurochem.* 1993; 60:228–235. [PubMed: 8417144]
231. Tanaka J, Maeda N. Microglial ramification requires nondiffusible factors derived from astrocytes. *Exp Neurol.* 1996; 137:367–375. [PubMed: 8635553]
232. Tanaka J, Okuma Y, Tomobe K, Nomura Y. The age-related degeneration of oligodendrocytes in the hippocampus of the senescence-accelerated mouse (SAM) P8: a quantitative immunohistochemical study. *Biol Pharm Bull.* 2005; 28:615–618. [PubMed: 15802797]
233. Tansey MG, Goldberg MS. Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. *Neurobiol Dis.* 2010; 37:510–518. [PubMed: 19913097]
234. Taylor DL, Pirianov G, Holland S, et al. Attenuation of proliferation in oligodendrocyte precursor cells by activated microglia. *J Neurosci Res.* 2010; 88:1632–1644. [PubMed: 20091773]
235. Teismann P, Ferger B. Inhibition of the cyclooxygenase isoenzymes COX-1 and COX-2 provide neuroprotection in the MPTP-mouse model of Parkinson's disease. *Synapse.* 2001; 39:167–174. [PubMed: 11180504]
236. Theodore S, Cao S, McLean PJ, Standaert DG. Targeted overexpression of human alpha-synuclein triggers microglial activation and an adaptive immune response in a mouse model of Parkinson disease. *J Neuropathol Exp Neurol.* 2008; 67:1149–1158. [PubMed: 19018246]

237. Thorburne SK, Juurlink BH. Low glutathione and high iron govern the susceptibility of oligodendroglial precursors to oxidative stress. *J Neurochem.* 1996; 67:1014–1022. [PubMed: 8752107]
238. Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR. Oligodendrocytes and myelination: the role of iron. *Glia.* 2009; 57:467–478. [PubMed: 18837051]
239. Tofaris GK, Razzaq A, Ghetti B, Lilley KS, Spillantini MG. Ubiquitination of alpha-synuclein in Lewy bodies is a pathological event not associated with impairment of proteasome function. *J Biol Chem.* 2003; 278:44405–44411. [PubMed: 12923179]
240. Togo T, Dickson DW. Tau accumulation in astrocytes in progressive supranuclear palsy is a degenerative rather than a reactive process. *Acta Neuropathol.* 2002; 104:398–402. [PubMed: 12200627]
241. Trojanowski JQ, Revesz T. Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. *Neuropathol Appl Neurobiol.* 2007; 33:615–620. [PubMed: 17990994]
242. Tsuboi K, Grzesiak JJ, Bouvet M, Hashimoto M, Masliah E, Shults CW. Alpha-synuclein overexpression in oligodendrocytic cells results in impaired adhesion to fibronectin and cell death. *Mol Cell Neurosci.* 2005; 29:259–268. [PubMed: 15911350]
243. Ubhi K, Rockenstein E, Mante M, et al. Neurodegeneration in a transgenic mouse model of multiple system atrophy is associated with altered expression of oligodendroglial-derived neurotrophic factors. *J Neurosci.* 2010; 30:6236–6246. [PubMed: 20445049]
244. van Rossum D, Hanisch UK. Microglia. *Metab Brain Dis.* 2004; 19:393–411. [PubMed: 15554430]
245. Verkhratsky A, Kettenmann H. Calcium signalling in glial cells. *Trends Neurosci.* 1996; 19:346–352. [PubMed: 8843604]
246. Vila M, Jackson-Lewis V, Guegan C, et al. The role of glial cells in Parkinson's disease. *Curr Opin Neurol.* 2001; 14:483–489. [PubMed: 11470965]
247. Wakabayashi K, Hayashi S, Yoshimoto M, Kudo H, Takahashi H. NACP/alpha-synuclein-positive filamentous inclusions in astrocytes and oligodendrocytes of Parkinson's disease brains. *Acta Neuropathol.* 2000; 99:14–20. [PubMed: 10651022]
248. Wakabayashi K, Takahashi H. Cellular pathology in multiple system atrophy. *Neuropathology.* 2006; 26:338–345. [PubMed: 16961071]
249. Wakabayashi K, Yoshimoto M, Tsuji S, Takahashi H. Alpha-synuclein immunoreactivity in glial cytoplasmic inclusions in multiple system atrophy. *Neurosci Lett.* 1998; 249:180–182. [PubMed: 9682846]
250. Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *J Neurosci.* 2009; 29:3974–3980. [PubMed: 19339593]
251. Wang X, Zhu S, Drozda M, et al. Minocycline inhibits caspase-independent and -dependent mitochondrial cell death pathways in models of Huntington's disease. *Proc Natl Acad Sci USA.* 2003; 100:10483–10487. [PubMed: 12930891]
252. Wenning GK, Quinn N, Magalhaes M, Mathias C, Daniel SE. "Minimal change" multiple system atrophy. *Mov Disord.* 1994; 9:161–166. [PubMed: 8196676]
253. Wenning GK, Stefanova N, Jellinger KA, Poewe W, Schlossmacher MG. Multiple system atrophy: a primary oligodendroglialopathy. *Ann Neurol.* 2008; 64:239–246. [PubMed: 18825660]
254. Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord.* 1997; 12:133–147. [PubMed: 9087971]
255. Wilhelmsson U, Bushong EA, Price DL, et al. Redefining the concept of reactive astrocytes as cells that remain within their unique domains upon reaction to injury. *Proc Natl Acad Sci USA.* 2006; 103:17513–17518. [PubMed: 17090684]
256. Wu DC, Jackson-Lewis V, Vila M, et al. Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease. *J Neurosci.* 2002; 22:1763–1771. [PubMed: 11880505]
257. Wullner U, Schmitt I, Kammal M, Kretschmar HA, Neumann M. Definite multiple system atrophy in a German family. *J Neurol Neurosurg Psychiatry.* 2009; 80:449–450. [PubMed: 19289484]

258. Yamada T, McGeer PL, McGeer EG. Lewy bodies in Parkinson's disease are recognized by antibodies to complement proteins. *Acta Neuropathol.* 1992; 84:100–104. [PubMed: 1502878]
259. Yamada T, McGeer PL, McGeer EG. Some immunohistochemical features of argyrophilic grain dementia with normal cortical choline acetyltransferase levels but extensive subcortical pathology and markedly reduced dopamine. *J Geriatr Psychiatry Neurol.* 1992; 5:3–13. [PubMed: 1315137]
260. Yao SY, Ljunggren-Rose A, Chandramohan N, Whetsell WO Jr, Sriram S. In vitro and in vivo induction and activation of nNOS by LPS in oligodendrocytes. *J Neuroimmunol.* 2010; 229:146–156. [PubMed: 20724006]
261. Yazawa I, Giasson BI, Sasaki R, et al. Mouse model of multiple system atrophy alpha-synuclein expression in oligodendrocytes causes glial and neuronal degeneration. *Neuron.* 2005; 45:847–859. [PubMed: 15797547]
262. Zarranz JJ, Alegre J, Gomez-Esteban JC, et al. The new mutation, E46 K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol.* 2004; 55:164–173. [PubMed: 14755719]
263. Zhang W, Wang T, Pei Z, et al. Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. *FASEB J.* 2005; 19:533–542. [PubMed: 15791003]
264. Zhang X, Haaf M, Todorich B, et al. Cytokine toxicity to oligodendrocyte precursors is mediated by iron. *Glia.* 2005; 52:199–208. [PubMed: 15968631]

Fig. 1. Microglia visualised in the mouse brain by CD11b immunohistochemistry. **a** Ramified quiescent microglia, **b** activated microglia in the SNpc of PLP- α -synuclein transgenic mouse model of MSA with shortened processes and amoeboid form. Scale bar 50 μ m

Fig. 2. Astroglia visualised by GFAP immunohistochemistry **a** in the healthy mouse SNpc and **b** activated in SNpc of PLP- α -synuclein transgenic mouse model of MSA. *Scale bar 50 μ m*

Fig. 3.
The specific morphology of mature oligodendroglia labelled by CNP immunofluorescence (*red*) in a purified murine OPCs culture. OPCs were identified by Olig-2 immunofluorescence (*green*). *Scale bar* 20 μ m

Fig. 4.

Main CNS cell types in the healthy brain and their involvement in PD/DLB and MSA pathogenesis. **a** In the healthy brain neurons are intact. Microglia are in a quiescent state, scanning the brain microenvironment for possible injuries or invaders [157]. Astroglial cells support the neurons by providing nutrient support, secure synaptic transmission and control of extracellular homeostasis [8, 78, 91, 118, 245]. Oligodendrocytes myelinate the axons to contribute to the saltatory conduction of action potentials [13, 29, 33]. **b** In PD/DLB, aggregation of α -synuclein in neurons (Lewy bodies, *white arrow*) occurs and leads to dramatic changes in the neuronal viability. Furthermore, cytoplasmic inclusions of non-fibrillar α -synuclein in astrocytes can appear (*grey arrow*) [24, 166, 247] and astroglia may show a mild activation [95, 150, 246]. Microglia are recruited and activated, even before neuronal cell death, changing their morphology, releasing pro-inflammatory cytokines and phagocytosing extracellular α -synuclein and cell debris [47, 157, 244, 263]. The α -synuclein aggregation leads to over-activation of glial cells and a prominent degeneration of mainly nigral dopaminergic neurons. **c** In MSA, α -synuclein inclusions in the cytoplasm and nucleus of neurons may also occur (*grey arrow*); however, α -synuclein is mainly aggregated in oligodendroglial cells (GCIs, *white arrow*). This can lead to oligodendroglial dysfunction,

demyelination and secondary axonal degeneration and neuronal cell death [203, 215, 219]. Similar to PD, microglia are highly activated and produce pro-inflammatory cytokines [7, 34, 45]. Cell debris and aggregated α -synuclein can be partly cleared by phagocytic microglia [47, 263]. Prominent astrogliosis combined with increased production of pro-inflammatory cytokines occurs in the MSA brain [166]. The consequence of the oligodendroglial dysfunction in MSA is reactive gliosis and widespread neurodegeneration