Review

Glia and alpha-synuclein in neurodegeneration: A complex interaction

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A B S T R A C T

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 astroglia 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.

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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) (Fujisawa 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., 2000).

Contents

Introduction ................................................................. 262
Glia in PD and DLB .......................................................... 263
Microglia ........................................................................ 264
Astroglia ........................................................................ 265
Oligodendroglia ............................................................... 266
Glia in MSA ................................................................. 267
Microglia ........................................................................ 267
Astroglia ........................................................................ 268
Oligodendroglia ............................................................... 268
Conclusion .................................................................... 270
Acknowledgments ............................................................ 270
References ...................................................................... 270

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2004; Song et al., 2009; Fellner et al., 2011; Fellner and Stefanova, 2013). Furthermore, PD and DBL show AS deposits 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; Gitter 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 DBL 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 (Gissone 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).

Glia in PD and DBL

PD and DBL 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 DBL (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 DBL 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 DBL 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 DBL 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 DBL (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 DBL 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 DBL compared to PD brains. Additionally, Jellinger and Attems suggested an elevated level of AS lesions in DBL 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; Nishiooka 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 DBL. 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 DBL patients. However, also sporadic PD and DBL 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 presentation and processing 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 (Álvarez-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, it has been suggested that modified forms of AS, particularly nitrate 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).

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).

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, monocysteine proteotatic 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-Enrivi et al., 2011; Rojanathammaree 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; Reyesolos et al., 2008). Thereby, dying neurons might release accumulated AS that stays in the extracellular space and gain 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.
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 (Knot 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-SYSY 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 or 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 oligodendroglial cells in the beginning of neuronal ASP has not been fully elucidated by now.
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 hallmarkied by so-called Papp bodies or GCIs which are located in the cytoplasm of oligodendroglia. The inclusions are histopathologically characterized by aggregated proteins, including the PHFs in MSA-P, and phosphorylated (Ser129) α-Synuclein in MSA-C (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 (Kudzhas-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 α-Synuclein 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 [11C](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 α-Synuclein 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 phagocytic 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 phagocytic 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-nitropipionic acid (3-NP) (Stefanova et al., 2005a) (Table 1).

Astrogliosis 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.

| 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) Wide spread AS inclusion pathology SND and OPCA Profound astrogliosis and microgliosis Profound motor and behavioral deficits (Stefanova et al., 2005a, 2005b) Increased fibrillized AS in oligodendroglia Myelin disruption and demyelination Axonal degeneration Motor impairment |
| 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 Astroglial 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 Astroglial Reduced levels of several neurotrophic factors Impaired motor phenotype (Shults et al., 2005; Ubhi et al., 2010) Augmented neurodegeneration Altered levels of oxidized and nitrosated AS (Ubhi et al., 2009) |

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-nitropipionic 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.
endocytotic activity resulting in the incorporation of elevated levels of Rab5 and Rabaptin-5 in GCIs of human oligodendrocytes. The enhanced cells of control and MSA brains (Ozawa et al., 2001; Miller et al., 2005). from the extracellular space or neurons. data indicate that AS can be incorporated by oligodendroglial cells cellular expression analysis and suggested that oligodendroglial SNCA laser-capture microdissection from MSA and control cases to perform In a very recent study Asi and colleagues isolated oligodendroglia by (Pukass and Richter-Landsberg, 2014)( Table 2). quantization of AS by OLN-93 oligodendroglial cells was demonstrated (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-, dynamic 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 endocytic 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 p25, an oligodendroglial phosphoprotein (tubulin polymerization promoting protein) was shown to promote AS aggregation in vitro (Lindersson et al., 2005). Song and colleagues found that p25 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

| Cell type | Type of AS | Outcome |
|----------|------------|---------|
| U373     | Human astrocytoma cell line | Wild type C-terminally truncated |
| CG-4     | Rat oligodendroglial progenitor cells | Wild type |
| OLN-140-AS | Rat oligodendroglial cells | Wild type |
| OLN-93   | Rat oligodendroglial cell line | Wild type mutant A53T |
| Uptake in vitro models | | |
| KG1C, M03.13 | Human oligodendroglial cell lines | Mutant A30P |
| Oli-neu, OLN-93 | Rat oligodendroglial cell line | Wild type mutant A53T |
| OLN-93 | Rat oligodendroglial cell line | Wild type (monomeric, oligomeric, fibrillized) |

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.
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
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 dysfunc-
tion were found in the MSA mouse models overexpressing AS under
an oligodendroglial promoter (Shults et al., 2005; Yazzawa et al., 2005;
Stefanova et al., 2007). Oligodendroglial AS overexpression but not neu-
ronal AS overexpression led to a significant decrease of gial cell-derived
neuropathic factor (GDNF) as was also found in brain samples of MSA
patients (Ubbi 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 patho-
genesis of MSA including their vulnerability to different stress re-
ponses, 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 pro-
gression. 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 under-
standing of the MSA pathogenesis and might lead to the development
of new therapeutic targets.

Conclusion

Gial 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 re-
ponse can lead to neuronal dysfunction and degeneration due to the
chronic microgliosis and astrogliosis in brains of ASP patients. Further-
more, oligodendroglial cells develop AS-positive inclusions in MSA
inducing oligodendroglial dysfunction including demyelination and
reduced trophic support. All these detrimental features of gial cells
affect neuronal viability and survival. However, gial 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 gial cells in the initiation and progression of ASP. To understand
the full contribution of gial cells to the pathogenesis of ASP further

studies are needed. To clarify the development of the inclusion bodies
in gial cells and neurons should be a main focus for researchers regard-
ing 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 trans-
ferred successfully into an in vivo system. Moreover, animal models,
especially rodent models, replicate rarely all aspects of the human dis-
eases 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., Shinskey,
N., Verdugo, J.M., Armanini, M., Ryan, A., Hynes, M., Phillips, H., Suizer, 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., Revets, 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),
et al., 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. Lett. 49 (6), 337–340.
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.
Arina, K., Ueda, K., Sunohara, N., Arakawa, K., Hirai, S., Nakamura, M., Tonozuka-Uehara,
H., Kawai, M., 1998. NACP/alpha-synuclein immunoreactivity in fibrillary compo-
nents 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., Revets, T., Houlden, H., Holton,
J.L., 2014. Alpha-synuclein mRNA expression in oligodendrocytes in MSA. Glia 62 (6),
594–570.
Asher, 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.J., 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., Yang, Y.W., 1996. Astrocyte reactivity in neonatal
mice: apparent dependence on the presence of reactive microglia/macrophages.
Glia 18 (1), 11–26.
Barcia, C., Roı, C.M., Anness, V., Gomez, A., Ros-Bernal, F., Aguado-Yera, D., Martinez-
Pagan, M.E., de Pablo, V., Fernandez-Villalba, E., Herrero, M.T., 2011. IFN-gamma
signaling, with the synergistic contribution of TNF-alpha, mediates cell specific
neuronal and microglial 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, T., Baner, P., Joosse, M., van Dongen, J.W., Vanacore, N., van Swieten, J.C.,
Brice, A., Meco, G., van Duijn, C.M., Ostra, B.A., Heutink, P., 2003. Mutations in the
DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science
299 (5604), 256–259.
Boudes, U., Uvin, P., Pinto, S., Voets, T., Fowler, C.J., Wenning, G.K., De Ridder, D., Stefanova, N., 2013. Blood dysynchrony in a transgenic mouse model of multiple system atrophy. J. Neurol. 260 (3), 347–356.

Braak, H., Del Tredici, K., 2004. Protracted and deep neuronal loss in multiple system atrophy brains. Acta Neuropathol. 108 (4), 399–412.

Braak, H., Del Tredici, K., 2009. Neuroanatomy and pathology of sporadic Parkinson's disease. Acta Neuropathol. 118 (4), 429–452.

Braak, H., Del Tredici, K., Bratke, 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) (I/1–5).

Braak, H., Del Tredici, K., I. de Vos, R.A., Janse, J.N., Braak, E.N., 2003a. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24 (2), 197–211.

Braak, H., Rub, U., Gai WP., Del Tredici, K., 2003b. Idiopathic Parkinson's disease: possible route for chronic misfolding of 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 parallel stages of intraneuronal pathology in sporadic Parkinson's disease. Acta Neuropathol. 114 (3), 231–241.

Braak, H., Uvin, P., Dobson, S., Del Tredici, K., 2009. Synucleinopathy: the lighthouse for Lewy body disorders. Neurology 67 (5), 908–910.

De Pablo, R.M., Herrera, A.J., Espinosa-Oliva, A.M., Sarmiento, M., Munoz, M.F., Machado, A., Fernandez-Chacon, R., Schluter, O.M., Sudhof, T.C., 2005. Alpha-synuclein and its molecular pathophysiological role in neurodegenerative disease. 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), 14–11.

Dixon, D.W., Lin, W., Liu, W.K., Yen, S.H., 1999. Blood dysynchrony in a transgenic mouse model of multiple system atrophy. J. Neurol. 246 (3), 243–247.

Doorn, KJ., M. Moores, T., Drukker, B., van der Weg, W., Lucassen, P.J., van Dam, AM., 2010. Microglial phenotypes and toll-like receptor 2 in the substantia nigra and hippocampus of incidental Lewy body disease cases and Parkinson's disease patients. Parkinsonism Relat. Disord. 16 (2), 142–145.

Dumitru, D., Cantuti-Castelvetri, I., Fan, Z., Rockenstein, E., Masliah, E., Hyman, B.T., 2010. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner through exosomes and impacts neuronal survival. J. Neurosci. 30 (20), 6838–6851.

Erikson, J.L., Dawson, T.M., Dickson, D.W., Petrucelli, L., 2003. Caught in the act: alpha-synuclein in Lewy bodies. Neuron 39 (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 Neuropatholog. 121 (6), 675–699.

Fellner, L., Fischl, 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. Neurol. Disord. 12, 1–41.

Foulds, P.G., Mitchell, J.D., Parker, A., Turner, R., Green, G., Diggie, P., Hasegawa, M., Taylor, M., Mann, D., Aliopoli, 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), 4137–4147.

Fujisawa, H., Hasegawa, M., Doehme, N., Kawashima, A., Masliah, E., Goldberg, M.S., Shen, J., Takio, K., Iwatsubo, T., 2002. Alpha-synuclein is phosphorylated in synucleinopathy lesions. J. Neurosci. Cell Biol. 8 (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: a diagnostic study with randomised expert review. Int. J. Neurosci. 124 (9), 666–678.

Grossman, M.P., Fang, Z.M., Chong, B.H., Chan, D.K., 2013. Uptake and mitochondrial dysfunction of alpha-synuclein in AAV-synuclein mouse model of Parkinson’s disease. Mol. Neurodegener. 8 (1), 262.

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 lacking alpha-synuclein. J. Neurosci. 30 (20), 6838–6851.

Hamzah, T.H., Zabetian, C.P., Tenesa, A., Laederach, A., Montumuro, J., Yeartout, K., Kay, D.M., Dohnen, K.F., Paschall, J., Pugh, E., Kusel, V., Collura, R., Robert, 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), 140–149.

Hansen, C., Angot, E., Bergstrom, A.L., Steiner, J.A., Pieri, L., Paul, G., Outeiro, T.F., Melki, R., Braak, E., 2002. Microglia as a source and target of cytokines. Glia 40 (2), 140–149.

Hanisch, U.K., 2002. Microglia as a source and target of cytokines. Glia 40 (2), 140–149.

Harms, A.S., Cao, S., Rowse, A.L., Thome, A.D., Li, X., Mangieri, L.R., Cron, R.Q., Shacka, J.J., 2013. Transgenic models of Parkinson's disease: a systematic review and meta-analysis. Int. J. Neurosci. 123 (23), 243–2443.

Hansen, C., Angot, E., Bergstrom, A.L., Steiner, J.A., Pieri, L., Paul, G., Outeiro, T.F., Melki, R., Braak, E., 2002. Microglia as a source and target of cytokines. Glia 40 (2), 140–149.
Ishizawa, K., Komori, T., Sasaki, S., Arai, N., Mizutani, T., Hirose, T., 2004. Microglial activation.

Iwai, A., Masliah, E., Yoshimoto, M., Ge, N., Flanagan, L., de Silva, H.A., Kittel, A., Saitoh, T., Ibanez, P., Bonnet, A.M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Durr, A., Kato, S., Nakamura, H., 1990. Cytoplasmic argyrophilic inclusions in neurons of pontine nuclei in patients with olivopontocerebellar atrophy: immunohistochemical and ultrastructural study. Lancet Neurol. 11 (4), 361–368.

Jellinger, K.A., 2002. Neuropathological spectrum of synucleinopathies. Mov. Disord. 18 (8), 512–521.

Jellinger, K.A., 2009. A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. Biochem. Biophys. Acta 1792 (7), 730–740.

Jellinger, K.A., Amstull, E., 2006. Does striatal pathology distinguish Parkinson disease with dementia and dementia with Lewy bodies? Acta Neuropathol. 112 (3), 253–260.

Jellinger, K.A., Lonto, P.L., 2005. Papp–Lantos inclusions and the pathogenesis of multiple system atrophy: an update. Acta Neuropathol. 119 (6), 657–667.

Jellinger, K.A., Seppi, K., Wesseling, G.K., 2005. Coding of amyloid pathology in multiple system atrophy: proposal for a novel scale. Mov. Disord. (20 Suppl. 12), S59–S62.

Jeon, B.S., Farrer, M.J., Bortnick, S.F., 2011. Exogenous alpha-synuclein fibrils seed the formation of Lewy body-like intracellular inclusions in cultured cells. Proc. Natl. Acad. Sci. U. S. A. 108 (47), 18001–20005.

Kaczor, M.J., 2000. Activated microglia in dementia with Lewy bodies. Neurology 55 (1), 132–134.

Matsuda-Suzukioka, M., Nonaka, T., Hosokawa, M., Ikawa, T., Arai, T., Akiyama, H., Mann, D.M., Hasegawa, M., 2013. Prion-like spreading of pathological alpha-synuclein in brain. Brain 136 (P4), 1128–1138.

McKeith, I.G., 2004. Dementia with Lewy bodies. Dialogues Clin. Neuropathol. 6 (3), 331–341.

Miki, Y., Morii, T., Tanji, K., Akita, T., Yakushiji, H., Wakabayashi, K., 2011. Accumulation of histone deacetylase 6, an aggresome-related protein, is specific to Lewy bodies and glial cytoplasmic inclusions. Neoplasiology 31 (6), 561–568.

Miller, D.W., Johnson, J.M., Solano, S.M., Hollingsworth, Z.B., Standaert, D.G., Young, A.B., 2005. Absence of alpha-synuclein mRNA expression in normal and multiple system atrophy oligodendroglia. J. Neurosci. 25 (12), 432–435.

Mizuno, T., Kuno, R., Nitta, A., Nambashi, T., Zhang, K., Kawanokuchi, J., Wang, J., Jin, S., Takeuchi, H., Suzumura, A., 2005. Protective effects of nigrocaudal protein against neuronal cell death induced by activated microglia and astrocytes. Brain Res. 1066 (1–2), 78–85.

Mollenhauer, B., Ebeling, H., Roever, S., Schütz-Schweffler, W., Schimke, K., Schubert, W., Ebeling, R., 2010. Different CSF beta-amyloid profiles in Alzheimer’s and Creutzfeld-jakob disease. J. Neurotransm. 112 (5), 613–624.

Multiple-System Atrophy Research, C., 2013. Mutations in COQ2 in familial and sporadic multiple system atrophy. N. Engl. J. Med. 367 (11), 231–232.

Nagatsu, T., Sawada, M., 2005. Inflammatory processes in Parkinson’s disease: role for cytokines. Curr. Pharm. Des. 11 (8), 999–1016.

Nakamura, S., Kawamoto, N., Nakano, S., Akiguchi, I., 2000. Expression of the endocytosis regulatory proteins Rab5 and Rabap5-5 in glial cytoplasmic inclusions from brains with multiple system atrophy. Clin. Neuropathol. 19 (2), 51–61.

Neumann, H., Schweigerer, R., Yamashita, T., Rosenkranz, K., Wekerle, H., Barde, Y.A., 2005. Titin-necrosis factor alpha not only inhibits neurite outgrowth and branching of hippocampal neurons by a rho-dependent mechanism. J. Neurosci. 22 (3), 852–862.

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., Hwaswabu, T., Takahashi, K., Wakabayashi, K., 2004. Accumulation of phosphorylated alpha-synuclein in the brain and peripheral ganglia of patients with multiple system atrophy. Acta Neuropathol. 107 (3), 292–298.

Nishina, K., Hayashi, S., Poewe, W., Singleton, A.B., Yoshino, H., Imai, H., Kitamori, T., Sato, K., Kuroda, R., Tomiyama, H., Mizoguchi, K., Murata, T., Doda, I., Inazawa, J.,...
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. Neurosci. Lett. 307 (2), 172–176.

Ozawa, T., Williams, D.R., Lockhart, P.J., Revesz, T.R., 2009. Degeneration in different regions of the brain in Parkinson’s disease. Ann. Neurol. 65 (4), 471–478.

Ozawa, T., Takano, H., Onodera, O., Kobayashi, H., Ikeuchi, T., Koide, R., Okuizumi, K., 2014. The role of microglia in Parkinson’s disease. J. Neuroinflammation 11 (1), 104 (6), 1504–1509.

Ozawa, T., Vaviour, D., Quinn, N.P., Josephs, K.A., Sangha, H., Kifflord, 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 tacoxystin-induced neurodegeneration via autophagy enhancement. Neurobiol. Dis. 31 (2), 166–175.

Papa, M., De Luca, C., Petta, F., Alberghina, L., Cirillo, G., 2014. Astrocyte-neuron interplay in maladaptive plasticity. Neurobiol. 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 (striatoniigral degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome). J. Neurol. Sci. 84 (1–3), 79–100.

Park, J.Y., Park, S.R., You, J., Park, S.M., 2008. Microglial phagocytosis is enhanced by mono-meric alpha-synuclein, not aggregated alpha-synuclein: implications for Parkinson’s disease. Glia 56 (11), 1215–1223.

Parkin, D.M., Knappe, P.S., Perlin, T., Aueter, J.M., Aflaciousu, I., 2005. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann. Neurol. 57 (1), 82–91.

Polymeropoulos, M.H., Lavedan, C., Leroy, I., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, M., Rubenstein, J., Boyer, R., Steen, E.S., Chauvat, Carles, A., Sanyasid, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Golde, T.E., Giasson, B.I., 2003. A mutation in the parkin gene causes autosomal recessive parkinsonism-dementia with Lewy bodies. Science 296 (5567), 2066–2069.

Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Golde, T.E., Giasson, B.I., 2003. A mutation in the parkin gene causes autosomal recessive parkinsonism-dementia with Lewy bodies. Science 296 (5567), 2066–2069.

Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, 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., 1999. An update on the genetic mouse models for Parkinson’s disease. Parkinsons Dis. 32 (1), 16–26.

Papp, M.I., Lantos, P.L., 1999. The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. Brain 117 (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 (striatoniigral degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome). J. Neurol. Sci. 84 (1–3), 79–100.

Park, J.Y., Park, S.R., You, J., Park, S.M., 2008. Microglial phagocytosis is enhanced by mono-meric alpha-synuclein, not aggregated alpha-synuclein: implications for Parkinson’s disease. Glia 56 (11), 1215–1223.

Parkin, D.M., Knappe, P.S., Perlin, T., Aueter, J.M., Aflaciousu, I., 2005. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann. Neurol. 57 (1), 82–91.

Polymeropoulos, M.H., Lavedan, C., Leroy, I., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, M., Rubenstein, J., Boyer, R., Steen, E.S., Chauvat, Carles, A., Sanyasid, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Golde, T.E., Giasson, B.I., 2003. A mutation in the parkin gene causes autosomal recessive parkinsonism-dementia with Lewy bodies. Science 296 (5567), 2066–2069.
Stefanova, N., Georgievskia, B., Eriksson, H., Poeve, 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., Poeve, W., Wenning, G.K., 2012b. Systemic proteasome inhibition neurodegeneration in a transgenic mouse model expressing human alpha-synuclein in oligodendrocyte promoter: implications for multiple system atrophy. Acta Neuropathol. 124 (1), 51–65.

Stenberger, S., Poeve, 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., Prifti, L., Venkatesh, K., Fedder, H.J., 2008. Mutant alpha-synuclein overexpression in oligodendrocytic cells results in impaired adhesion to fibronectin and cell death. Mol. Cell. Neurosci. 29 (2), 259–268.

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 (1), 624–637.

Su, X., Federoff, H.J., Maguire-Zeiss, K.A., 2009. Alpha-synuclein overexpression in oligodendrocytes: implications for multiple system atrophy. Acta Neuropathol. 99 (1), 14–20.

Wang, Y., Shi, M., Chung, K.A., Zabetian, C.P., Leverenz, J.B., Berg, D., Slujslies, 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., Cai, 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., Alba, 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., Aström, K.E., 2009. Glia: genes and function. 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 epitphenomena 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), 1791–1806.

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., Geri, F., Poeve, W., 2004. Multiple system atrophy. Lancet Neurol. 3 (2), 93–103.

Wilhelmsson, U., Bushong, E.A., Price, D.L., Smart, B.L., Phung, V., Terada, M., Ellisman, 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., Smart, B.L., Phung, V., Terada, M., Ellisman, H.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., Arocena-Arozona, 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., Isagao, B.I., Sasaki, R., Zhang, B., Joyce, S., Uryu, K., Trojanowski, J.Q., Lee, V.M., 2004. 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, Y., Gomez Tortosa, E., del Ser, T., Munoz, D.G., de Yevenes, J.C., 2004. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann. Neurol. 55 (2), 164–173.

Zhang, W., Wang, T., Wei, 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), 532–543.

Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Zarranz, J.J., Alegre, J., Gomez-Esteban, J.C., Lezcano, E., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atares, B., Llorens, Y., Gomez Tortosa, E., del Ser, T., Munoz, D.G., de Yevenes, J.C., 2004. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann. Neurol. 55 (2), 164–173.