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The neuropathology of multiple system atrophy and its therapeutic implications

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Abstract

Multiple system atrophy (MSA) is a fatal neurodegenerative disorder characterized by the abnormal accumulation of toxic forms of the synaptic protein alpha-synuclein (α-syn) within oligodendrocytes and neurons. The presence of α-syn within oligodendrocytes in the form of glial cytoplasmic inclusions is the diagnostic hallmark of MSA. However, it has been postulated that α-syn is produced in neurons and propagates to oligodendrocytes, where unknown mechanisms lead to its accumulation. The presence of α-syn within neurons in MSA has not been so extensively studied, but it may shed light into neuropathological mechanisms leading to oligodendroglial accumulation. Here we summarize the principal neuropathological events of MSA, and discuss how a deeper knowledge of these mechanisms may help develop effective therapies targeting α-syn accumulation and spreading.

Multiple system atrophy (MSA) is a rapidly progressing, sporadic and fatal neurodegenerative disorder that belongs to the synucleino-pathy spectrum (Farrer et al., 1999; Spillantini, 1999; Takeda et al., 1998; Wakabayashi et al., 1998a). Clinically, MSA is characterized by parkinsonian features and cerebellar, autonomic and urogenital dysfunction, which are a reflection of striatonigral degeneration and oli-vopontocerebellar atrophy (Gilman et al., 2008). There are two major subtypes of MSA, distinguished by their symptoms at the time of diagnosis (Gilman et al., 2008): the parkinsonian subtype (MSA-P), where parkinsonism is predominant, including bradykinesia, muscle rigidity, tremors, and postural instability; and the cerebellar subtype (MSA-C), characterized by cerebellar ataxia. The prevalence of MSA is between 3.4 and 4.9 cases per 100,000 people, and the mean incidence is 0.6–0.7 cases per 100,000 people and year (Fanciulli and Wenning, 2015; Stefanova et al., 2009), making MSA an orphan disease (Lavandeira, 2002). In Western countries, MSA-P predominates, occurring in 66–82% of MSA patients (Wenning et al., 2013). However, MSA-C is more common in Eastern countries, occurring in 67% of MSA

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Conflict of interest

The authors declare that they have no conflict of interest.

patients (Yabe et al., 2006). The rapid progression, its orphan disease status, and its neuropathological features make MSA an ideal candidate for accelerated drug development.

1. The neuropathology of MSA

The principal neuropathological characteristic of MSA is the presence of aggregates containing the synaptic protein alpha-synuclein (α-syn) within brain cells (Spillantini et al., 1998). Specifically, the presence of α-syn-positive inclusions in oligodendroglial cells in the form of glial cytoplasmic inclusions (GCIs) is the diagnostic hallmark of MSA (Dickson et al., 1999; Papp et al., 1989; Spillantini, 1999; Wakabayashi et al., 1998b). Interestingly, α-syn aggregates can also be observed as glial nuclear inclusions, neuronal cytoplasmic inclusions (NCIs), neuronal nuclear inclusions (NNIs) and dystrophic neurites, however these lesions all appear at lower frequencies than the GCIs (Papp and Lantos, 1992). The cellular distribution of α-syn aggregates in MSA has been the cause of intense research, as α-syn is considered a neuronal protein (Fortin et al., 2005; George et al., 1995) that abnormally accumulates within glial cells (oligodendrocytes). Although several groups have found no evidence of increased SNCA expression in MSA oligoden-drocytes (Jin et al., 2008; Miller et al., 2005; Ozawa et al., 2001), a more recent study reported that there is a 3-fold increase in SNCA mRNA levels in postmortem MSA oligodendrocytes (Asi et al., 2014). It is unknown if this increase would be enough to induce a significant accumulation of α-syn in oligodendrocytes, a cell type that does not express high basal levels of α-syn; or if the increased expression is a consequence of α-syn accumulation, rather than its cause.

Achieving a deeper understanding of the neuropathology of MSA has been one of the primary goals in the field. In this sense, a major unanswered question is why α-syn tends to accumulate to a greater extent in oligodendrocytes than in neurons. One possibility is that α-syn is produced by oligodendroglial cells which in turn over-express or fail to intrinsically clear out α-syn (Fig. 1); the other is that α-syn that propagates from neurons and cannot be cleared out by oligoden-drocytes due to defective clearance mechanisms (Fig. 1). In any case, the source of α-syn in oligodendroglial cells in MSA is still unclear. Given the high levels and widespread distribution of α-syn aggregates in MSA, it is possible that both propagation and oligodendroglial α-syn expression might be occurring simultaneously. Supporting the possibility of propagation, several studies have shown that α-syn aggregates can transmit from neuron to neuron (Desplats et al., 2009; Lee et al., 2012b), neuron to astroglial and oligodendroglial cells (Lee et al., 2010; Reyes et al., 2014), and oligodendroglial to astroglial cells (Valera et al., 2014), leading to neuronal dysfunction, apoptosis and neuroin-flammation (Desplats et al., 2009; Klucken et al., 2012; Lee et al., 2010; Valera et al., 2014; Volpicelli-Daley et al., 2011). Moreover, recent studies have shown that injection of homogenates from MSA brains propagate α-syn pathology in a prion-like fashion in the murine brain (Prusiner et al., 2015; Watts et al., 2013). Neuronal cells (donors) release α-syn aggregates into the extracellular environment by exocytosis and in clear vesicles and exosomes (Danzer et al., 2012; Lee et al., 2005), and α-syn is taken up by other neurons, oligodendrocytes and astrocytes (acceptors) via endocytosis (Lee et al., 2008a) (Fig. 1). This scenario could explain the presence of NCIs and NNIs in MSA neurons, however whether neurons showing α-syn accumulation are the source of extracellular α-syn in MSA has not been investigated.

Whether its origin is intracellular or due to cell-to-cell propagation, recent evidence supports the notion that failure of intracellular protein clearance mechanisms (e.g. autophagy, unfolded protein response, proteolysis) might play a role in the process of α-syn aggregation, release and subsequent accumulation of α-syn pathological species in donor and acceptor cells (Klucken et al., 2012; Lee et al., 2013) (Fig. 1). Accumulation of toxic α-syn within MSA oligodendrocytes might be a direct consequence of impairments on those mechanisms. Free extracellular oligomeric α-syn is taken up by oligodendrocytes by clathrin-dependent endocytosis (Kisos et al., 2012; Konno et al., 2012), and endocytic vesicles containing α-syn are then directed to lysosomal degradation; however, cytosolic α-syn might also be degraded by other mechanisms such as UPR and proteolysis (Hoozemans et al., 2007; Xilouri et al., 2013). Impairments in clearance mechanisms such as autophagy have already been described in MSA and other synucleino-pathies (Lynch-Day et al., 2012; Schwarz et al., 2012).

1.1. Neuronal neuropathology in MSA

Histopathologically, the morphology and immunoreactivity of NCIs differ from that of the neuronal aggregates found in other synucleino-pathies (Spillantini et al., 1998), known as Lewy bodies. Interestingly, the immunohistochemical and ultrastructural features of NCIs seem to be virtually identical to those of GCIs (Yokoyama et al., 2001). NCIs are observed in the putamen and pons of all MSA cases, and they can also be observed in the cerebral cortex, medulla oblongata and spinal cord, with no NCIs present in the cerebellum and midbrain (Sugiura et al., 1995). NCI pathology follows a hierarchy of region-specific susceptibility, independent of the clinical phenotype, and the severity of the pathology is duration-dependent (Cykowski et al., 2015). Widespread NCIs have been identified not only in regions typically associated with the disease, but also within other areas such as anterior cingulate cortex, amygdala, entorhinal cortex, basal forebrain, hypothalamus, and in some cases cerebellar roof nuclei (Cykowski et al., 2015). These findings suggest that the neuronal pathology plays an important role in the developmental and progression of MSA. Interestingly, NCIs are heterogeneous, and in uncommon cases they may include Pick body-like inclusions that are strongly associated with neuronal loss in the hippocampus and amygdala (Aoki et al., 2015), potentially representing a novel subtype of frontotemporal lobar degeneration associated with α-syn.

In contrast, NNIs appear as a loosely woven network or irregularly arranged fibrils beneath the nuclear membrane (Nishie et al., 2004), occasionally coexisting with NCIs in the same neurons. Due to their count number and correlation with disease progression, it has been suggested that NNI formation is an earlier phenomenon than NCI formation (Nishie et al., 2004). One question that remains to be answered is if NCIs and GCIs share mechanistic origins, or if they are originated by independent mechanisms; the shared features between both structures would suggest the former.

The presence of α-syn-positive aggregates within neurons suggests that these cells fail to clear out increased intracellular levels of mis-folded α-syn. It is possible that a significant inhibition of clearance mechanisms is related to the origin of the disease, fueled by the fact that misfolded, aggregated α-syn is also able to inhibit its own degradation (Snyder et al.,

2003; Winslow and Rubinsztein, 2011). Supporting this notion, it has been observed that autophagic failure promotes the exocytosis and intercellular transfer of α-syn (Lee et al., 2013). It is possible that the release of α-syn to the extracellular environment is an attempt to reduce its intracellular levels, however more research is needed to elucidate if this is the case. In the past few years, strong evidence has been provided supporting the prion-like behavior of α-syn, which has been confirmed in cellular models (Desplats et al., 2009; Lee et al., 2012b), animal models (Luk et al., 2012; Masuda-Suzukake et al., 2014; Prusiner et al., 2015), and indirectly in patients with PD that received neuronal grafts (Kordower et al., 2008; Li et al., 2008). Moreover, the fact that α-syn accumulation has been observed in cell types other than neurons in animal models of PD and in PD brains (Bruck et al., 2016) further supports this hypothesis.

1.2. Glial neuropathology in MSA

According to the α-syn propagation hypothesis of MSA, oligoden-drocytes would incorporate extracellular α-syn and accumulate it in the form of GCIs (Fig. 1) and nuclear inclusions (Nishie et al., 2004). However, it is unclear why oligodendrocytes preferentially uptake and/or fail to clear α-syn in MSA brains, a neuropathological event not widely observed in other synucleinopathies. One hypothesis is that the incorporation of extracellular, misfolded α-syn may impair the endogenous clearance machinery of the oligodendrocyte, progressively leading to α-syn accumulation (Pukass and Richter-Landsberg, 2015; Schwarz et al., 2012). Another option is that a dysfunction in the clearance machinery is a prerequisite for α-syn uptake and/or accumulation in oligodendrocytes. In both scenarios, the oligodendroglial accumulation of α-syn may be further potentiated by increased expression of its gene (Asi et al., 2014; Djelloul et al., 2015) and oligo-dendrocyte-to-oligodendrocyte propagation. Finally, other suggested mechanisms are the involvement of altered iron metabolism in oligo-dendrocytes (Visanji et al., 2013), and epigenetic and/or environmental factors (Sturm et al., 2016). Furthermore, it is possible that multiple mechanisms combine, leading to the pathological, progressive oligo-dendroglial accumulation of α-syn observed in MSA brains. In light of these observations, it could also be concluded that there may exist a genetic predisposition for oligodendrocytes to develop abnormal α-syn accumulation (Sturm et al., 2016). The genetic risk factors with the most evidence in MSA are variants in the SNCA and COQ2 genes (Collaboration, 2013; Scholz et al., 2009), however genome-wide association studies have failed to find association between common genetic variations in those genes and MSA (Sailer et al., 2016).

The principal consequences of α-syn-induced oligodendroglial degeneration are the loss of trophic support to neurons and demyelination (Ettle et al., 2016; Stefanova and Wenning, 2016; Ubhi et al., 2011; Wong et al., 2014), which in turn lead to further neurodegeneration. This secondary neurodegeneration may explain the lack of response to L-DOPA observed in MSA patients and the fast progression of this devastating disease. One of the most relevant characteristics of MSA is the selective neuronal loss and axonal degeneration in the central autonomic, striatonigral and olivopontocerebellar networks, with cell loss also present in autonomic brain stem nuclei (Jellinger, 1998; Kuzdas-Wood et al., 2014; Wakabayashi et al., 2010). Moreover, the presence of misfolded α-syn in the extracellular compartment can result not only in oligodendroglial dysfunction, but also in the overstimulation of as-troglia

and microglia (Bae et al., 2012; Lee et al., 2010; Vieira et al., 2015) (Fig. 1). Both astrogliosis and microgliosis have been observed in MSA brains (Schwarz et al., 1996), and in transgenic mouse models of MSA (Ubhi et al., 2012; Valera et al., 2015; Valera et al., 2014). As-trocytes are able to accumulate α-syn in MSA and in tg mouse models (Mandler et al., 2015; Nakamura et al., 2016), and stimulate the release of pro-inflammatory cytokines (Lee et al., 2010). MSA brains exhibit widespread astrogliosis (Schwarz et al., 1996) correlated to the presence of nearby GCI-positive oligodendrocytes (Radford et al., 2015), suggesting that localized presence of extracellular α-syn may underlie the astrocytic pathology in MSA. Additionally, microglia phagocytize α-syn (Lee et al., 2008b; Park et al., 2008) and also release pro-in-flammatory factors and reactive oxygen species in response to extracellular α-syn (Beraud et al., 2013; Fellner et al., 2013). Microgliosis has been described and identified as one of the main features of the disease process in MSA (Ishizawa et al., 2004; Stefanova et al., 2007). However, there is evidence of both neuroprotective and detrimental effects of microglial activation in MSA and MSA models. This dual role seems to be associated with the capacity of microglia to both remove extracellular α-syn and produce neurotrophic factors, and their ability to release pro-inflammatory mediators (Fellner et al., 2013; Stefanova et al., 2011). These neuroinflammatory mechanisms would create a hostile environment for neurons in the MSA brain.

Finally, it is worth mentioning that, although the principal component of GCIs is fibrillar α-syn, other proteins such as p25α, tau, ubiquitin, tubulin, Cdk5 and MAP2 can also be found (Cairns et al., 1997; Chiba et al., 2011; Gai et al., 1999; Nakamura et al., 1998; Wakabayashi et al., 1998b). Interestingly, p25α is an oligodendroglial protein that can induce aggregation of α-syn (Hasegawa et al., 2010). Changes in the cellular interactions between the myelin protein MBP and p25α occur early in MSA and contribute to abnormalities in myelin and subsequent α-syn aggregation (Song et al., 2007).

2. Therapeutic opportunities based on the MSA neuropathology

The neuropathological features of MSA suggest that targeting the oligodendroglial α-syn accumulation, neuronal α-syn accumulation, or common mechanisms leading to α-syn accumulation in both cell types, may be potential therapeutic alternatives. In this sense, it is likely that approaches that lead to a reduction in α-syn accumulation in both oligodendrocytes and neurons may be more effective that cell-specific approaches. Moreover, the important component of α-syn propagation and the pathological accumulation of α-syn within two different cell types, and its orphan disease status make MSA a strong synucleinopathy candidate for accelerated drug discovery (Krismer et al., 2014).

Most of the research aimed at developing new therapeutic candidates for MSA has been primarily focused on targeting oligodendroglial α-syn accumulation. The use of transgenic models that express α-syn directly in oligodendroglial cells, under the control of the PLP (Kahle et al., 2002), MBP (Shults et al., 2005), or CNP (Yazawa et al., 2005) promoters, is a reflection of this trend. However, this approach does not cover an important part of the neuropathological landscape: the presence of α-syn within neurons, and its pathological propagation from neurons to oligodendrocytes. Another important limitation of these models lays on the fact that the mechanisms leading to α-syn accumulation within oligodendrocytes

in MSA are still unknown, thus limiting the possibility of finding suitable targets or preventing α-syn accumulation from early stages (Stefanova and Wenning, 2015). In this scenario, approaches limited to reducing α-syn accumulation in oligo-dendrocytes may not provide enough disease modification to be able to stop or delay the progression of the disease.

Expanding the MSA therapeutic landscape beyond the oligoden-drocyte, the neuronal pathology of MSA has not been so extensively explored. While neuronal α-syn accumulation has been greatly studied (and targeted) in PD and other synucleinopathies, less is known of its potential as a target for MSA, and its interest has been mostly limited to act as α-syn source for oligodendrocytes. The involvement of neuronal α-syn accumulation as a main pathological event in MSA remains to be investigated. Nevertheless, according to the propagation model of MSA pathology, a reduction in the neuronal expression, release and accumulation of α-syn may translate in a decrease in oligodendroglial α-syn levels and lead to disease modification. Moreover, supporting and repairing neuronal function by restoring trophic support (e.g. BDNF, GDNF) (Ubhi et al., 2010), myelination (Ettle et al., 2016), and by the use of regenerative therapies (Lee et al., 2012a) are therapeutic alternatives to consider for MSA.

Recently, therapies aimed at reducing α-syn propagation have been extensively explored. That is the case in immunotherapies, which not only block toxic propagation of α-syn species, but are also able to reduce intracellular α-syn accumulation (Games et al., 2014; Mandler et al., 2015; Mandler et al., 2014). The Austrian company AFFiRiS recently completed an active immunotherapy Phase I clinical trial with the α-syn vaccine PD03A. Both low and high doses were well tolerated and no serious adverse events were reported. PD03A induced a dose-dependent immune response against both the vaccine itself and the α-syn epitope over time. An α-syn passive immunotherapy approach using a humanized monoclonal antibody against α-syn (Prothena, PRX002) has also been tested in Phase Ia and Ib clinical trials. In both trials, free serum α-syn levels were drastically reduced (Schenk et al., 2017). A dose-dependent increase in PRX002 levels in cerebrospinal fluid was observed, without serious adverse events. PRX002 has move forward to Phase II trials in patients with early PD. A Phase I passive immunotherapy trial using the anti α-syn antibody BIIB-054 (Biogen) is also ongoing. Preliminary reports suggest that this antibody was well tolerated in healthy volunteers, and was detectable in the cerebrospinal fluid (Brundin et al., 2017). Additional clinical trials to commence soon include the α-syn antibodies BAN0805 (BioArctic & AbbVie), targeting oligomeric forms of α-syn, and MEDI1341 (AstraZeneca & Takeda). Moreover, the therapeutic potential of stimulating α-syn degradation pathways, such as autophagy, is also being investigated at the preclinical level (Xilouri et al., 2013). Neuroinflammation induced by extracellular α-syn contributes to MSA pathology, thus therapies reducing the overactivation of glial cells and the production of pro-inflammatory cytokines are also being explored (Stefanova et al., 2012; Stefanova et al., 2007; Vieira et al., 2015). Finally, using strategic drug combinations or multi-target drugs might increase the efficiency of therapeutic treatments for MSA (Valera and Masliah, 2016). Therapies aimed at reducing α-syn accumulation and cell-to-cell transfer, such as immunotherapy, could be combined with agents that reduce neuroin-flammation with synergistic outcomes (Valera et al., 2017).

It can be concluded that more research is needed to elucidate how neurons, oligodendrocytes and other glial types interplay at the origin of the MSA pathology and during the progression of the disease. The pathological production, accumulation and propagation of α-syn between different cell types may be a significant therapeutic target not only limited to the oligodendroglial aspect of the disease. Investigating the role of neurons on the pathology as source and accumulators of toxic protein species may lead to more effective therapies for reducing neurodegeneration in MSA.

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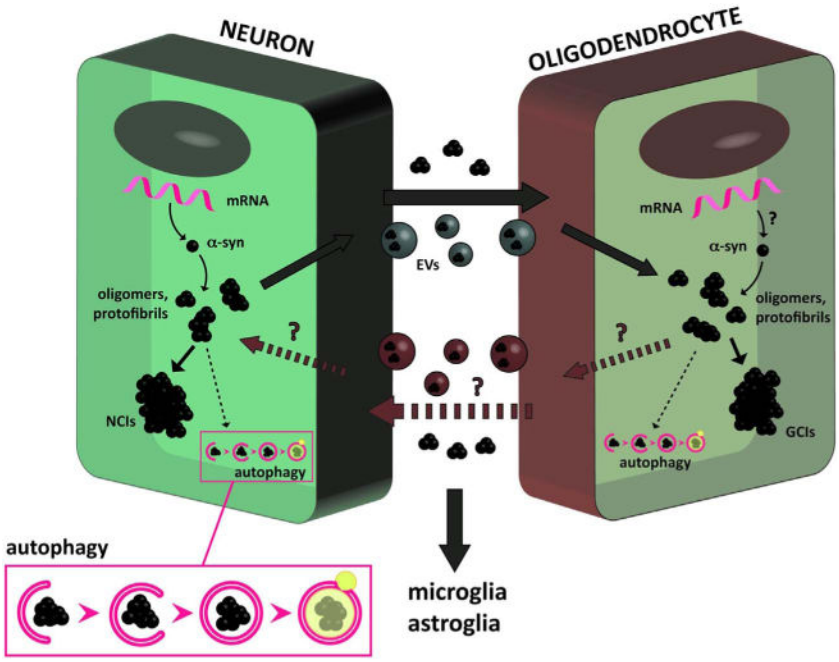

Fig. 1.

Neuropathology of MSA and cell-to-cell propagation of α-syn. It is believed that in MSA oligodendrocytes accumulate α-syn after a process of propagation from neurons or other oligodendroglial cells. Increased expression and/or reduced α-syn clearance in neurons may stimulate the accumulation of misfolded forms of the protein as NCIs, and their release and propagation to oligodendrocytes via exocytosis or within extracellular vesicles (EVs). Reduced α-syn clearance in oligodendrocytes may also enhance its accumulation in the form of GCIs, and induce its release to the extracellular environment. It is also possible that enhanced expression of the α-syn gene is present in oligodendrocytes. These neuropathological events represent potential targets for therapeutic intervention in MSA.