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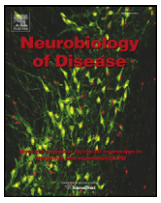

Review

Glia and alpha-synuclein in neurodegeneration: A complex interaction

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ABSTRACT

α-Synucleinopathies (ASP) comprise adult-onset, progressive neurodegenerative disorders such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) that are characterized by α-synuclein (AS) aggregates in neurons or glia. PD and DLB feature neuronal AS-positive inclusions termed Lewy bodies (LB) whereas glial cytoplasmic inclusions (GCIs, Papp–Lantos bodies) are recognized as the defining hallmark of MSA. Furthermore, AS-positive cytoplasmic aggregates may also be seen in astroglial cells of PD/DLB and MSA brains. The glial AS-inclusions appear to trigger reduced trophic support resulting in neuronal loss. Moreover, microgliosis and astrogliosis can be found throughout the neurodegenerative brain and both are key players in the initiation and progression of ASP. In this review, we will highlight AS-dependent alterations of glial function and their impact on neuronal vulnerability thereby providing a detailed summary on the multifaceted role of glia in ASP.

Contents

Introduction

α-Synucleinopathies (ASP) are progressive, adult-onset neurodegenerative diseases that include Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) (Spillantini and Goedert, 2000; Goedert, 2001; Beyer and Ariza, 2007). The main pathological hallmark of these diseases is the occurrence of hyperphosphorylated, misfolded and fibrillized α-synuclein (AS)-positive inclusions throughout the central nervous system (CNS) (Fujiwara et al., 2002; Uversky, 2008; Vilar et al., 2008). In PD and DLB, neurons are the main cell type displaying cytoplasmic AS-positive aggregations which are called Lewy bodies (LB) and Lewy neurites (LN) (Baba et al., 1998; Beyer and Ariza, 2007), whereas in MSA, these inclusions predominantly develop in oligodendroglia and are therefore named glial cytoplasmic inclusions (GCIs, Papp–Lantos bodies) (Spillantini et al., 1998; Dickson et al., 1999; Hasegawa et al.,

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2004; Song et al., 2009; Fellner et al., 2011; Fellner and Stefanova, 2013). Furthermore, PD and DLB show AS depositions in astrocytes and oligodendrocytes (Wakabayashi et al., 2000; Braak et al., 2007; Song et al., 2009). Wenning and Jellinger described AS-positive deposits in astroglial cells in MSA (Wenning and Jellinger, 2005), however they appear to be less prominent and sometimes absent (Song et al., 2009) compared to neuronal and oligodendroglial inclusion pathology. AS aggregation in astroglial cells and its relevance to disease initiation and progression require further attention in MSA.

The brain protein AS is predominantly located in presynaptic terminals of neurons in the hippocampus, striatum, thalamus, cerebellum and neocortex (Iwai et al., 1995; Norris et al., 2004). AS belongs to a family of three distinct genes, including *SNCA*, *SNCB* and *SNCG* (α-, β- and γ-synuclein) and is composed of 140 amino-acids (Dev et al., 2003; Eriksen et al., 2003). Although the precise function of the protein is not solved yet, the importance of AS in folding and refolding of synaptic proteins has been proven (Chandra et al., 2005). Moreover, AS directly interacts with phospholipid vesicle membranes suggesting an important regulatory role in both inhibitory and facilitatory transmitter releases (Auluck et al., 2010) (Abeliovich et al., 2000; Cabin et al., 2002; Gitler and Shorter, 2007).

The development of the AS-positive GCI, LB and LN has not been completely elucidated yet. However, different studies demonstrated that AS overexpression impairs macroautophagy suggesting that reduced AS clearance is involved in the generation of AS inclusions in DLB and PD (Winslow et al., 2010; Xilouri and Stefanis, 2011). Furthermore, alterations in the autophagosomal proteins in MSA brains and the participation of macroautophagy in the MSA pathogenesis have been suggested (Tanji et al., 2011; Schwarz et al., 2012). Post-translational modifications of AS, such as ubiquitination, nitration and phosphorylation may promote pathological inclusion formation and enhance disease progression (Giasson et al., 2000; Tofaris et al., 2003; Xilouri and Stefanis, 2011). Moreover, Ozawa et al. showed a connection between neuronal cell loss, aggregation of AS and disease severity in MSA (Ozawa et al., 2004). Prion-like cell-to-cell propagation of AS has been suggested a crucial contributor to neurodegeneration and therefore to the progression of ASP (Desplats et al., 2009; Lee et al., 2010; Hansen et al., 2011; Reyes et al., 2014).

Glial cells are important in supporting neuronal survival, synaptic functions and local immunity (Webster and Astrom, 2009; Hauser and Cookson, 2011). However, glial cells might be crucial for the initiation and progression of different neurodegenerative diseases, including ASP (Gerhard et al., 2003, 2006; Fellner et al., 2011; Halliday and Stevens, 2011). Due to various stimuli, e.g. infection or injury, astroglial and microglial cells get activated (Nimmerjahn et al., 2005; Wilhelmsson et al., 2006). Neurons may benefit from activated microglia and astroglia due to the release of trophic factors or the clearance of damaged cells by microglia (Liberto et al., 2004; van Rossum and Hanisch, 2004; Nimmerjahn et al., 2005; Wilhelmsson et al., 2006).

Especially in neurodegenerative diseases microglia and astroglia can get over activated resulting in reactive microgliosis and astrogliosis. It was described that astroglial cells can activate microglial cells (Gu et al., 2010; Halliday and Stevens, 2011; Schmidt et al., 2011), or vice versa microglial activation can induce astrogliosis (Balasingam et al., 1996; Hanisch, 2002; Rohl et al., 2007). Reactive gliosis might induce neurotoxicity, perturbation of the neuronal network, and maladaptive plasticity and further lead to tissue damage (Papa et al., 2014). Moreover, it was demonstrated that neuronal cells have the ability to release excessive AS leading to the activation of an inflammatory response in microglia (Lee et al., 2010; Kim et al., 2013). Furthermore, the before mentioned prion-like spreading of pathological AS (Luk et al., 2009; Hansen et al., 2011; Masuda-Suzukake et al., 2013; Watts et al., 2013) could be a possible mechanism of AS aggregation in ASP and further cause activation of microglia and astroglia. Aggregated AS was shown to induce reactive microgliosis resulting in dopaminergic cell death (Zhang et al., 2005). Glial overactivation results in the release of (pro)-inflammatory cytokines, nitric oxide (NO) and reactive oxygen species (ROS) (Neumann et al., 2002; Deshpande et al., 2005; Mizuno et al., 2005; Zhang et al., 2005; Qian and Flood, 2008; Dean et al., 2010; Lee et al., 2010; Qian et al., 2010).

Besides, oligodendroglial cells that are exposed to oxidative stress and cytokines present with cellular dysfunction, demyelination and cell death, as well as reduced trophic support which consequently affects neuronal survival (Thorburne and Juurlink, 1996; Jurewicz et al., 2005).

This review summarizes the main features of ASP and the involvement of glial cells regarding the initiation and progression of these neurodegenerative diseases. We will discuss the main changes of glial cells during disease initiation and progression.

Glia in PD and DLB

PD and DLB are common neurodegenerative diseases in the population over the age of 65. About 3% of the general population develops PD after the age of 65, whereas about 20% of all diagnosed dementia patients have DLB (McKeith, 2004; Dorsey et al., 2007). In both disorders movement and cognition, as well as mood and autonomic function are severely affected. Diagnosis to distinguish PD and DLB is very difficult, because of the overlap of symptoms and signs (Henchcliffe et al., 2011). In search for new biomarkers different factors were examined in the cerebrospinal fluid (CSF) of PD and DLB patients in comparison with Alzheimer disease (AD) patients and controls. Nagatsu and colleagues described elevated levels of pro-inflammatory cytokines such as Interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6, as well as decreased levels of neurotrophins such as brain-derived neurotrophic factor (BDNF) in the ventricular or lumbar CSF of PD patients (Nagatsu and Sawada, 2005). Moreover, elevated levels of the astroglial protein glial fibrillary acidic protein (GFAP), as well as the neurofilament light protein (NFL), which is used as a marker of neuronal damage, and AS were found in the CSF of PD patients (Constantinescu et al., 2010; Gao et al., 2014). Different studies could show that CSF AS levels are lower in PD and DLB compared to AD patients and controls (Mollenhauer et al., 2008; Wennstrom et al., 2013). Additionally, Wennstrom and colleagues described a decrease of neurosin, an AS degrading protease, in the CSF of patients with PD and DLB (Wennstrom et al., 2013). Furthermore, it was suggested that an altered ratio of phosphorylated AS CSF levels might serve as a biomarker to distinguish PD from controls (Foulds et al., 2011).

Both diseases feature LB consisting of aggregated AS as a hallmark lesion of degenerating neurons. PD patients show enhanced neuronal loss in the substantia nigra (SN) compared to DLB patients (Tsuboi and Dickson, 2005). Immunohistochemical studies showed a significantly higher amount of amyloid plaques in the putamen and caudate nucleus and more severe tau pathology in DLB compared to PD brains. Additionally, Jellinger and Attems suggested an elevated level of AS-lesions in DLB compared to PD (Jellinger and Attems, 2006). The accumulation of AS is increased with the occurrence of point mutations or duplications as well as triplications of the SNCA gene (Polymeropoulos et al., 1997; Singleton et al., 2003; Zarranz et al., 2004; Nishioka et al., 2006). Recent studies confirmed the association between PD and both SNCA single nucleotide polymorphisms (SNPs) and the H1 haplotype of microtubule-associated protein tau (MAPT) (Edwards et al., 2010; Elbaz et al., 2011; Trotta et al., 2012). Other genetic risk factors in the development of PD include leucine-rich repeat kinase 2 (LRRK2), the human leukocyte antigen (HLA) region and DJ-1 (Bonifati et al., 2003; Zimprich et al., 2004; Simon-Sanchez et al., 2009; Hamza et al., 2010). Genetic observations show also overlaps between PD and DLB. Mutations in the genes encoding AS (El-Agnaf et al., 1998; Ibanez et al., 2004), LRRK (Zimprich et al., 2004) and glucocerebrosidase (Goker-Alpan et al., 2006) were found in some DLB patients. However, also sporadic PD and DLB cases occur suggesting that genetic

predisposition and environmental factors might play together in the initiation of the disease.

Due to PD progression and the development of LB and LN, dopaminergic terminals in the striatum and dopaminergic neurons in SN get affected and finally degenerate (Fearnley and Lees, 1991; Jellinger, 2003; Savitt et al., 2006). An attempt to classify the stages of PD was undertaken in 2003 by Braak and colleagues: (1) The stages 1–2 affect the lower raphe nuclei, lower brainstem nuclei, including the dorsal motor nucleus of the vagus, the locus coeruleus as well as the olfactory system. (2) Thereafter, LB pathology affects the SN pars compacta (SNpc), intralaminar thalamic nuclei, hippocampal CA2 and amygdala (stages 3–4). (3) Finally, in stages 5–6 of PD LB pathology expands to the neocortex (Braak et al., 2002, 2003b). Yet, the suggested Braak stages were challenged for different reasons, one being the lack of a definite correlation between clinical course and neuronal loss (Calne et al., 1992; Parkkinen et al., 2005; Burke et al., 2008; Jellinger, 2009). Given that neuronal loss is not only dependent on the occurrence of AS aggregates, different other factors must have a major impact on disease progression in PD and DLB. Additionally to the AS positive aggregations in neurons and glia, it is suggested that reactive astrogliosis and microgliosis and therefore chronic inflammation play a crucial role in the initiation and progression of PD and DLB (Fellner et al., 2011; Halliday and Stevens, 2011). However, as microglia and astroglia might display beneficial and detrimental effects on neuronal cells, the complete involvement of glial activation in PD and DLB is contradictory and has not been elucidated yet (Knott et al., 2002; Hashioka et al., 2009).

AS-positive inclusions in oligodendroglial cells were also confirmed in PD brains (Wakabayashi et al., 2000). However, oligodendroglial involvement in neuronal ASP seems not so profound for disease initiation, but in late disease progression nonmyelinating oligodendroglial cells may play a more crucial role (Halliday and Stevens, 2011).

Microglia

[(11)C]-PK11195 Positron Emission Tomography (PET) imaging revealed profound microglial activation especially in pons, basal ganglia, frontal and temporal cortical regions of PD patients (Gerhard et al., 2006). Iannaccone et al. described microglial activation in SN and putamen in PD as revealed by PET (Iannaccone et al., 2013). Moreover, early-stage drug-naïve PD patients displayed enhanced microglial activation only in the midbrain which correlated with the loss of dopaminergic terminals in the striatum using [(11)C]-PK11195 PET and [(11)C]CFT binding the dopamine transporter (Ouchi et al., 2005). In a follow-up study, microgliosis also affected extra-striatal regions of the brain in these PD patients (Ouchi et al., 2009). In post-mortem PD brains, microglial activation has been identified in different brain regions, including SN, putamen, hippocampus, transentorhinal, cingulate and temporal cortex, as well as the limbic system (Imamura et al., 2003). However, profound activation of microglia in the SN, but no inflammatory changes such as microgliosis was reported in the putamen (Mirza et al., 2000). The inconsistent reports regarding microglial activation in different regions of PD brains might reflect the various stages of the disease and the individual differences of the disease pattern. In DLB patients, microglial activation in the SN and putamen was found. Further, comparisons of PD with DLB patients using the [(11)C]-PK11195 PET revealed additional microglial activation in several associative cortices in early DLB patients (Iannaccone et al., 2013). Moreover, reactive microglial cells were found to be more frequent around AS-positive LB in PD and also DLB (Mackenzie, 2000; Gerhard et al., 2003), and they were described in close proximity of dying neurons (Imamura et al., 2003).

In a recent study, post-mortem analyses of PD brains revealed region-specific variations of different microglial phenotypes in the SN and the hippocampus (Doorn et al., 2014). Furthermore, an enhanced expression of Toll-like receptor 2 (TLR2) on microglia in SN and hippocampus of incidental Lewy Body disease cases, which is thought to be a prodromal state of PD, and PD patients was described indicating a role for TLR2 and also microglia in the early stages of PD pathology (Doorn et al., 2014).

The hypothesis that microglial cells get activated by extracellular AS or astroglia even before neuronal loss occurs in SNpc has been proposed previously (Su et al., 2009; Halliday and Stevens, 2011). These data and the observations in PD patients support the presumption that microglial activation is involved in the initiation and progression of PD and DLB including the secretion of pro-inflammatory cytokines and ROS.

Especially in many cell culture studies a correlation between AS and microglial activation was described. The treatment of murine wild type (wt) microglia with aggregated AS in vitro led to the activation of antigen processing and presentation of antigen, inducing e.g. cytokine release (Harms et al., 2013). The PD-associated mutant forms of AS (A30P, E46K and A53T) extracellular applied, induced microglial activation in vitro and thus the release of pro-inflammatory cytokines including IL-6, IL-1β and TNF-α and the anti-inflammatory cytokine IL-10 as well as chemokines such as RANTES, monocyte chemotactic protein 1 (MCP-1), (C-X-C motif) ligand 10 (CXCL-10) and the macrophage inflammatory protein 1α (MIP-1α) respectively (Roodveldt et al., 2010). Moreover, it was also shown that AS treatment of human primary microglial cells causes a dose-dependent release of pro-inflammatory molecules (Klegeris et al., 2008; Su et al., 2008). Experiments with the microglial cell line BV2 revealed that neuron-derived wt and mutant AS increased the pro-inflammatory response, and primarily mutant AS induced an enhanced release of NO and inflammatory cytokines, such as IL-6 and TNF-α (Alvarez-Erviti et al., 2011; Rojanathammanee et al., 2011). Furthermore, it was demonstrated that especially recombinant C-terminally truncated AS induced an enhanced release of pro-inflammatory cytokines (e.g. IL-6, TNF-α) or chemokines (e.g. CXCL-1) and production of ROS (Fellner et al., 2013a). In another study it was also found that extracellular aggregated AS induced NADPH oxidase activation and ROS production in rat primary mesencephalic microglia which led to dopaminergic neuronal loss (Zhang et al., 2005). In addition, nitrated and aggregated AS increased oxidative stress, inflammation and neuronal cell death in mesencephalic neuron microglia co-cultures (Zhang et al., 2005; Reynolds et al., 2008). These studies highlight the impact of AS on microglial cells and suggest the importance of microglial overactivation on neuronal survival and therefore, in the progression of PD and DLB.

Another important feature of microglial cells is the clearance of debris, including dead cells and AS (del Rio-Hortega, 1932; Zhang et al., 2005; Park et al., 2008), thereby supporting neuronal survival. Different studies could show that microglial cells are capable of internalizing and degrading different forms of extracellular and cell-derived AS in vitro (Lee et al., 2008; Park et al., 2008; Stefanova et al., 2011; Fellner et al., 2013a). Recently, it was described that Toll-like receptors (TLRs) might play an important role in the recognition, internalization and activation of microglial cells. Particularly, the pattern-recognition receptors TLR2 and TLR4 were found to play a crucial role regarding AS phagocytosis and AS-dependent activation (Stefanova et al., 2011; Fellner et al., 2013a; Kim et al., 2013). Kim and colleagues suggested TLR2 as a fundamental link between recognition of neuron-released oligomeric AS, microglial activation and inflammatory responses (Kim et al., 2013). In vivo and in vitro studies showed that TLR4 ablation led to a disturbed clearance of overexpressed or recombinant AS by mouse microglia linked to aggravated nigral neurodegeneration (Stefanova et al., 2011; Fellner et al., 2013a). On the other hand TLR4 deficiency in microglia induced a decreased release of pro-inflammatory cytokines and ROS in response to AS exposure suggesting an involvement of TLR4 in inflammation and oxidative stress in ASP (Fellner et al., 2013a).

Studies performed in different animal models overexpressing AS highlight the link between AS or modified forms of AS and microglial

activation. The following studies were able to demonstrate the importance of microglial activation in PD and DLB and the impact of microglial activation on dopaminergic neuronal survival which indicates a leading role for microglial cells in disease initiation and progression. In a mouse model overexpressing wt AS under the rat tyrosine hydroxylase promoter premature microglial activation was detected (Su et al., 2008). Moreover, enhanced microglial activation was described in mice overexpressing mutant human AS (A53T and A30P homozygous double-mutants) under a neuronal promoter (Su et al., 2009). Interestingly, the intramuscular injections of fibrillized AS in mice expressing the mutant human A53T AS led to a widespread CNS AS-inclusion pathology with elevated levels of microgliosis in brain areas presenting AS pathology compared to control animals (Sacino et al., 2014). A correlation between the level of AS expression and cell numbers of microglia was found in a rat PD model with rAAV-based overexpression of AS in midbrain (Sanchez-Guajardo et al., 2010). Furthermore, in this rat model delayed but long lasting microglial activation upon dopaminergic degeneration was described. An early and transient activation of microglial cells was induced although no dopaminergic cell death occurred. In the rat model with rAAV-based overexpression of AS the progression of the neurodegeneration was associated with four different types of microglial activation (Sanchez-Guajardo et al., 2010). Moreover, it has been suggested that modified forms of AS, particularly nitrated species, may be released as a consequence of dopaminergic neurodegeneration and that these trigger subsequent immune responses (Theodore et al., 2008). Evidence has been provided that a PD mouse model with rAAV-based human AS overexpression triggered microglial activation and further stimulated the adaptive immune system (Theodore et al., 2008). Microglial cells lacking the Fc gamma receptor, which participates in the regulation of the immune response by binding antibodies, can be activated by AS, further leading to stress and therefore to NF-κB/p65 expression, the release of pro-inflammatory cytokines as well as neurodegeneration respectively. These results suggest an involvement of the humoral adaptive immune system in AS-mediated microglial activation and neuronal cell death (Cao et al., 2010). It was described that glucocorticoid receptors are decreased in the SN of PD patients and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated mice. Therefore, in a recent study the knock-out of glucocorticoid receptors, which are involved in the immune response and inflammation by binding cortisol and glucocorticoids that can be released during stress, on microglia in an MPTP mouse model has been characterized and revealed increased dopaminergic neurodegeneration in a model for parkinsonism (Ros-Bernal et al., 2011). In a different approach it was found that rats with induced inflammation in the midbrain and exposed to stress showed an increased microglial activation resulting in a higher rate of dopaminergic neuronal cell death, suggesting that stress might increase the progression of PD (de Pablos et al., 2014).

In conclusion, microglial activation is a very important mechanism in PD and DLB and seems to occur in correlation with the AS pathology in the CNS as seen in experimental models. However, the exact role of microglial cells has not been elucidated completely in these neurodegenerative diseases. On the one hand, microglial cells contribute to the clearance of debris, dead cells and AS thereby supporting neuronal survival. But on the other hand, microglial cells can get over activated in the course of the disease and might contribute to disease initiation and progression by enhancing neurodegeneration through elevated oxidative stress and inflammatory processes (Fig. 1).

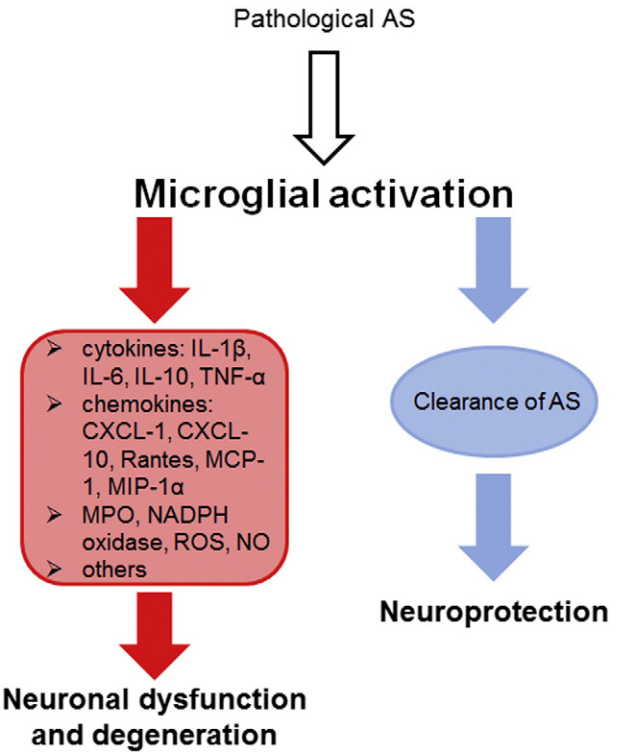

Fig. 1. Microglial involvement in α-synucleinopathies (ASP). Microglial cells can get activated by pathological α-synuclein (AS) (Su et al., 2009; Halliday and Stevens, 2011; Fellner et al., 2013a). Different sources of these pathological AS species were proposed including release by neurons to the extracellular space or cell-to-cell propagation (Braak et al., 2007; Lee et al., 2010). Activation of microglial cells induces an oxidative stress response including the release of reactive oxygen species (ROS) and nitric oxide (NO) as well as the production of NADPH oxidase. Furthermore, pro-inflammatory cytokines, such as Interleukin-1β (IL-1β), IL-6, and tumor necrosis factor α (TNF-α), and the anti-inflammatory cytokine IL-10 as well as pro-inflammatory chemokines including (C-X-C motif) ligand 1 (CXCL-1), CXCL-10, Rantes, monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 1α (MIP-1α) are released by activated microglial cells (Zhang et al., 2005; Su et al., 2008; Roodveldt et al., 2010; Alvarez-Erviti et al., 2011; Rojanathammanee et al., 2011; Fellner et al., 2013a). An involvement of Toll-like receptor 4 (TLR4), TLR2 and myeloperoxidase (MPO, key enzyme related to oxidative stress during inflammation) in inflammation and oxidative stress has been suggested (Stefanova et al., 2012a; Fellner et al., 2013a; Kim et al., 2013). Inflammation and oxidative stress mediated through microglial cells can further lead to neuronal dysfunction and cell death (Zhang et al., 2005; Reynolds et al., 2008). Thereby, dying neurons might release accumulated AS that stays in the extracellular space and again leads to the activation of microglial cells. This feedback loop might increase microglial activation leading to microgliosis. However, microglial cells are also able to phagocytose different forms of extracellular AS via TLR4 (Stefanova et al., 2011; Fellner et al., 2013a). This clearance mechanism might be even beneficial for neuronal survival. The different features displayed by microglial cells make it hard to categorize the role of microglial cells in ASP. Yet, the detrimental and beneficial functions of microglial cells suggest an involvement of microglial activation in the initiation and progression of ASP (Halliday and Stevens, 2011). However, further studies have to be conducted to understand the complete participation of microglial activation in ASP.

Astroglia

Astroglial cells may play an important role in PD and DLB, as they display AS-positive accumulations in the cytoplasm and an activated phenotype in these diseases. In DLB brains, processes of astroglia that were TNF-α and inducible nitric oxide synthase (iNOS)-positive were characterized around AS-positive irregular LB (Katsuse et al., 2003). Different reports exist on astroglial activation in PD. Astroglial activation in PD post-mortem brains has been described as not existing, mild or marked. Different studies proposed that no reactive astroglial cells occurred in the SN, putamen and pons of PD brains (Mirza et al., 2000; Song et al., 2009). Hirsch and colleagues conducted PD post-mortem examinations and revealed massive astrogliosis and loss of dopaminergic neurons in the SN (Hirsch et al., 2005), whereas Vila et al. suggested a mild extent of reactive astroglia (Vila et al., 2001). At this time point regarding the current literature, it is not possible to conclude if astroglial activation occurs in PD brains, suggesting a large variability in human PD patients. Moreover, many different factors could be responsible for the activation of astroglial cells in PD and also the different methods used for the analyses of astroglial activation in post-mortem brains could lead to these differing results. More neuropathological studies

are necessary to evaluate astroglial activation in PD brains, however experimental data favor astroglial activation triggered by AS, as discussed further in the text.

Furthermore, in PD post-mortem brains, it was described that interferon-γ (IFN-γ) activation might lead to a neurotoxic reaction indicated by an increased amount of IFN-γ receptor on astroglia (Hashioka et al., 2009, 2010). In addition, an astroglial-dependent upregulation of the expression of myeloperoxidase, a key enzyme related to oxidative stress during inflammation, in the ventral midbrain of PD patients was found (Choi et al., 2005). However, also the release of beneficial factors by human astroglial cells was reported, including e.g. the brain-derived neurotrophic factors in SN of PD brains (Knott et al., 2002). Moreover, enhanced levels of glutathione peroxidase (GPx), a crucial protective enzyme against oxidative damage, in association with astroglial proliferation were reported in the SN of PD brains (Damier et al., 1993). Thus, the enhanced GPx activity was associated with elevated levels of the astroglial marker GFAP (Mythri et al., 2011) indicating that astroglial cells might be crucial for the protection of neurons against oxidative stress.

It is well known that neuronal depositions of AS serve as a pathological hallmark of PD and DLB, however AS-positive protein aggregates were also described in human astroglial cells (Wakabayashi et al., 2000). Moreover, it was proposed that PD initiation starts inter alia with early nonfibrillized AS deposition in the cytoplasm of astroglia leading to the activation of microglial cells and neuronal cell death respectively (Halliday and Stevens, 2011) as supported in two independent in vivo studies described further in the following section (Gu et al., 2010; Schmidt et al., 2011). Furthermore, it is suggested that altered AS, released by axon terminals, is taken up by astroglial cells surrounding the synapses (Braak et al., 2007), supporting the hypothesis of neuron-to-astroglia propagation of AS characterized in a different study (Lee et al., 2010). Moreover, Song and colleagues discovered that only human protoplasmic astroglia showed an elevated cytoplasmic AS accumulation in PD, whereas no obvious changes were seen in fibrous astroglia (Song et al., 2009). A more detailed characterization would be beneficial to clarify if and why only certain astroglial subgroups are accumulating AS and the impact of astroglial AS aggregation on neuron and other glial cell survival as well as disease progression.

Various experimental studies were able to shed light on different aspects of incorporation of AS by astroglial cells resulting in the release of pro-inflammatory but also anti-inflammatory molecules. Lee and colleagues confirmed that direct transfer of overexpressed AS from human derived SH-SY5Y neurons to rat astroglial cells takes place and furthermore, induces an inflammatory response in ASP suggesting a prion-like spread of the disease (Lee et al., 2010). Furthermore, uptake of neuronal-derived or recombinant AS in a time-dependent manner by human astroglial cells leading to impaired mitochondrial function was reported recently (Lee et al., 2010; Braidy et al., 2013). In another cell culture study, primary murine astroglial cells incorporated different forms of recombinant AS (soluble, fibrillized and truncated) by a TLR4-independent mechanism suggesting an endocytotic pathway of uptake (Fellner et al., 2013a) as also proposed by Lee et al. (2010). The addition of extracellular AS to human astroglial cell cultures led to an accelerated production and release of pro-inflammatory cytokines including IL-6 and intercellular adhesion molecule 1 (ICAM-1), and in murine astroglia it induced the release of IL-6, TNF-α, the chemokine CXCL-1 and ROS (Klegeris et al., 2006; Fellner et al., 2013a). However, TLR4 ablation led to a decreased production of pro-inflammatory cytokines and ROS upon treatment with recombinant AS (Fellner et al., 2013a) indicating an important role for TLR4 in astroglial activation. Moreover, neuroprotective molecules might be released by astroglial cells when activated. It was found that hydrogen sulfide, a potential anti-inflammatory and neuroprotective agent, was downregulated upon astroglial activation indicating a possible role in neurodegeneration (Lee et al., 2009). In addition, the release of the glial cell line-derived neurotrophic factor (GDNF) by astroglia activated by selective dopaminergic neuronal damage was reported (Saavedra et al., 2006) suggesting a neuroprotective function for astroglial cells. Supporting the neuroprotective function of astroglia, the release of the antioxidant glutathione by astroglia upon dopaminergic injury was described (Sandhu et al., 2009).

Different in vivo studies could show that astroglial activation or astrogliosis in combination with the secretion of pro-inflammatory cytokines contribute to the progression of PD and eventually also DLB confirming human post-mortem data. An increased expression of INF-γ receptor on astroglia, as well as TNF-α immunoreactivity related to astroglia were characterized in MPTP-treated monkeys (Parkinsonian macaques), suggesting that astroglial overactivation could play a crucial role in the progression of PD (Barcia et al., 2011). Furthermore, microgliosis and fast progressing paralysis triggered by widespread astrogliosis was the main finding in an inducible mouse model expressing the mutant A53T AS variant in astroglial cells. In addition, the overexpression of the mutant AS in astroglial cells in mice altered the normal function of astrocytes leading to a reduced integrity of the blood–brain barrier, a decreased homeostasis of extracellular glutamate and inducing a significant loss of dopaminergic neurons in the midbrain and motor neurons in the spinal cord (Gu et al., 2010). In a different study, the PD mouse model overexpressing mutant AS presented with morphological and functional alterations in astroglial mitochondria and a deranged secretion of factors fundamental for neuronal differentiation (Schmidt et al., 2011). These findings suggest that the accumulation of AS in astroglial cells might be of importance in the initiation of PD as also suggested by Halliday and Stevens in 2011 (Halliday and Stevens, 2011). In a recent study, it was shown that PD mutant mice overexpressing human AS and the transglutaminase 2 (TG2) showed a promoted aggregation of AS and also an elevated astroglial activation compared to mice only overexpressing AS suggesting a significant contribution of TG2 to the accumulation of AS and pathogenesis of PD and other ASP and therefore a novel target regarding therapeutic approaches (Grosso et al., 2014).

In summary, the accumulation of AS in astroglial cells may function as a crucial factor in the initiation of PD (Halliday and Stevens, 2011). In addition, progression of disease might be driven by astroglial release of pro-inflammatory cytokines/chemokines, ROS and recruiting microglial cells (Fig. 2). However, astroglial cells might also support neuronal survival through the secretion and production of neurotrophic and antioxidant factors induced by neuronal cell death. As there are not enough data supporting AS-dependent astroglial neuroprotection, more research will be necessary to identify the role of astroglial cells in the initiation and progression of PD and DLB.

Oligodendroglia

It is suggested that oligodendroglial cells do not play a leading role in PD and DLB, however they might be involved in the late disease progression of these neuronal ASP (Halliday and Stevens, 2011). Oligodendroglial AS-positive inclusions are present in the brains of clinical overt PD cases, yet with a rather low distribution that correlates with the degree of neurodegeneration in SN (Arai et al., 1999; Wakabayashi et al., 2000). However, no inclusions in oligodendroglial cells of preclinical Lewy body disease have been described (Wakabayashi et al., 2000). In addition, the occurrence of oligodendroglial cells showing complement-activation has been shown in some brain regions of PD and DLB cases (Yamada et al., 1992). Poor and protracted myelination due to neurodegeneration in PD and DLB led to a higher susceptibility of oligodendroglial cells (Braak and Del Tredici, 2004). Moreover, a co-localization of AS-affected neurons with an enhanced number of nonmyelinating oligodendroglial cells has been described (Braak et al., 2003a; Braak and Del Tredici, 2009). These findings highlight that oligodendroglial cells might not play a crucial role in the initiation and progression of disease pathology in PD and DLB. However, the involvement of oligodendroglial cells in the beginning of neuronal ASP has not been fully elucidated by now.

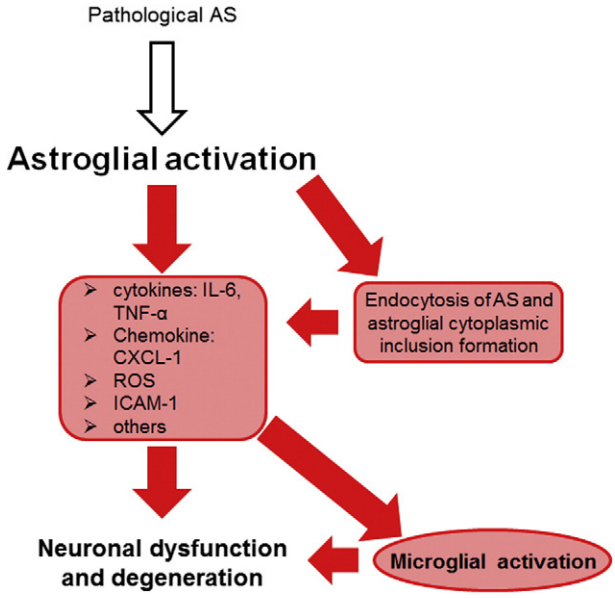

Fig. 2. Astroglial involvement in α-synucleinopathies (ASP). Astroglial cells are activated by different forms of α-synuclein (AS). Different sources of these pathological AS species were proposed including release by neurons or cell-to-cell propagation (Braak et al., 2007; Lee et al., 2010). Thereby AS-induced release of intercellular adhesion molecule 1 (ICAM-1), reactive oxygen species (ROS) and pro-inflammatory cytokines [e.g. Interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α)] was measured (Klegeris et al., 2006; Fellner et al., 2013a). An involvement of Toll-like receptor 4 (TLR4), myeloperoxidase (MPO, key enzyme related to oxidative stress during inflammation) and hydrogen sulfide in inflammation and oxidative stress has been suggested (Choi et al., 2005; Lee et al., 2009; Fellner et al., 2013a). Furthermore, various studies found that astroglial cells can internalize extracellular or neuron-derived AS via endocytosis (Lee et al., 2010; Braidy et al., 2013; Fellner et al., 2013a). As a consequence, AS-dependent inflammation and oxidative stress and the uptake and accumulation of AS might induce microglial activation as well as neuronal dysfunction and neurodegeneration (Lee et al., 2009; Gu et al., 2010). Astroglial cells are highly involved in inflammation and neuronal cell death. Some neuroprotective features were described for astroglial cells, yet not in an AS-dependent context (Saavedra et al., 2006; Sandhu et al., 2009). Further studies have to be completed to elucidate the role of AS-endocytosis and to understand the complete picture of astroglial involvement in ASP.

Glia in MSA

MSA is a progressive neurodegenerative disorder characterized by cerebellar ataxia, parkinsonism and autonomic dysfunction in any combination. MSA is categorized as a rare disease with a prevalence of about 4.4 per 100,000 cases (Schrag et al., 1999) and an onset of disease at about 52–57 years of age (Kollensperger et al., 2008; O'Sullivan et al., 2008). Furthermore, MSA is classified into 2 different clinical subtypes, being on the one hand MSA-P presenting levodopa-unresponsive Parkinsonism due to SND and on the other hand MSA-C mainly showing cerebellar ataxia reflecting olivopontocerebellar atrophy (Gilman et al., 1999; Wenning et al., 2004, 2013; Stefanova et al., 2009; Wenning and Stefanova, 2009; Jecmenica-Lukic et al., 2012). Both subtypes are characterized by progressive autonomic failure combined with degeneration in intermediolateral cell columns, Onuf's nucleus in the spinal cord and autonomic brainstem centers (Wenning et al., 1997; Ozawa et al., 2004). Furthermore, MSA is hallmarked by so called Papp–Lantos bodies or GCIs which are located in the cytoplasm of oligodendroglia. The inclusions are histopathologically characterized by aggregated and phosphorylated (Ser129) AS similar to LB and reside in the movement, balance, and autonomic control centers of the brain (Jellinger and Lantos, 2010). Due to these AS-positive GCIs and their broad distribution throughout the CNS, MSA is conceptualized as a primary oligodendrogliopathy (Wenning et al., 2008).

Polymorphisms within the SNCA gene might induce the development of MSA (Al-Chalabi et al., 2009; Scholz et al., 2009). However, in different studies and in a genome-wide association study the polymorphisms in the SNCA gene in MSA could not be confirmed (Ozawa et al., 1999; Yun et al., 2010; Ahmed et al., 2012). Impairment of *COQ2* and therefore inducing a functional impairment of the mitochondrial respiratory chain and enhanced vulnerability to oxidative stress were described in Japanese patients recently (Multiple-System Atrophy Research, C, 2013), yet no such correlation between loss-of-function of *COQ2* variants and increased risk of MSA in Europeans and Koreans was found (Jeon et al., 2014; Schottlaender et al., 2014; Sharma et al., 2014). These genetic data suggest that possible environmental risk factors and genetic predisposition might lead to MSA (Kuzdas-Wood et al., 2014). Furthermore, MSA is also characterized by microgliosis and astrogliosis in different affected regions of the brain (Gerhard et al., 2003; Ishizawa et al., 2004). However, the exact function of microglial and astroglial cells in MSA has not been completely elucidated to this date.

Similar to PD and DLB, biomarkers to distinguish MSA from other ASP and AD would increase the probability of an early diagnosis. A CSF study in MSA described a significant decrease of SNCA levels compared to controls and AD cases. However, no significant differences were determined between MSA and PD or DLB (Tateno et al., 2012). Furthermore, it was suggested that an altered ratio of phosphorylated AS CSF levels might serve as a biomarker to distinguish PD from MSA (Wang et al., 2012). Yet, others did not find significant differences between CSF samples of MSA patients and PD or DLB patients or controls (Mollenhauer et al., 2011; Shi et al., 2011; Aerts et al., 2012).

Microglia

Similar to PD and DLB microglial activation has been described repeatedly in MSA. Using [^{11}C](R)-PK11195 PET imaging microglial activation was detected in the dorsolateral prefrontal cortex, putamen, pallidum, pons and SN in MSA patients (Gerhard et al., 2003). Additionally, an upregulation of activated microglial cells was found to be associated with GCI pathology in motor-related structures (Ishizawa et al., 2004).

Various in vitro data on AS-dependent microglial activation are of equal relevance for PD, DLB and MSA. The appropriate studies are already discussed in the first part of the review "glia in PD and DLB" (microglia) and AS-dependent microglial activation might contribute similarly to the initiation and progression in MSA compared to PD and DLB.

Age-dependent, region-specific chronic microglial activation was also demonstrated in the transgenic MSA mouse model overexpressing AS under an oligodendroglial promoter (Stefanova et al., 2007). It was shown that early microglial activation in SNpc of MSA mice was associated with an elevated expression of iNOS. The increased expression of iNOS correlated with dopaminergic neuronal loss (Stefanova et al., 2007; Fellner et al., 2013b). Furthermore, in this transgenic MSA mouse model and in human MSA brains, an upregulation of TLR4 was demonstrated, suggesting a possible attempt to increase phagocytotic activity in these brains (Stefanova et al., 2007; Brudek et al., 2013). In vivo experiments in a double transgenic mouse with a knock-out of TLR4 and oligodendroglial overexpression of AS under the proteolipid protein (PLP) promoter showed an impaired phagocytotic activity similar to the in vitro experiments which presented with increased motor disability and enhanced loss of nigrostriatal dopaminergic neurons in the mouse. In addition, increased brain levels of AS were linked to disturbed TLR4-mediated microglial phagocytosis of AS. Conclusively, TLR4 upregulation in microglial cells is suggested as a natural mechanism to promote the clearance of extracellular AS in MSA (Stefanova et al., 2011). In a very recent study, myeloperoxidase (MPO), a key enzyme important for the production of ROS by phagocytotic cells, was found to be upregulated in microglia of MSA post-mortem brains, as well as in a MSA mouse model (Stefanova et al., 2012a). Inhibition of this enzyme in the MSA mouse model revealed a rescue of neurons, a reduced amount of intracellular AS and suppressed microgliosis

indicating that MPO might be involved in the AS-dependent activation of microglial cells as well as in the aggregation process of AS in MSA (Stefanova et al., 2012a). Microglial cells play an important role in the initiation and progression of MSA regarding phagocytosis, oxidative stress and inflammation. However, the complete mechanisms inducing AS-dependent microglial activation have not been elucidated to this date. The role of microglial activation might be equally relevant in MSA if compared to PD and DLB. Also in the context of MSA researchers have to resolve the complete involvement of microglia in the disease initiation and progression. Elucidation of the beneficial and detrimental functions of microglial activation on neuronal survival in ASP will remain a major challenge for research.

Astroglia

Astroglial activation is present in all ASP including MSA, and seems to play a role in disease initiation and progression respectively. In a Japanese study on the prognosis and progression of MSA, astrogliosis was demonstrated in the striatonigral, olivopontocerebellar and autonomic system, as well as in the corticospinal tract in MSA post-mortem brains (Watanabe et al., 2002). Furthermore, extensive astrogliosis has been confirmed in MSA brains (Ozawa et al., 2004; Jellinger et al., 2005) and moreover, AS-positive astroglial inclusions have been described in MSA brains, however in a decreased density compared to GCIs (Wenning and Jellinger, 2005). On the other hand Song et al. rejected the assumption that astroglial AS accumulation occurs in MSA cases (Song et al., 2009).

Different experimental data suggested that AS might be endocytosed by astroglial cells and furthermore, AS might induce astroglial activation, including the release of pro-inflammatory cytokines and increased oxidative stress (Lee et al., 2010; Fellner et al., 2013a). The summarized in vitro studies for PD and DLB on AS-dependent astroglial activation might be equally relevant for MSA (Fig. 2). Moreover, in different MSA mouse models a role for astrogliosis in MSA-like neurodegeneration has been indicated. Astrogliosis in various brain areas as well as changes in cytokine and chemokine expression levels were detected in a MSA mouse model overexpressing AS in oligodendroglial cells under the myelin basic protein promoter (Shults et al., 2005; Valera et al., 2014). Moreover, astrogliosis has been also described in another MSA mouse model overexpressing AS under the 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) promoter (Yazawa et al., 2005). Furthermore, astroglial activation accompanying neurodegeneration was reported in a different MSA mouse model overexpressing AS under the PLP promoter exposed to 3-nitropropionic acid (3-NP) (Stefanova et al., 2005a) (Table 1).

Astroglial activation seems to be an important factor in the pathogenesis of MSA. However, to this date there is still insufficient data on the specific facets of astroglial responses related to MSA strengthening the necessity for further studies to understand astrogliosis in the pathogenesis of MSA.

Oligodendroglia

As mentioned above the hallmark of MSA are GCIs which are mainly located in oligodendroglial cells characterized by their major component

Table 1
MSA in vivo models with AS pathology. In this table we summarize all in vivo models that were generated to imitate the main pathological hallmarks of MSA, including the accumulation of α-synuclein (AS) in oligodendroglial cells and neuronal loss. The replication of AS-positive accumulations in vivo was initiated by using various oligodendroglial specific promoters. Furthermore, different stressors [e.g. 3-nitropropionic acid (3-NP), inducing mitochondrial dysfunction] were tested to induce a full-blown MSA pathology, including wide-spread GCI-like inclusions, microglial and astroglial activation as well as neuronal loss. For a more detailed description of in vivo MSA models see Stefanova et al. (2005b), Ubhi et al. (2011), Fellner et al. (2013b), and Kuzdas-Wood et al. (2014)). This table is illustrative, but by no means complete. Additional abbreviations: SNpc — substantia nigra pars compacta, SND — striatonigral degeneration, OPCA — olivopontocerebellar atrophy.

	Promoter	Additional stressor	Outcome
PLP-AS MSA mouse model	Proteolipid protein promoter		Insoluble AS inclusions, hyperphosphorylation at Serine 129 (Kahle et al., 2002) Moderate dopaminergic neuronal loss in SNpc (Stefanova et al., 2005a) Microglial activation (Stefanova et al., 2005a) Cardiovascular autonomic and bladder dysfunction (Stemberger et al., 2010; Boudes et al., 2013; Kuzdas et al., 2013) Progressive motor phenotype (Stefanova et al., 2005a)
PLP-AS MSA mouse model	Proteolipid protein promoter	Mitochondrial inhibition by systemic 3-NP administration	Widespread AS inclusion pathology SND and OPCA Profound astrogliosis and microgliosis Profound motor and behavioral deficits (Stefanova et al., 2005a,2005b)
PLP-AS MSA mouse model	Proteolipid protein promoter	Systemic proteasome inhibition	Increased fibrillized AS in oligodendroglia Accelerated SND and OPCA Myelin disruption and demyelination Axonal degeneration Motor impairment (Stefanova et al., 2012b)
CNP-AS MSA mouse model	2′,3′-Cyclic nucleotide 3′-phosphodiesterase promoter		Accumulation of endogenous mouse AS in axons and axon terminals predominantly in the spinal cord Brain atrophy Axonal degeneration Astrogliosis Neuronal and oligodendroglial loss in the spinal cord Motor impairment (Yazawa et al., 2005)
MBP-AS MSA mouse model	Myelin basic protein promoter		Widespread insoluble AS inclusions, phosphorylation of AS at Serine 129 Loss of dopaminergic terminals in striatum Astrogliosis Reduced levels of several neurotrophic factors Impaired motor phenotype (Shults et al., 2005; Ubhi et al., 2010)
MBP-AS MSA mouse model	Myelin basic protein promoter	Mitochondrial inhibition by systemic 3-NP administration	Augmented neurodegeneration Altered levels of oxidized and nitrated AS (Ubhi et al., 2009)

namely AS (Papp et al., 1989; Kato and Nakamura, 1990; Kato et al., 1991; Papp and Lantos, 1992; Arima et al., 1998; Spillantini et al., 1998; Tu et al., 1998; Wakabayashi et al., 1998). The occurrence and distribution of these GCIs in MSA led to the assumption that oligodendroglial cells must play a leading role in the initiation and progression of MSA (Wenning and Quinn, 1994; Ozawa et al., 2001; Wenning et al., 2008). In a postmortem study a correlation of GCI occurrence and neurodegeneration was reported suggesting the important role of oligodendroglial dysfunction in MSA progression (Ozawa et al., 2004). GCIs have an extensive distribution throughout the CNS including areas such as pons, medulla, putamen, SN, cerebellum and preganglionic autonomic brain structures (Papp and Lantos, 1994; Nishie et al., 2004; Beyer and Ariza, 2007; Jellinger and Lantos, 2010).

It is still an ongoing debate whether oligodendroglial cells do actively incorporate and accumulate AS released by neurons or an elevated expression and slow degradation of AS in oligodendroglial cells occur and lead to GCI formation in MSA (Fellner et al., 2011; Ubhi et al., 2011). Different studies demonstrated the active release of AS by neurons into the extracellular space (Emmanouilidou et al., 2010; Hansen et al., 2011). In a very recent study it was shown that grafted OLN-93 rat oligodendroglial cells can incorporate extracellular injected AS and AS from host rat brain neurons overexpressing human AS in vivo (Reyes et al., 2014) strengthening the assumption of cell-to-cell propagation mechanisms in MSA. A concentration-, time-, dynamin GTPase-, clathrin- and dynasore-dependent uptake mechanism of different forms of AS in oligodendroglial cells has been described in vitro (Kisos et al., 2012; Konno et al., 2012; Reyes et al., 2014). Furthermore, a role for oxidative stress regarding the uptake, accumulation and oligomerization of AS by OLN-93 oligodendroglial cells was demonstrated (Pukass and Richter-Landsberg, 2014) (Table 2).

Moreover, Nakamura and colleagues found an ectopic expression of Rab5 and Rabaptin-5 in GCIs of human oligodendrocytes. The enhanced expression of Rab5 may trigger endocytosis and lead to abnormal endocytotic activity resulting in the incorporation of elevated levels of AS into oligodendroglial cells (Nakamura et al., 2000). These recent data indicate that AS can be incorporated by oligodendroglial cells from the extracellular space or neurons.

Different studies have shown lack of SNCA mRNA in oligodendroglial cells of control and MSA brains (Ozawa et al., 2001; Miller et al., 2005). In a very recent study Asi and colleagues isolated oligodendroglia by laser-capture microdissection from MSA and control cases to perform cellular expression analysis and suggested that oligodendroglial SNCA mRNA expression had a tendency of elevation in MSA oligodendroglia however without reaching statistical significance as compared to healthy controls. Furthermore, no significant differences were found regarding the SNCA mRNA expression between MSA and control cases in tissue extracts of various brain regions (Asi et al., 2014).

It is suggested that oligodendroglial cells are primarily injured in MSA (Wenning et al., 2008) which might offer an explanation for the pathological accumulation of AS in these cells. One mechanism could be a defective degradation of AS in oligodendroglia in MSA inducing an enhanced accumulation in these cells (Ebrahimi-Fakhari et al., 2011; Schwarz et al., 2012; Stefanova et al., 2012b). A role for macroautophagy regarding the degradation of AS in human oligodendroglial cells was proposed given that the inhibition of the proteasomal system led to an increase of autophagy markers in cultured oligodendroglial cells. However, elevated levels of autophagy markers did not enhance the degradation of AS. Moreover, the autophagy protein LC3 was found in GCIs suggesting a major role for macroautophagy in MSA (Schwarz et al., 2012). Recently, it was suggested that the ubiquitin–proteasome system might contribute to the aggregation of AS in MSA (Stefanova et al., 2012b). Inhibition of the ubiquitin–proteasome system revealed enhanced aggregation of fibrillized AS in the cytoplasm of oligodendroglia inducing myelin disruption and demyelination in a MSA mouse model (Stefanova et al., 2012b). The histone deacetylase 6 (HDAC6) plays an important role in the regulation of the formation of aggresomes (Kawaguchi et al., 2003) and aggresome degradation (Iwata et al., 2005) regarding the transport of ubiquitinated misfolded proteins, as well as the control of autophagy pathways (Pan et al., 2008). The cytoplasmic enzyme HDAC6 was identified by Miki and colleagues in 98% of GCIs in post-mortem MSA brains (Miki et al., 2011). This indicates that HDAC6 may promote the formation of fibrillized AS inclusions in oligodendroglial cells and suggests an important role for HDAC6 in MSA progression. Furthermore, AS seems to be a major factor in the initiation of the formation of protein inclusions, as in the absence of AS no accumulation of tau and αB-crystallin, further GCI components, occurs (Riedel et al., 2009), indicating that AS acts as a major initiator of GCI formation.

Additionally p25α, an oligodendroglial phosphoprotein (tubulin polymerization promoting protein) was shown to promote AS aggregation in vitro (Lindersson et al., 2005). Song and colleagues found that p25α is able to relocate to oligodendroglial soma in MSA cases, leading to an early oligodendroglial dysfunction and causing MSA initiation and GCI formation (Song et al., 2007). Furthermore, it was demonstrated that

Table 2
MSA in vitro models. As the mechanisms of glial cytoplasmic inclusions (GCI) formation have not been elucidated to date, efforts are made to identify probable pathways in the initiation of this neurodegenerative disease in vitro. This table is illustrative, but by no means complete, of the various in vitro experiments trying to figure out the pathogenesis of MSA.

	Cell type	Type of AS	Outcome
Overexpression in vitro models			
U373 (Stefanova et al., 2001, 2003)	Human astrocytoma cell line	Wild type C-terminally truncated	Increased susceptibility to oxidative stress
Primary rat oligos (Stefanova et al., 2001, 2003)	Primary rat oligodendroglia		Induction of apoptotic cell death TNF-α induced cell death
CG-4 (Tsuboi et al., 2005)	Rat oligodendroglial progenitor cells	Wild type	Increased cell death Impaired adhesion to fibronectin
OLN-t40-AS (Kragh et al., 2009, 2013)	Rat oligodendroglial cell line	Wild type	Cytotoxicity: co-expression of AS and p25α relies on death
Primary mouse oligos (Kragh et al., 2009, 2013)	Primary mouse oligodendroglia		domain receptor FAS and caspase 8 activation Co-expression leads to the disorganization of micro-tubular cytoskeleton
OLN-93 (Pukass and Richter-Landsberg, 2014)	Rat oligodendroglial cell line	Wild type mutant A53T	Membrane lipid modification and oxidative stress increase
Primary rat oligos (Pukass and Richter-Landsberg, 2014)	Primary rat oligodendroglia		aggregate formation
Uptake in vitro models			
KG1C, MO3.13 (Konno et al., 2012)	Human oligodendroglial cell lines	Mutant A30P Mutant A53T	Inhibition of dynamin GTPase lead to reduced AS uptake
Oli-neu, OLN-93 (Kisos et al., 2012)	Rat oligodendroglial cell line	Wild type mutant A53T	Uptake of neuron-derived or exogenously given AS
Primary rat oligos (Kisos et al., 2012)	Primary rat oligodendroglia		Clathrin-dependent uptake of AS
OLN-93 (Reyes et al., 2014)	Rat oligodendroglial cell line	Wild type (monomeric, oligomeric, fibrillized)	Dynamin/dynasore-mediated uptake of exogenously given AS Rare internalization of fibrillized AS

overexpression of p25α and AS in OLN-93 rat oligodendroglial cells led to disorganization of the microtubular cytoskeleton and the stimulation of the death domain receptor FAS as well as the activation of caspase-8 (Kragh et al., 2009, 2013). In addition, more recently an up-regulation of FAS receptor in MSA brains was found, indicating that oligodendroglial FAS ligand-mediated apoptosis might play an important role in MSA (Kragh et al., 2013). The inhibition of the phosphorylation of Ser129 of AS decreased the disorganization of the cytoskeleton and apoptosis suggesting that AS phosphorylation might be a key mechanism in the formation of AS oligomers and oligodendroglial cell death (Kragh et al., 2009).

Oligodendroglial cells featuring GCI pathology in vitro were found to have changed properties and they seem to be more vulnerable to different stimuli such as oxidative stress. In cell culture experiments, glial cells overexpressing AS were more susceptible to oxidative stress and TNF-α indicating that the higher oligodendroglial vulnerability to cytokines and stress plays an important role in MSA pathogenesis respectively (Stefanova et al., 2001, 2003). Moreover, a disturbed cell–extracellular matrix interaction was demonstrated by Tsuboi and colleagues who found that the overexpression of AS decreased the adhesion to fibronectin in CG-4 rat oligodendroglial cells (Tsuboi et al., 2005) (Table 2). In animal models the oligodendroglial overexpression of AS resulted in neuronal cell death in various regions of the brain such as SNpc, locus coeruleus, nucleus ambiguous, pedunculopontine tegmental nucleus, laterodorsal tegmental nucleus and Onuf's nucleus (Stefanova et al., 2005a; Stemberger et al., 2010; Kuzdas et al., 2013). Furthermore, increased myelin disruption and mitochondrial dysfunction were found in the MSA mouse models overexpressing AS under an oligodendroglial promoter (Shults et al., 2005; Yazawa et al., 2005; Stefanova et al., 2007). Oligodendroglial AS overexpression but not neuronal AS overexpression led to a significant decrease of glial cell-derived neurotrophic factor (GDNF) as was also found in brain samples of MSA patients (Ubhi et al., 2010) (Table 1).

These findings indicate that aggregation of AS in oligodendroglia may lead to alterations of neurotrophic factors, oxidative stress and neuroinflammation, which all together promote MSA pathogenesis.

In summary, oligodendroglial cells play a crucial role in the pathogenesis of MSA including their vulnerability to different stress responses, the loss of trophic support and demyelination that further lead to neurodegeneration. Moreover, the formation of AS inclusions in these cells seems to be a key mechanism in disease initiation and progression. Unfortunately, the precise molecular and cellular mechanisms underlying GCI formation and altered oligodendroglial function still need to be unraveled. Additionally, detailed investigations using cell culture and transgenic MSA models will greatly enhance the understanding of the MSA pathogenesis and might lead to the development of new therapeutic targets.

Conclusion

Glial cells play an important role in the initiation and progression of ASP due to their multifaceted responses to AS aggregation in various brain areas. Especially microglial and astroglial cells respond to various brain insults and get activated which includes the release of pro-inflammatory cytokines or chemokines, ROS and NO. This stress response can lead to neuronal dysfunction and degeneration due to the chronic microgliosis and astrogliosis in brains of ASP patients. Furthermore, oligodendroglial cells develop AS-positive inclusions in MSA inducing oligodendroglial dysfunction including demyelination and reduced trophic support. All these detrimental features of glial cells affect neuronal viability and survival. However, glial cells also display beneficial functions, i.e. phagocytosis of debris and AS by microglial cells and the release of neurotrophic factors upon dopaminergic cell death by astroglial cells. Therefore, it is impossible to categorize the role of glial cells in the initiation and progression of ASP. To understand the full contribution of glial cells to the pathogenesis of ASP further studies are needed. To clarify the development of the inclusion bodies in glial cells and neurons should be a main focus for researchers regarding ASP. If we understand the mechanisms of the accumulation and aggregation of AS and the impact of these inclusions on the progression of these diseases, interventions with new therapeutic targets would be possible. Furthermore, the understanding of these basic mechanisms might also enable us to develop new biomarkers that help clinicians to overcome limitations of early diagnoses of ASP. Moreover, an early diagnosis would increase the chance to halt disease progression maybe even with now available therapeutics that contain inflammation. However, in vitro and in vivo experiments feature different limitations that have to be taken into account. Generated in vitro data in mouse or rat cells have to be confirmed in human tissue and have to be transferred successfully into an in vivo system. Moreover, animal models, especially rodent models, replicate rarely all aspects of the human diseases and therefore gained results have to be carefully considered and conclusions regarding the human disease have to be drawn cautiously.

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References

Abeliovich, A., Schmitz, Y., Farinas, I., Choi-Lundberg, D., Ho, W.H., Castillo, P.E., Shinsky, N., Verdugo, J.M., Armanini, M., Ryan, A., Hynes, M., Phillips, H., Sulzer, D., Rosenthal, A., 2000. Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron 25 (1), 239–252.

Aerts, M.B., Esselink, R.A., Abdo, W.F., Bloem, B.R., Verbeek, M.M., 2012. CSF alpha-synuclein does not differentiate between parkinsonian disorders. Neurobiol. Aging 33 (2) (430 e431–433).

Ahmed, Z., Asi, Y.T., Sailer, A., Lees, A.J., Houlden, H., Revesz, T., Holton, J.L., 2012. The neuropathology, pathophysiology and genetics of multiple system atrophy. Neuropathol. Appl. Neurobiol. 38 (1), 4–24.

Al-Chalabi, A., Durr, A., Wood, N.W., Parkinson, M.H., Camuzat, A., Hulot, J.S., Morrison, K.E., Renton, A., Sussmuth, S.D., Landwehrmeyer, B.G., Ludolph, A., Agid, Y., Brice, A., Leigh, P.N., Bensimon, G., Group, N.G.S., 2009. Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. PLoS ONE 4 (9), e7114.

Alvarez-Erviti, L., Couch, Y., Richardson, J., Cooper, J.M., Wood, M.J., 2011. Alpha-synuclein release by neurons activates the inflammatory response in a microglial cell line. Neurosci. Res. 69 (4), 337–342.

Arai, T., Ueda, K., Ikeda, K., Akiyama, H., Haga, C., Kondo, H., Kuroki, N., Niizato, K., Iritani, S., Tsuchiya, K., 1999. Argyrophilic glial inclusions in the midbrain of patients with Parkinson's disease and diffuse Lewy body disease are immunopositive for NACP/alpha-synuclein. Neurosci. Lett. 259 (2), 83–86.

Arima, K., Ueda, K., Sunohara, N., Arakawa, K., Hirai, S., Nakamura, M., Tonozuka-Uehara, H., Kawai, M., 1998. NACP/alpha-synuclein immunoreactivity in fibrillary components of neuronal and oligodendroglial cytoplasmic inclusions in the pontine nuclei in multiple system atrophy. Acta Neuropathol. 96 (5), 439–444.

Asi, Y.T., Simpson, J.E., Heath, P.R., Wharton, S.B., Lees, A.J., Revesz, T., Houlden, H., Holton, J.L., 2014. Alpha-synuclein mRNA expression in oligodendrocytes in MSA. Glia 62 (6), 964–970.

Auluck, P.K., Caraveo, G., Lindquist, S., 2010. Alpha-synuclein: membrane interactions and toxicity in Parkinson's disease. Annu. Rev. Cell Dev. Biol. 26, 211–233.

Baba, M., Nakajo, S., Tu, P.H., Tomita, T., Nakaya, K., Lee, V.M., Trojanowski, J.Q., Iwatsubo, T., 1998. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. Am. J. Pathol. 152 (4), 879–884.

Balasingam, V., Dickson, K., Brade, A., Yong, V.W., 1996. Astrocyte reactivity in neonatal mice: apparent dependence on the presence of reactive microglia/macrophages. Glia 18 (1), 11–26.

Barcia, C., Ros, C.M., Annese, V., Gomez, A., Ros-Bernal, F., Aguado-Yera, D., Martinez-Pagan, M.E., de Pablos, V., Fernandez-Villalba, E., Herrero, M.T., 2011. IFN-gamma signaling, with the synergistic contribution of TNF-alpha, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. Cell Death Dis. 2, e142.

Beyer, K., Ariza, A., 2007. Protein aggregation mechanisms in synucleinopathies: commonalities and differences. J. Neuropathol. Exp. Neurol. 66 (11), 965–974.

Bonifati, V., Rizzu, P., van Baren, M.J., Schaap, O., Breedveld, G.J., Krieger, E., Dekker, M.C., Squitieri, F., Ibanez, P., Joosse, M., van Dongen, J.W., Vanacore, N., van Swieten, J.C., Brice, A., Meco, G., van Duijn, C.M., Oostra, B.A., Heutink, P., 2003. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 299 (5604), 256–259.

Boudes, M., Uvin, P., Pinto, S., Voets, T., Fowler, C.J., Wenning, G.K., De Ridder, D., Stefanova, N., 2013. Bladder dysfunction in a transgenic mouse model of multiple system atrophy. Mov. Disord. 28 (3), 347–355.
Braak, H., Del Tredici, K., 2004. Poor and protracted myelination as a contributory factor to neurodegenerative disorders. Neurobiol. Aging 25 (1), 19–23.
Braak, H., Del Tredici, K., 2009. Neuroanatomy and pathology of sporadic Parkinson's disease. Adv. Anat. Embryol. Cell Biol. 201, 1–119.
Braak, H., Del Tredici, K., Bratzke, H., Hamm-Clement, J., Sandmann-Keil, D., Rub, U., 2002. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J. Neurol. 249 (Suppl. 3) (III/1–5).
Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003a. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24 (2), 197–211.
Braak, H., Rub, U., Gai, W.P., Del Tredici, K., 2003b. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J. Neural Transm. 110 (5), 517–536.
Braak, H., Sastre, M., Del Tredici, K., 2007. Development of alpha-synuclein immunoreactive astrocytes in the forebrain parallels stages of intraneuronal pathology in sporadic Parkinson's disease. Acta Neuropathol. 114 (3), 231–241.
Braidy, N., Gai, W.P., Xu, Y.H., Sachdev, P., Guillemin, G.J., Jiang, X.M., Ballard, J.W., Horan, M.P., Fang, Z.M., Chong, B.H., Chan, D.K., 2013. Uptake and mitochondrial dysfunction of alpha-synuclein in human astrocytes, cortical neurons and fibroblasts. Transl. Neurodegener 2 (1), 20.
Brudek, T., Winge, K., Agander, T.K., Pakkenberg, B., 2013. Screening of Toll-like receptors expression in multiple system atrophy brains. Neurochem. Res. 38 (6), 1252–1259.
Burke, R.E., Dauer, W.T., Vonsattel, J.P., 2008. A critical evaluation of the Braak staging scheme for Parkinson's disease. Ann. Neurol. 64 (5), 485–491.
Cabin, D.E., Shimazu, K., Murphy, D., Cole, N.B., Gottschalk, W., McIlwain, K.L., Orrison, B., Chen, A., Ellis, C.E., Paylor, R., Lu, B., Nussbaum, R.L., 2002. Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha-synuclein. J. Neurosci. 22 (20), 8797–8807.
Calne, D.B., Snow, B.J., Lee, C., 1992. Criteria for diagnosing Parkinson's disease. Ann. Neurol. 32 (Suppl.), S125–S127.
Cao, S., Theodore, S., Standaert, D.G., 2010. Fcgamma receptors are required for NF-kappaB signaling, microglial activation and dopaminergic neurodegeneration in an AAV-synuclein mouse model of Parkinson's disease. Mol. Neurodegener. 5, 42.
Chandra, S., Gallardo, G., Fernandez-Chacon, R., Schluter, O.M., Sudhof, T.C., 2005. Alpha-synuclein cooperates with CSPalpha in preventing neurodegeneration. Cell 123 (3), 383–396.
Choi, D.K., Pennathur, S., Perier, C., Tieu, K., Teismann, P., Wu, D.C., Jackson-Lewis, V., Vila, M., Vonsattel, J.P., Heinecke, J.W., Przedborski, S., 2005. Ablation of the inflammatory enzyme myeloperoxidase mitigates features of Parkinson's disease in mice. J. Neurosci. 25 (28), 6594–6600.
Constantinescu, R., Rosengren, L., Johnels, B., Zetterberg, H., Holmberg, B., 2010. Consecutive analyses of cerebrospinal fluid axonal and glial markers in Parkinson's disease and atypical Parkinsonian disorders. Parkinsonism Relat. Disord. 16 (2), 142–145.
Damier, P., Hirsch, E.C., Zhang, P., Agid, Y., Javoy-Agid, F., 1993. Glutathione peroxidase, glial cells and Parkinson's disease. Neuroscience 52 (1), 1–6.
de Pablos, R.M., Herrera, A.J., Espinosa-Oliva, A.M., Sarmiento, M., Munoz, M.F., Machado, A., Venero, J.L., 2014. Chronic stress enhances microglia activation and exacerbates death of nigral dopaminergic neurons under conditions of inflammation. J. Neuroinflammation 11, 34.
Dean, J.M., Wang, X., Kaindl, A.M., Gressens, P., Fleiss, B., Hagberg, H., Mallard, C., 2010. Microglial MyD88 signaling regulates acute neuronal toxicity of LPS-stimulated microglia in vitro. Brain Behav. Immun. 24 (5), 776–783.
del Rio-Hortega, P., 1932. Microglia. Cytology and Cellular Pathology of the Nervous System. W. Penfield, New York, Hoeber (PB: 483–534).
Deshpande, M., Zheng, J., Borgmann, K., Persidsky, R., Wu, L., Schellpeper, C., Ghorpade, A., 2005. Role of activated astrocytes in neuronal damage: potential links to HIV-1-associated dementia. Neurotox. Res. 7 (3), 183–192.
Desplats, P., Lee, H.J., Bae, E.J., Patrick, C., Rockenstein, E., Crews, L., Spencer, B., Masliah, E., Lee, S.J., 2009. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proc. Natl. Acad. Sci. U. S. A. 106 (31), 13010–13015.
Dev, K.K., Hofele, K., Barbieri, S., Buchman, V.L., van der Putten, H., 2003. Part II: alpha-synuclein and its molecular pathophysiological role in neurodegenerative disease. Neuropharmacology 45 (1), 14–44.
Dickson, D.W., Lin, W., Liu, W.K., Yen, S.H., 1999. Multiple system atrophy: a sporadic synucleinopathy. Brain Pathol. 9 (4), 721–732.
Doorn, K.J., Moors, T., Drukarch, B., van de Berg, W., Lucassen, P.J., van Dam, A.M., 2014. Microglial phenotypes and toll-like receptor 2 in the substantia nigra and hippocampus of incidental Lewy body disease cases and Parkinson's disease patients. Acta Neuropathol. Commun. 2, 90.
Dorsey, E.R., Constantinescu, R., Thompson, J.P., Biglan, K.M., Holloway, R.G., Kieburtz, K., Marshall, F.J., Ravina, B.M., Schifitto, G., Siderowf, A., Tanner, C.M., 2007. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 68 (5), 384–386.
Ebrahimi-Fakhari, D., Cantuti-Castelvetri, I., Fan, Z., Rockenstein, E., Masliah, E., Hyman, B.T., McLean, P.J., Unni, V.K., 2011. Distinct roles in vivo for the ubiquitin–proteasome system and the autophagy–lysosomal pathway in the degradation of alpha-synuclein. J. Neurosci. 31 (41), 14508–14520.
Edwards, T.L., Scott, W.K., Almonte, C., Burt, A., Powell, E.H., Beecham, G.W., Wang, L., Zuchner, S., Konidari, I., Wang, G., Singer, C., Nahab, F., Scott, B., Stajich, J.M., Pericak-Vance, M., Haines, J., Vance, J.M., Martin, E.R., 2010. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. Ann. Hum. Genet. 74 (2), 97–109.
El-Agnaf, O.M., Curran, M.D., Wallace, A., Middleton, D., Murgatroyd, C., Curtis, A., Perry, R., Jaros, E., 1998. Mutation screening in exons 3 and 4 of alpha-synuclein in sporadic Parkinson's and sporadic and familial dementia with Lewy bodies cases. Neuroreport 9 (17), 3925–3927.
Elbaz, A., Ross, O.A., Ioannidis, J.P., Soto-Ortolaza, A.I., Moisan, F., Aasly, J., Annesi, G., Bozi, M., Brighina, L., Chartier-Harlin, M.C., Destee, A., Ferrarese, C., Ferraris, A., Gibson, J.M., Gispert, S., Hadjigeorgiou, G.M., Jasinska-Myga, B., Klein, C., Kruger, R., Lambert, J.C., Lohmann, K., van de Loo, S., Loriot, M.A., Lynch, T., Mellick, G.D., Mutez, E., Nilsson, C., Opala, G., Puschmann, A., Quattrone, A., Sharma, M., Silburn, P.A., Stefanis, L., Uitti, R.J., Valente, E.M., Vilarino-Guell, C., Wirdefeldt, K., Wszolek, Z.K., Xiromerisiou, G., Maraganore, D.M., Farrer, M.J., Genetic Epidemiology of Parkinson's Disease, C, 2011. Independent and joint effects of the MAPT and SNCA genes in Parkinson disease. Ann. Neurol. 69 (5), 778–792.
\Emmanouilidou, E., Melachroinou, K., Roumeliotis, T., Garbis, S.D., Ntzouni, M., Margaritis, L.H., Stefanis, L., Vekrellis, K., 2010. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. J. Neurosci. 30 (20), 6838–6851.
Eriksen, J.L., Dawson, T.M., Dickson, D.W., Petrucelli, L., 2003. Caught in the act: alpha-synuclein is the culprit in Parkinson's disease. Neuron 40 (3), 453–456.
Fearnley, J.M., Lees, A.J., 1991. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 (Pt 5), 2283–2301.
Fellner, L., Stefanova, N., 2013. The role of glia in alpha-synucleinopathies. Mol. Neurobiol. 47 (2), 575–586.
Fellner, L., Jellinger, K.A., Wenning, G.K., Stefanova, N., 2011. Glial dysfunction in the pathogenesis of alpha-synucleinopathies: emerging concepts. Acta Neuropathol. 121 (6), 675–693.
Fellner, L., Irschick, R., Schanda, K., Reindl, M., Klimaschewski, L., Poewe, W., Wenning, G.K., Stefanova, N., 2013a. Toll-like receptor 4 is required for alpha-synuclein dependent activation of microglia and astroglia. Glia 61 (3), 349–360.
Fellner, L., Wenning, G.K., Stefanova, N., 2013b. Models of multiple system atrophy. Curr. Top. Behav. Neurosci.
Foulds, P.G., Mitchell, J.D., Parker, A., Turner, R., Green, G., Diggle, P., Hasegawa, M., Taylor, M., Mann, D., Allsop, D., 2011. Phosphorylated alpha-synuclein can be detected in blood plasma and is potentially a useful biomarker for Parkinson's disease. FASEB J. 25 (12), 4127–4137.
Fujiwara, H., Hasegawa, M., Dohmae, N., Kawashima, A., Masliah, E., Goldberg, M.S., Shen, J., Takio, K., Iwatsubo, T., 2002. Alpha-synuclein is phosphorylated in synucleinopathy lesions. Nat. Cell Biol. 4 (2), 160–164.
Gao, L., Tang, H., Nie, K., Wang, L., Zhao, J., Gan, R., Huang, J., Zhu, R., Feng, S., Duan, Z., Zhang, Y., Wang, L., 2014. Cerebrospinal fluid alpha-synuclein as a biomarker for Parkinson's disease diagnosis: a systematic review and meta-analysis. Int. J. Neurosci.
Gerhard, A., Banati, R.B., Goerres, G.B., Cagnin, A., Myers, R., Gunn, R.N., Turkheimer, F., Good, C.D., Mathias, C.J., Quinn, N., Schwarz, J., Brooks, D.J., 2003. [^{11}C](R)-PK11195 PET imaging of microglial activation in multiple system atrophy. Neurology 61 (5), 686–689.
Gerhard, A., Trender-Gerhard, I., Turkheimer, F., Quinn, N.P., Bhatia, K.P., Brooks, D.J., 2006. In vivo imaging of microglial activation with [^{11}C](R)-PK11195 PET in progressive supranuclear palsy. Mov. Disord. 21 (1), 89–93.
Giasson, B.I., Duda, J.E., Murray, I.V., Chen, Q., Souza, J.M., Hurtig, H.I., Ischiropoulos, H., Trojanowski, J.Q., Lee, V.M., 2000. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. Science 290 (5493), 985–989.
Gilman, S., Low, P.A., Quinn, N., Albanese, A., Ben-Shlomo, Y., Fowler, C.J., Kaufmann, H., Klockgether, T., Lang, A.E., Lantos, P.L., Litvan, I., Mathias, C.J., Oliver, E., Robertson, D., Schatz, I., Wenning, G.K., 1999. Consensus statement on the diagnosis of multiple system atrophy. J. Neurol. Sci. 163 (1), 94–98.
Gitler, A.D., Shorter, J., 2007. Prime time for alpha-synuclein. J. Neurosci. 27 (10), 2433–2434.
Goedert, M., 2001. Parkinson's disease and other alpha-synucleinopathies. Clin. Chem. Lab. Med. 39 (4), 308–312.
Goker-Alpan, O., Giasson, B.I., Eblan, M.J., Nguyen, J., Hurtig, H.I., Lee, V.M., Trojanowski, J.Q., Sidransky, E., 2006. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. Neurology 67 (5), 908–910.
Grosso, H., Woo, J.M., Lee, K.W., Im, J.Y., Masliah, E., Junn, E., Mouradian, M.M., 2014. Transglutaminase 2 exacerbates alpha-synuclein toxicity in mice and yeast. FASEB J. 28 (10), 4280–4291.
Gu, X.L., Long, C.X., Sun, L., Xie, C., Lin, X., Cai, H., 2010. Astrocytic expression of Parkinson's disease-related A53T alpha-synuclein causes neurodegeneration in mice. Mol. Brain 3, 12.
Halliday, G.M., Stevens, C.H., 2011. Glia: initiators and progressors of pathology in Parkinson's disease. Mov. Disord. 26 (1), 6–17.
Hamza, T.H., Zabetian, C.P., Tenesa, A., Laederach, A., Montimurro, J., Yearout, D., Kay, D.M., Doheny, K.F., Paschall, J., Pugh, E., Kusel, V.I., Collura, R., Roberts, J., Griffith, A., Samii, A., Scott, W.K., Nutt, J., Factor, S.A., Payami, H., 2010. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat. Genet. 42 (9), 781–785.
Hanisch, U.K., 2002. Microglia as a source and target of cytokines. Glia 40 (2), 140–155.
Hansen, C., Angot, E., Bergstrom, A.L., Steiner, J.A., Pieri, L., Paul, G., Outeiro, T.F., Melki, R., Kallunki, P., Fog, K., Li, J.Y., Brundin, P., 2011. Alpha-synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. J. Clin. Invest. 121 (2), 715–725.
Harms, A.S., Cao, S., Rowse, A.L., Thome, A.D., Li, X., Mangieri, L.R., Cron, R.Q., Shacka, J.J., Raman, C., Standaert, D.G., 2013. MHCII is required for alpha-synuclein-induced activation of microglia, CD4 T cell proliferation, and dopaminergic neurodegeneration. J. Neurosci. 33 (23), 9592–9600.
Hasegawa, T., Matsuzaki, M., Takeda, A., Kikuchi, A., Akita, H., Perry, G., Smith, M.A., Itoyama, Y., 2004. Accelerated alpha-synuclein aggregation after differentiation of SH-SY5Y neuroblastoma cells. Brain Res. 1013 (1), 51–59.

Hashioka, S., Klegeris, A., Schwab, C., McGeer, P.L., 2009. Interferon-gamma-dependent cytotoxic activation of human astrocytes and astrocytoma cells. Neurobiol. Aging 30 (12), 1924–1935.
Hashioka, S., Klegeris, A., Schwab, C., Yu, S., McGeer, P.L., 2010. Differential expression of interferon-gamma receptor on human glial cells in vivo and in vitro. J. Neuroimmunol. 225 (1–2), 91–99.
Hauser, D.N., Cookson, M.R., 2011. Astrocytes in Parkinson's disease and DJ-1. J. Neurochem. 117 (3), 357–358.
Henchcliffe, C., Dodel, R., Beal, M.F., 2011. Biomarkers of Parkinson's disease and Dementia with Lewy bodies. Prog. Neurobiol. 95 (4), 601–613.
Hirsch, E.C., Hunot, S., Hartmann, A., 2005. Neuroinflammatory processes in Parkinson's disease. Parkinsonism Relat. Disord. 11 (Suppl. 1), S9–S15.
Iannaccone, S., Cerami, C., Alessio, M., Garibotto, V., Panzacchi, A., Olivieri, S., Gelsomino, G., Moresco, R.M., Perani, D., 2013. In vivo microglia activation in very early dementia with Lewy bodies, comparison with Parkinson's disease. Parkinsonism Relat. Disord. 19 (1), 47–52.
Ibanez, P., Bonnet, A.M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Durr, A., Brice, A., 2004. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet 364 (9440), 1169–1171.
Imamura, K., Hishikawa, N., Sawada, M., Nagatsu, T., Yoshida, M., Hashizume, Y., 2003. Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. Acta Neuropathol. 106 (6), 518–526.
Ishizawa, K., Komori, T., Sasaki, S., Arai, N., Mizutani, T., Hirose, T., 2004. Microglial activation parallels system degeneration in multiple system atrophy. J. Neuropathol. Exp. Neurol. 63 (1), 43–52.
Iwai, A., Masliah, E., Yoshimoto, M., Ge, N., Flanagan, L., de Silva, H.A., Kittel, A., Saitoh, T., 1995. The precursor protein of non-A beta component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. Neuron 14 (2), 467–475.
Iwata, A., Riley, B.E., Johnston, J.A., Kopito, R.R., 2005. HDAC6 and microtubules are required for autophagic degradation of aggregated huntingtin. J. Biol. Chem. 280 (48), 40282–40292.
Jecmenica-Lukic, M., Poewe, W., Tolosa, E., Wenning, G.K., 2012. Premotor signs and symptoms of multiple system atrophy. Lancet Neurol. 11 (4), 361–368.
Jellinger, K.A., 2003. Neuropathological spectrum of synucleinopathies. Mov. Disord. 18 (Suppl. 6), S2–S12.
Jellinger, K.A., 2009. A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. Biochim. Biophys. Acta 1792 (7), 730–740.
Jellinger, K.A., Attems, J., 2006. Does striatal pathology distinguish Parkinson disease with dementia and dementia with Lewy bodies? Acta Neuropathol. 112 (3), 253–260.
Jellinger, K.A., Lantos, P.L., 2010. Papp–Lantos inclusions and the pathogenesis of multiple system atrophy: an update. Acta Neuropathol. 119 (6), 657–667.
Jellinger, K.A., Seppi, K., Wenning, G.K., 2005. Grading of neuropathology in multiple system atrophy: proposal for a novel scale. Mov. Disord. 20 (Suppl. 12), S29–S36.
Jeon, B.S., Farrer, M.J., Bortnick, S.F., Korean Canadian Alliance on Parkinson's, D., Related, D, 2014. Mutant COQ2 in multiple-system atrophy. N. Engl. J. Med. 371 (1), 80.
Jurewicz, A., Matysiak, M., Tybor, K., Kilianek, L., Raine, C.S., Selmaj, K., 2005. Tumour necrosis factor-induced death of adult human oligodendrocytes is mediated by apoptosis inducing factor. Brain 128 (Pt 11), 2675–2688.
Kahle, P.J., Neumann, M., Ozmen, L., Muller, V., Jacobsen, H., Spooren, W., Fuss, B., Mallon, B., Macklin, W.B., Fujiwara, H., Hasegawa, M., Iwatsubo, T., Kretzschmar, H.A., Haass, C., 2002. Hyperphosphorylation and insolubility of alpha-synuclein in transgenic mouse oligodendrocytes. EMBO Rep. 3 (6), 583–588.
Kato, S., Nakamura, H., 1990. Cytoplasmic argyrophilic inclusions in neurons of pontine nuclei in patients with olivopontocerebellar atrophy: immunohistochemical and ultrastructural studies. Acta Neuropathol. 79 (6), 584–594.
Kato, S., Nakamura, H., Hirano, A., Ito, H., Llena, J.F., Yen, S.H., 1991. Argyrophilic ubiquitinated cytoplasmic inclusions of Leu-7-positive glial cells in olivopontocerebellar atrophy (multiple system atrophy). Acta Neuropathol. 82 (6), 488–493.
Katsuse, O., Iseki, E., Kosaka, K., 2003. Immunohistochemical study of the expression of cytokines and nitric oxide synthases in brains of patients with dementia with Lewy bodies. Neuropathology 23 (1), 9–15.
Kawaguchi, Y., Kovacs, J.J., McLaurin, A., Vance, J.M., Ito, A., Yao, T.P., 2003. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 115 (6), 727–738.
Kim, C., Ho, D.H., Suk, J.E., You, S., Michael, S., Kang, J., Joong Lee, S., Masliah, E., Hwang, D., Lee, H.J., Lee, S.J., 2013. Neuron-released oligomeric alpha-synuclein is an endogenous agonist of TLR2 for paracrine activation of microglia. Nat. Commun. 4, 1562.
Kisos, H., Pukass, K., Ben-Hur, T., Richter-Landsberg, C., Sharon, R., 2012. Increased neuronal alpha-synuclein pathology associates with its accumulation in oligodendrocytes in mice modeling alpha-synucleinopathies. PLoS ONE 7 (10), e46817.
Klegeris, A., Giasson, B.I., Zhang, H., Maguire, J., Pelech, S., McGeer, P.L., 2006. Alpha-synuclein and its disease-causing mutants induce ICAM-1 and IL-6 in human astrocytes and astrocytoma cells. FASEB J. 20 (12), 2000–2008.
Klegeris, A., Pelech, S., Giasson, B.I., Maguire, J., Zhang, H., McGeer, E.G., McGeer, P.L., 2008. Alpha-synuclein activates stress signaling protein kinases in THP-1 cells and microglia. Neurobiol. Aging 29 (5), 739–752.
Knott, C., Stern, G., Kingsbury, A., Welcher, A.A., Wilkin, G.P., 2002. Elevated glial brain-derived neurotrophic factor in Parkinson's diseased nigra. Parkinsonism Relat. Disord. 8 (5), 329–341.
Kollensperger, M., Geser, F., Seppi, K., Stampfer-Kountchev, M., Sawires, M., Scherfler, C., Boesch, S., Mueller, J., Koukouni, V., Quinn, N., Pellecchia, M.T., Barone, P., Schimke, N., Dodel, R., Oertel, W., Dupont, E., Ostergaard, K., Daniels, C., Deuschl, G., Gurevich, T., Giladi, N., Coelho, M., Sampaio, C., Nilsson, C., Widner, H., Sorbo, F.D., Albanese, A., Cardozo, A., Tolosa, E., Abele, M., Klockgether, T., Kamm, C., Gasser, T., Djaldetti, R., Colosimo, C., Meco, G., Schrag, A., Poewe, W., Wenning, G.K., European, M. S. A. S. G., 2008. Red flags for multiple system atrophy. Mov. Disord. 23 (8), 1093–1099.
Konno, M., Hasegawa, T., Baba, T., Miura, E., Sugeno, N., Kikuchi, A., Fiesel, F.C., Sasaki, T., Aoki, M., Itoyama, Y., Takeda, A., 2012. Suppression of dynamin GTPase decreases alpha-synuclein uptake by neuronal and oligodendroglial cells: a potent therapeutic target for synucleinopathy. Mol. Neurodegener. 7, 38.
Kragh, C.L., Lund, L.B., Febbraro, F., Hansen, H.D., Gai, W.P., El-Agnaf, O., Richter-Landsberg, C., Jensen, P.H., 2009. Alpha-synuclein aggregation and Ser-129 phosphorylation-dependent cell death in oligodendroglial cells. J. Biol. Chem. 284 (15), 10211–10222.
Kragh, C.L., Fillon, G., Gysbers, A., Hansen, H.D., Neumann, M., Richter-Landsberg, C., Haass, C., Zalc, B., Lubetzki, C., Gai, W.P., Halliday, G.M., Kahle, P.J., Jensen, P.H., 2013. FAS-dependent cell death in alpha-synuclein transgenic oligodendrocyte models of multiple system atrophy. PLoS ONE 8 (1), e55243.
Kuzdas, D., Stemberger, S., Gaburro, S., Stefanova, N., Singewald, N., Wenning, G.K., 2013. Oligodendroglial alpha-synucleinopathy and MSA-like cardiovascular autonomic failure: experimental evidence. Exp. Neurol. 247, 531–536.
Kuzdas-Wood, D., Stefanova, N., Jellinger, K.A., Seppi, K., Schlossmacher, M.G., Poewe, W., Wenning, G.K., 2014. Towards translational therapies for multiple system atrophy. Prog. Neurobiol. 118, 19–35.
Lee, H.J., Suk, J.E., Bae, E.J., Lee, J.H., Paik, S.R., Lee, S.J., 2008. Assembly-dependent endocytosis and clearance of extracellular alpha-synuclein. Int. J. Biochem. Cell Biol. 40 (9), 1835–1849.
Lee, M., Schwab, C., Yu, S., McGeer, E., McGeer, P.L., 2009. Astrocytes produce the antiinflammatory and neuroprotective agent hydrogen sulfide. Neurobiol. Aging 30 (10), 1523–1534.
Lee, H.J., Suk, J.E., Patrick, C., Bae, E.J., Cho, J.H., Rho, S., Hwang, D., Masliah, E., Lee, S.J., 2010. Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. J. Biol. Chem. 285 (12), 9262–9272.
Liberto, C.M., Albrecht, P.J., Herx, L.M., Yong, V.W., Levison, S.W., 2004. Pro-regenerative properties of cytokine-activated astrocytes. J. Neurochem. 89 (5), 1092–1100.
Lindersson, E., Lundvig, D., Petersen, C., Madsen, P., Nyengaard, J.R., Hojrup, P., Moos, T., Otzen, D., Gai, W.P., Blumbergs, P.C., Jensen, P.H., 2005. p25alpha stimulates alpha-synuclein aggregation and is co-localized with aggregated alpha-synuclein in alpha-synucleinopathies. J. Biol. Chem. 280 (7), 5703–5715.
Luk, K.C., Song, C., O'Brien, P., Stieber, A., Branch, J.R., Brunden, K.R., Trojanowski, J.Q., Lee, V.M., 2009. Exogenous alpha-synuclein fibrils seed the formation of Lewy body-like intracellular inclusions in cultured cells. Proc. Natl. Acad. Sci. U. S. A. 106 (47), 20051–20056.
Mackenzie, I.R., 2000. Activated microglia in dementia with Lewy bodies. Neurology 55 (1), 132–134.
Masuda-Suzukake, M., Nonaka, T., Hosokawa, M., Oikawa, T., Arai, T., Akiyama, H., Mann, D.M., Hasegawa, M., 2013. Prion-like spreading of pathological alpha-synuclein in brain. Brain 136 (Pt 4), 1128–1138.
McKeith, I., 2004. Dementia with Lewy bodies. Dialogues Clin. Neurosci. 6 (3), 333–341.
Miki, Y., Mori, F., Tanji, K., Kakita, A., Takahashi, H., Wakabayashi, K., 2011. Accumulation of histone deacetylase 6, an aggresome-related protein, is specific to Lewy bodies and glial cytoplasmic inclusions. Neuropathology 31 (6), 561–568.
Miller, D.W., Johnson, J.M., Solano, S.M., Hollingsworth, Z.R., Standaert, D.G., Young, A.B., 2005. Absence of alpha-synuclein mRNA expression in normal and multiple system atrophy oligodendroglia. J. Neural Transm. 112 (12), 1613–1624.
Mirza, B., Hadberg, H., Thomsen, P., Moos, T., 2000. The absence of reactive astrocytosis is indicative of a unique inflammatory process in Parkinson's disease. Neuroscience 95 (2), 425–432.
Mizuno, T., Kuno, R., Nitta, A., Nabeshima, T., Zhang, G., Kawanokuchi, J., Wang, J., Jin, S., Takeuchi, H., Suzumura, A., 2005. Protective effects of nicergoline against neuronal cell death induced by activated microglia and astrocytes. Brain Res. 1066 (1–2), 78–85.
Mollenhauer, B., Cullen, V., Kahn, I., Krastins, B., Outeiro, T.F., Pepivani, I., Ng, J., Schulz-Schaeffer, W., Kretzschmar, H.A., McLean, P.J., Trenkwalder, C., Sarracino, D.A., Vonsattel, J.P., Locascio, J.J., El-Agnaf, O.M., Schlossmacher, M.G., 2008. Direct quantification of CSF alpha-synuclein by ELISA and first cross-sectional study in patients with neurodegeneration. Exp. Neurol. 213 (2), 315–325.
Mollenhauer, B., Esselmann, H., Roeber, S., Schulz-Schaeffer, W.J., Trenkwalder, C., Bibl, M., Steinacker, P., Kretzschmar, H.A., Wiltfang, J., Otto, M., 2011. Different CSF beta-amyloid processing in Alzheimer's and Creutzfeldt–Jakob disease. J. Neural Transm. 118 (5), 691–697.
Multiple-System Atrophy Research, C, 2013. Mutations in COQ2 in familial and sporadic multiple-system atrophy. N. Engl. J. Med. 369 (3), 233–244.
Mythri, R.B., Venkateshappa, C., Harish, G., Mahadevan, A., Muthane, U.B., Yasha, T.C., Srinivas Bharath, M.M., Shankar, S.K., 2011. Evaluation of markers of oxidative stress, antioxidant function and astrocytic proliferation in the striatum and frontal cortex of Parkinson's disease brains. Neurochem. Res. 36 (8), 1452–1463.
Nagatsu, T., Sawada, M., 2005. Inflammatory process in Parkinson's disease: role for cytokines. Curr. Pharm. Des. 11 (8), 999–1016.
Nakamura, S., Kawamoto, Y., Nakano, S., Akiguchi, I., 2000. Expression of the endocytosis regulatory proteins Rab5 and Rabaptin-5 in glial cytoplasmic inclusions from brains with multiple system atrophy. Clin. Neuropathol. 19 (2), 51–56.
Neumann, H., Schweigreiter, R., Yamashita, T., Rosenkranz, K., Wekerle, H., Barde, Y.A., 2002. Tumor necrosis factor inhibits neurite outgrowth and branching of hippocampal neurons by a rho-dependent mechanism. J. Neurosci. 22 (3), 854–862.
Nimmerjahn, A., Kirchhoff, F., Helmchen, F., 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308 (5726), 1314–1318.
Nishie, M., Mori, F., Fujiwara, H., Hasegawa, M., Yoshimoto, M., Iwatsubo, T., Takahashi, H., Wakabayashi, K., 2004. Accumulation of phosphorylated alpha-synuclein in the brain and peripheral ganglia of patients with multiple system atrophy. Acta Neuropathol. 107 (4), 292–298.
Nishioka, K., Hayashi, S., Farrer, M.J., Singleton, A.B., Yoshino, H., Imai, H., Kitami, T., Sato, K., Kuroda, R., Tomiyama, H., Mizoguchi, K., Murata, M., Toda, T., Imoto, I., Inazawa, J.,

Mizuno, Y., Hattori, N., 2006. Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. Ann. Neurol. 59 (2), 298–309.
Norris, E.H., Giasson, B.I., Lee, V.M., 2004. Alpha-synuclein: normal function and role in neurodegenerative diseases. Curr. Top. Dev. Biol. 60, 17–54.
O'Sullivan, S.S., Massey, L.A., Williams, D.R., Silveira-Moriyama, L., Kempster, P.A., Holton, J.L., Revesz, T., Lees, A.J., 2008. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain 131 (Pt 5), 1362–1372.
Ouchi, Y., Yoshikawa, E., Sekine, Y., Futatsubashi, M., Kanno, T., Ogusu, T., Torizuka, T., 2005. Microglial activation and dopamine terminal loss in early Parkinson's disease. Ann. Neurol. 57 (2), 168–175.
Ouchi, Y., Yagi, S., Yokokura, M., Sakamoto, M., 2009. Neuroinflammation in the living brain of Parkinson's disease. Parkinsonism Relat. Disord. 15 (Suppl. 3), S200–S204.
Ozawa, T., Takano, H., Onodera, O., Kobayashi, H., Ikeuchi, T., Koide, R., Okuizumi, K., Shimohata, T., Wakabayashi, K., Takahashi, H., Tsuji, S., 1999. No mutation in the entire coding region of the alpha-synuclein gene in pathologically confirmed cases of multiple system atrophy. Neurosci. Lett. 270 (2), 110–112.
Ozawa, T., Okuizumi, K., Ikeuchi, T., Wakabayashi, K., Takahashi, H., Tsuji, S., 2001. Analysis of the expression level of alpha-synuclein mRNA using postmortem brain samples from pathologically confirmed cases of multiple system atrophy. Acta Neuropathol. 102 (2), 188–190.
Ozawa, T., Paviour, D., Quinn, N.P., Josephs, K.A., Sangha, H., Kilford, L., Healy, D.G., Wood, N.W., Lees, A.J., Holton, J.L., Revesz, T., 2004. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain 127 (Pt 12), 2657–2671.
Pan, T., Kondo, S., Zhu, W., Xie, W., Jankovic, J., Le, W., 2008. Neuroprotection of rapamycin in lactacystin-induced neurodegeneration via autophagy enhancement. Neurobiol. Dis. 32 (1), 16–25.
Papa, M., De Luca, C., Petta, F., Alberghina, L., Cirillo, G., 2014. Astrocyte–neuron interplay in maladaptive plasticity. Neurosci. Biobehav. Rev. 42, 35–54.
Papp, M.I., Lantos, P.L., 1992. Accumulation of tubular structures in oligodendroglial and neuronal cells as the basic alteration in multiple system atrophy. J. Neurol. Sci. 107 (2), 172–182.
Papp, M.I., Lantos, P.L., 1994. The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. Brain 117 (Pt 2), 235–243.
Papp, M.I., Kahn, J.E., Lantos, P.L., 1989. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome). J. Neurol. Sci. 94 (1–3), 79–100.
Park, J.Y., Paik, S.R., Jou, I., Park, S.M., 2008. Microglial phagocytosis is enhanced by monomeric alpha-synuclein, not aggregated alpha-synuclein: implications for Parkinson's disease. Glia 56 (11), 1215–1223.
Parkkinen, L., Kauppinen, T., Pirttila, T., Autere, J.M., Alafuzoff, I., 2005. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann. Neurol. 57 (1), 82–91.
Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I., Nussbaum, R.L., 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276 (5321), 2045–2047.
Pukass, K., Richter-Landsberg, C., 2014. Oxidative stress promotes uptake, accumulation, and oligomerization of extracellular alpha-synuclein in oligodendrocytes. J. Mol. Neurosci. 52 (3), 339–352.
Qian, L., Flood, P.M., 2008. Microglial cells and Parkinson's disease. Immunol. Res. 41 (3), 155–164.
Qian, L., Flood, P.M., Hong, J.S., 2010. Neuroinflammation is a key player in Parkinson's disease and a prime target for therapy. J. Neural Transm. 117 (8), 971–979.
Reyes, J.F., Rey, N.L., Bousset, L., Melki, R., Brundin, P., Angot, E., 2014. Alpha-synuclein transfers from neurons to oligodendrocytes. Glia 62 (3), 387–398.
Reynolds, A.D., Glanzer, J.G., Kadiu, I., Ricardo-Dukelow, M., Chaudhuri, A., Ciborowski, P., Cerny, R., Gelman, B., Thomas, M.P., Mosley, R.L., Gendelman, H.E., 2008. Nitrated alpha-synuclein-activated microglial profiling for Parkinson's disease. J. Neurochem. 104 (6), 1504–1525.
Riedel, M., Goldbaum, O., Richter-Landsberg, C., 2009. Alpha-synuclein promotes the recruitment of tau to protein inclusions in oligodendroglial cells: effects of oxidative and proteolytic stress. J. Mol. Neurosci. 39 (1–2), 226–234.
Rohl, C., Lucius, R., Sievers, J., 2007. The effect of activated microglia on astrogliosis parameters in astrocyte cultures. Brain Res. 1129 (1), 43–52.
Rojanathammanee, L., Murphy, E.J., Combs, C.K., 2011. Expression of mutant alpha-synuclein modulates microglial phenotype in vitro. J. Neuroinflammation 8, 44.
Roodveldt, C., Labrador-Garrido, A., Gonzalez-Rey, E., Fernandez-Montesinos, R., Caro, M., Lachaud, C.C., Waudby, C.A., Delgado, M., Dobson, C.M., Pozo, D., 2010. Glial innate immunity generated by non-aggregated alpha-synuclein in mouse: differences between wild-type and Parkinson's disease-linked mutants. PLoS ONE 5 (10), e13481.
Ros-Bernal, F., Hunot, S., Herrero, M.T., Parnadeau, S., Corvol, J.C., Lu, L., Alvarez-Fischer, D., Carrillo-de Sauvage, M.A., Saurini, F., Coussieu, C., Kinugawa, K., Prigent, A., Hoglinger, G., Hamon, M., Tronche, F., Hirsch, E.C., Vyas, S., 2011. Microglial glucocorticoid receptors play a pivotal role in regulating dopaminergic neurodegeneration in parkinsonism. Proc. Natl. Acad. Sci. U. S. A. 108 (16), 6632–6637.
Saavedra, A., Baltazar, G., Santos, P., Carvalho, C.M., Duarte, E.P., 2006. Selective injury to dopaminergic neurons up-regulates GDNF in substantia nigra postnatal cell cultures: role of neuron–glia crosstalk. Neurobiol. Dis. 23 (3), 533–542.
Sacino, A.N., Brooks, M., Thomas, M.A., McKinney, A.B., Lee, S., Regenhardt, R.W., McGarvey, N.H., Ayers, J.I., Notterpek, L., Borchelt, D.R., Golde, T.E., Giasson, B.I., 2014. Intramuscular injection of alpha-synuclein induces CNS alpha-synuclein pathology and a rapid-onset motor phenotype in transgenic mice. Proc. Natl. Acad. Sci. U. S. A. 111 (29), 10732–10737.
Sanchez-Guajardo, V., Febbraro, F., Kirik, D., Romero-Ramos, M., 2010. Microglia acquire distinct activation profiles depending on the degree of alpha-synuclein neuropathology in a rAAV based model of Parkinson's disease. PLoS ONE 5 (1), e8784.
Sandhu, J.K., Gardaneh, M., Iwasiow, R., Lanthier, P., Gangaraju, S., Ribecco-Lutkiewicz, M., Tremblay, R., Kiuchi, K., Sikorska, M., 2009. Astrocyte-secreted GDNF and glutathione antioxidant system protect neurons against 6OHDA cytotoxicity`. Neurobiol. Dis. 33 (3), 405–414.
Savitt, J.M., Dawson, V.L., Dawson, T.M., 2006. Diagnosis and treatment of Parkinson disease: molecules to medicine. J. Clin. Invest. 116 (7), 1744–1754.
Schmidt, S., Linnartz, B., Mendritzki, S., Sczepan, T., Lubbert, M., Stichel, C.C., Lubbert, H., 2011. Genetic mouse models for Parkinson's disease display severe pathology in glial cell mitochondria. Hum. Mol. Genet. 20 (6), 1197–1211.
Scholz, S.W., Houlden, H., Schulte, C., Sharma, M., Li, A., Berg, D., Melchers, A., Paudel, R., Gibbs, J.R., Simon-Sanchez, J., Paisan-Ruiz, C., Bras, J., Ding, J., Chen, H., Traynor, B.J., Arepalli, S., Zonozi, R.R., Revesz, T., Holton, J., Wood, N., Lees, A., Oertel, W., Wullner, U., Goldwurm, S., Pellecchia, M.T., Illig, T., Riess, O., Fernandez, H.H., Rodriguez, R.L., Okun, M.S., Poewe, W., Wenning, G.K., Hardy, J.A., Singleton, A.B., Del Sorbo, F., Schneider, S., Bhatia, K.P., Gasser, T., 2009. SNCA variants are associated with increased risk for multiple system atrophy. Ann. Neurol. 65 (5), 610–614.
Schottlaender, L.V., Houlden, H., Multiple-System Atrophy Brain Bank, C, 2014. Mutant COQ2 in multiple-system atrophy. N. Engl. J. Med. 371 (1), 81.
Schrag, A., Ben-Shlomo, Y., Quinn, N.P., 1999. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 354 (9192), 1771–1775.
Schwarz, L., Goldbaum, O., Bergmann, M., Probst-Cousin, S., Richter-Landsberg, C., 2012. Involvement of macroautophagy in multiple system atrophy and protein aggregate formation in oligodendrocytes. J. Mol. Neurosci. 47 (2), 256–266.
Sharma, M., Wenning, G., Kruger, R., European Multiple-System Atrophy Study G, 2014. Mutant COQ2 in multiple-system atrophy. N. Engl. J. Med. 371 (1), 80–81.
Shi, M., Bradner, J., Hancock, A.M., Chung, K.A., Quinn, J.F., Peskind, E.R., Galasko, D., Jankovic, J., Zabetian, C.P., Kim, H.M., Leverenz, J.B., Montine, T.J., Ginghina, C., Kang, U.J., Cain, K.C., Wang, Y., Aasly, J., Goldstein, D., Zhang, J., 2011. Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression. Ann. Neurol. 69 (3), 570–580.
Shults, C.W., Rockenstein, E., Crews, L., Adame, A., Mante, M., Larrea, G., Hashimoto, M., Song, D., Iwatsubo, T., Tsuboi, K., Masliah, E., 2005. Neurological and neurodegenerative alterations in a transgenic mouse model expressing human alpha-synuclein under oligodendrocyte promoter: implications for multiple system atrophy. J. Neurosci. 25 (46), 10689–10699.
Simon-Sanchez, J., Schulte, C., Bras, J.M., Sharma, M., Gibbs, J.R., Berg, D., Paisan-Ruiz, C., Lichtner, P., Scholz, S.W., Hernandez, D.G., Kruger, R., Federoff, M., Klein, C., Goate, A., Perlmutter, J., Bonin, M., Nalls, M.A., Illig, T., Gieger, C., Houlden, H., Steffens, M., Okun, M.S., Racette, B.A., Cookson, M.R., Foote, K.D., Fernandez, H.H., Traynor, B.J., Schreiber, S., Arepalli, S., Zonozi, R., Gwinn, K., van der Brug, M., Lopez, G., Chanock, S.J., Schatzkin, A., Park, Y., Hollenbeck, A., Gao, J., Huang, X., Wood, N.W., Lorenz, D., Deuschl, G., Chen, H., Riess, O., Hardy, J.A., Singleton, A.B., Gasser, T., 2009. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat. Genet. 41 (12), 1308–1312.
Singleton, A.B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R., Lincoln, S., Crawley, A., Hanson, M., Maraganore, D., Adler, C., Cookson, M.R., Muenter, M., Baptista, M., Miller, D., Blancato, J., Hardy, J., Gwinn-Hardy, K., 2003. Alpha-Synuclein locus triplication causes Parkinson's disease. Science 302 (5646), 841.
Song, Y.J., Lundvig, D.M., Huang, Y., Gai, W.P., Blumbergs, P.C., Hojrup, P., Otzen, D., Halliday, G.M., Jensen, P.H., 2007. p25alpha relocalizes in oligodendroglia from myelin to cytoplasmic inclusions in multiple system atrophy. Am. J. Pathol. 171 (4), 1291–1303.
Song, Y.J., Halliday, G.M., Holton, J.L., Lashley, T., O'Sullivan, S.S., McCann, H., Lees, A.J., Ozawa, T., Williams, D.R., Lockhart, P.J., Revesz, T.R., 2009. Degeneration in different parkinsonian syndromes relates to astrocyte type and astrocyte protein expression. J. Neuropathol. Exp. Neurol. 68 (10), 1073–1083.
Spillantini, M.G., Goedert, M., 2000. The alpha-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Ann. N. Y. Acad. Sci. 920, 16–27.
Spillantini, M.G., Crowther, R.A., Jakes, R., Cairns, N.J., Lantos, P.L., Goedert, M., 1998. Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. Neurosci. Lett. 251 (3), 205–208.
Stefanova, N., Klimaschewski, L., Poewe, W., Wenning, G.K., Reindl, M., 2001. Glial cell death induced by overexpression of alpha-synuclein. J. Neurosci. Res. 65 (5), 432–438.
Stefanova, N., Schanda, K., Klimaschewski, L., Poewe, W., Wenning, G.K., Reindl, M., 2003. Tumor necrosis factor-alpha-induced cell death in U373 cells overexpressing alpha-synuclein. J. Neurosci. Res. 73 (3), 334–340.
Stefanova, N., Reindl, M., Neumann, M., Haass, C., Poewe, W., Kahle, P.J., Wenning, G.K., 2005a. Oxidative stress in transgenic mice with oligodendroglial alpha-synuclein overexpression replicates the characteristic neuropathology of multiple system atrophy. Am. J. Pathol. 166 (3), 869–876.
Stefanova, N., Tison, F., Reindl, M., Poewe, W., Wenning, G.K., 2005b. Animal models of multiple system atrophy. Trends Neurosci. 28 (9), 501–506.
Stefanova, N., Reindl, M., Neumann, M., Kahle, P.J., Poewe, W., Wenning, G.K., 2007. Microglial activation mediates neurodegeneration related to oligodendroglial alpha-synucleinopathy: implications for multiple system atrophy. Mov. Disord. 22 (15), 2196–2203.
Stefanova, N., Bucke, P., Duerr, S., Wenning, G.K., 2009. Multiple system atrophy: an update. Lancet Neurol. 8 (12), 1172–1178.
Stefanova, N., Fellner, L., Reindl, M., Masliah, E., Poewe, W., Wenning, G.K., 2011. Toll-like receptor 4 promotes alpha-synuclein clearance and survival of nigral dopaminergic neurons. Am. J. Pathol. 179 (2), 954–963.

Stefanova, N., Georgievska, B., Eriksson, H., Poewe, W., Wenning, G.K., 2012a. Myeloperoxidase inhibition ameliorates multiple system atrophy-like degeneration in a transgenic mouse model. Neurotox. Res. 21 (4), 393–404.
Stefanova, N., Kaufmann, W.A., Humpel, C., Poewe, W., Wenning, G.K., 2012b. Systemic proteasome inhibition triggers neurodegeneration in a transgenic mouse model expressing human alpha-synuclein under oligodendrocyte promoter: implications for multiple system atrophy. Acta Neuropathol. 124 (1), 51–65.
Stemberger, S., Poewe, W., Wenning, G.K., Stefanova, N., 2010. Targeted overexpression of human alpha-synuclein in oligodendroglia induces lesions linked to MSA-like progressive autonomic failure. Exp. Neurol. 224 (2), 459–464.
Su, X., Maguire-Zeiss, K.A., Giuliano, R., Prifti, L., Venkatesh, K., Federoff, H.J., 2008. Synuclein activates microglia in a model of Parkinson's disease. Neurobiol. Aging 29 (11), 1690–1701.
Su, X., Federoff, H.J., Maguire-Zeiss, K.A., 2009. Mutant alpha-synuclein overexpression mediates early proinflammatory activity. Neurotox. Res. 16 (3), 238–254.
Tanji, K., Mori, F., Kakita, A., Takahashi, H., Wakabayashi, K., 2011. Alteration of autophagosomal proteins (LC3, GABARAP and GATE-16) in Lewy body disease. Neurobiol. Dis. 43 (3), 690–697.
Tateno, F., Sakakibara, R., Kawai, T., Kishi, M., Murano, T., 2012. Alpha-synuclein in the cerebrospinal fluid differentiates synucleinopathies (Parkinson Disease, dementia with Lewy bodies, multiple system atrophy) from Alzheimer disease. Alzheimer Dis. Assoc. Disord. 26 (3), 213–216.
Theodore, S., Cao, S., McLean, P.J., Standaert, D.G., 2008. 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. 67 (12), 1149–1158.
Thorburne, S.K., Juurlink, B.H., 1996. Low glutathione and high iron govern the susceptibility of oligodendroglial precursors to oxidative stress. J. Neurochem. 67 (3), 1014–1022.
Tofaris, G.K., Razzaq, A., Ghetti, B., Lilley, K.S., Spillantini, M.G., 2003. Ubiquitination of alpha-synuclein in Lewy bodies is a pathological event not associated with impairment of proteasome function. J. Biol. Chem. 278 (45), 44405–44411.
Trotta, L., Guella, I., Solda, G., Sironi, F., Tesei, S., Canesi, M., Pezzoli, G., Goldwurm, S., Duga, S., Asselta, R., 2012. SNCA and MAPT genes: independent and joint effects in Parkinson disease in the Italian population. Parkinsonism Relat. Disord. 18 (3), 257–262.
Tsuboi, Y., Dickson, D.W., 2005. Dementia with Lewy bodies and Parkinson's disease with dementia: are they different? Parkinsonism Relat. Disord. 11 (Suppl. 1), S47–S51.
Tsuboi, K., Grzesiak, J.J., Bouvet, M., Hashimoto, M., Masliah, E., Shults, C.W., 2005. Alpha-synuclein overexpression in oligodendrocytic cells results in impaired adhesion to fibronectin and cell death. Mol. Cell. Neurosci. 29 (2), 259–268.
Tu, P.H., Galvin, J.E., Baba, M., Giasson, B., Tomita, T., Leight, S., Nakajo, S., Iwatsubo, T., Trojanowski, J.Q., Lee, V.M., 1998. Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble alpha-synuclein. Ann. Neurol. 44 (3), 415–422.
Ubhi, K., Lee, P.H., Adame, A., Inglis, C., Mante, M., Rockenstein, E., Stefanova, N., Wenning, G.K., Masliah, E., 2009. Mitochondrial inhibitor 3-nitroproprionic acid enhances oxidative modification of alpha-synuclein in a transgenic mouse model of multiple system atrophy. J. Neurosci. Res. 87 (12), 2728–2739.
Ubhi, K., Rockenstein, E., Mante, M., Inglis, C., Adame, A., Patrick, C., Whitney, K., Masliah, E., 2010. Neurodegeneration in a transgenic mouse model of multiple system atrophy is associated with altered expression of oligodendroglial-derived neurotrophic factors. J. Neurosci. 30 (18), 6236–6246.
Ubhi, K., Low, P., Masliah, E., 2011. Multiple system atrophy: a clinical and neuropathological perspective. Trends Neurosci. 34 (11), 581–590.
Uversky, V.N., 2008. Alpha-synuclein misfolding and neurodegenerative diseases. Curr. Protein Pept. Sci. 9 (5), 507–540.
Valera, E., Ubhi, K., Mante, M., Rockenstein, E., Masliah, E., 2014. Antidepressants reduce neuroinflammatory responses and astroglial alpha-synuclein accumulation in a transgenic mouse model of multiple system atrophy. Glia 62 (2), 317–337.
van Rossum, D., Hanisch, U.K., 2004. Microglia. Metab. Brain Dis. 19 (3–4), 393–411.
Vila, M., Jackson-Lewis, V., Guegan, C., Wu, D.C., Teismann, P., Choi, D.K., Tieu, K., Przedborski, S., 2001. The role of glial cells in Parkinson's disease. Curr. Opin. Neurol. 14 (4), 483–489.
Vilar, M., Chou, H.T., Luhrs, T., Maji, S.K., Riek-Loher, D., Verel, R., Manning, G., Stahlberg, H., Riek, R., 2008. The fold of alpha-synuclein fibrils. Proc. Natl. Acad. Sci. U. S. A. 105 (25), 8637–8642.
Wakabayashi, K., Hayashi, S., Kakita, A., Yamada, M., Toyoshima, Y., Yoshimoto, M., Takahashi, H., 1998. Accumulation of alpha-synuclein/NACP is a cytopathological feature common to Lewy body disease and multiple system atrophy. Acta Neuropathol. 96 (5), 445–452.
Wakabayashi, K., Hayashi, S., Yoshimoto, M., Kudo, H., Takahashi, H., 2000. NACP/alpha-synuclein-positive filamentous inclusions in astrocytes and oligodendrocytes of Parkinson's disease brains. Acta Neuropathol. 99 (1), 14–20.
Wang, Y., Shi, M., Chung, K.A., Zabetian, C.P., Leverenz, J.B., Berg, D., Srulijes, K., Trojanowski, J.Q., Lee, V.M., Siderowf, A.D., Hurtig, H., Litvan, I., Schiess, M.C., Peskind, E.R., Masuda, M., Hasegawa, M., Lin, X., Pan, C., Galasko, D., Goldstein, D.S., Jensen, P.H., Yang, H., Cain, K.C., Zhang, J., 2012. Phosphorylated alpha-synuclein in Parkinson's disease. Sci. Transl. Med. 4 (121) (121ra120).
Watanabe, H., Saito, Y., Terao, S., Ando, T., Kachi, T., Mukai, E., Aiba, I., Abe, Y., Tamakoshi, A., Doyu, M., Hirayama, M., Sobue, G., 2002. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 125 (Pt 5), 1070–1083.
Watts, J.C., Giles, K., Oehler, A., Middleton, L., Dexter, D.T., Gentleman, S.M., DeArmond, S.J., Prusiner, S.B., 2013. Transmission of multiple system atrophy prions to transgenic mice. Proc. Natl. Acad. Sci. U. S. A. 110 (48), 19555–19560.
Webster, H., Astrom, K.E., 2009. Gliogenesis: historical perspectives, 1839–1985. Adv. Anat. Embryol. Cell Biol. 202, 1–109.
Wenning, G.K., Jellinger, K.A., 2005. The role of alpha-synuclein in the pathogenesis of multiple system atrophy. Acta Neuropathol. 109 (2), 129–140.
Wenning, G., Quinn, N., 1994. Are Lewy bodies non-specific epiphenomena of nigral damage? Mov. Disord. 9 (3), 378–379.
Wenning, G.K., Stefanova, N., 2009. Recent developments in multiple system atrophy. J. Neurol. 256 (11), 1791–1808.
Wenning, G.K., Tison, F., Ben Shlomo, Y., Daniel, S.E., Quinn, N.P., 1997. Multiple system atrophy: a review of 203 pathologically proven cases. Mov. Disord. 12 (2), 133–147.
Wenning, G.K., Colosimo, C., Geser, F., Poewe, W., 2004. Multiple system atrophy. Lancet Neurol. 3 (2), 93–103.
Wenning, G.K., Stefanova, N., Jellinger, K.A., Poewe, W., Schlossmacher, M.G., 2008. Multiple system atrophy: a primary oligodendrogliopathy. Ann. Neurol. 64 (3), 239–246.
Wenning, G.K., Geser, F., Krismer, F., Seppi, K., Duerr, S., Boesch, S., Kollensperger, M., Goebel, G., Pfeiffer, K.P., Barone, P., Pellecchia, M.T., Quinn, N.P., Koukouni, V., Fowler, C.J., Schrag, A., Mathias, C.J., Giladi, N., Gurevich, T., Dupont, E., Ostergaard, K., Nilsson, C.F., Widner, H., Oertel, W., Eggert, K.M., Albanese, A., del Sorbo, F., Tolosa, E., Cardozo, A., Deuschl, G., Hellriegel, H., Klockgether, T., Dodel, R., Sampaio, C., Coelho, M., Djaldetti, R., Melamed, E., Gasser, T., Kamm, C., Meco, G., Colosimo, C., Rascol, O., Meissner, W.G., Tison, F., Poewe, W., European Multiple System Atrophy Study, G., 2013. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 12 (3), 264–274.
Wennstrom, M., Surova, Y., Hall, S., Nilsson, C., Minthon, L., Bostrom, F., Hansson, O., Nielsen, H.M., 2013. Low CSF levels of both alpha-synuclein and the alpha-synuclein cleaving enzyme neurosin in patients with synucleinopathy. PLoS ONE 8 (1), e53250.
Wilhelmsson, U., Bushong, E.A., Price, D.L., Smarr, B.L., Phung, V., Terada, M., Ellisman, M.H., Pekny, M., 2006. Redefining the concept of reactive astrocytes as cells that remain within their unique domains upon reaction to injury. Proc. Natl. Acad. Sci. U. S. A. 103 (46), 17513–17518.
Winslow, A.R., Chen, C.W., Corrochano, S., Acevedo-Arozena, A., Gordon, D.E., Peden, A.A., Lichtenberg, M., Menzies, F.M., Ravikumar, B., Imarisio, S., Brown, S., O'Kane, C.J., Rubinsztein, D.C., 2010. Alpha-Synuclein impairs macroautophagy: implications for Parkinson's disease. J. Cell Biol. 190 (6), 1023–1037.
Xilouri, M., Stefanis, L., 2011. Autophagic pathways in Parkinson disease and related disorders. Expert Rev. Mol. Med. 13, e8.
Yamada, T., McGeer, P.L., McGeer, E.G., 1992. Lewy bodies in Parkinson's disease are recognized by antibodies to complement proteins. Acta Neuropathol. 84 (1), 100–104.
Yazawa, I., Giasson, B.I., Sasaki, R., Zhang, B., Joyce, S., Uryu, K., Trojanowski, J.Q., Lee, V.M., 2005. Mouse model of multiple system atrophy alpha-synuclein expression in oligodendrocytes causes glial and neuronal degeneration. Neuron 45 (6), 847–859.
Yun, J.Y., Lee, W.W., Lee, J.Y., Kim, H.J., Park, S.S., Jeon, B.S., 2010. SNCA variants and multiple system atrophy. Ann. Neurol. 67 (4), 554–555.
Zarranz, J.J., Alegre, J., Gomez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atares, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Munoz, D.G., de Yebenes, J.G., 2004. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann. Neurol. 55 (2), 164–173.
Zhang, W., Wang, T., Pei, Z., Miller, D.S., Wu, X., Block, M.L., Wilson, B., Zhang, W., Zhou, Y., Hong, J.S., Zhang, J., 2005. Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. FASEB J. 19 (6), 533–542.
Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R.J., Calne, D.B., Stoessl, A.J., Pfeiffer, R.F., Patenge, N., Carbajal, I.C., Vieregge, P., Asmus, F., Muller-Myhsok, B., Dickson, D.W., Meitinger, T., Strom, T.M., Wszolek, Z.K., Gasser, T., 2004. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 44 (4), 601–607.