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Review

The neuropathology of multiple system atrophy and its therapeutic implications

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A B S T R A C T

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 synucleinopathy 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 olivopontocerebellar 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 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 oligodendrocytes (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.

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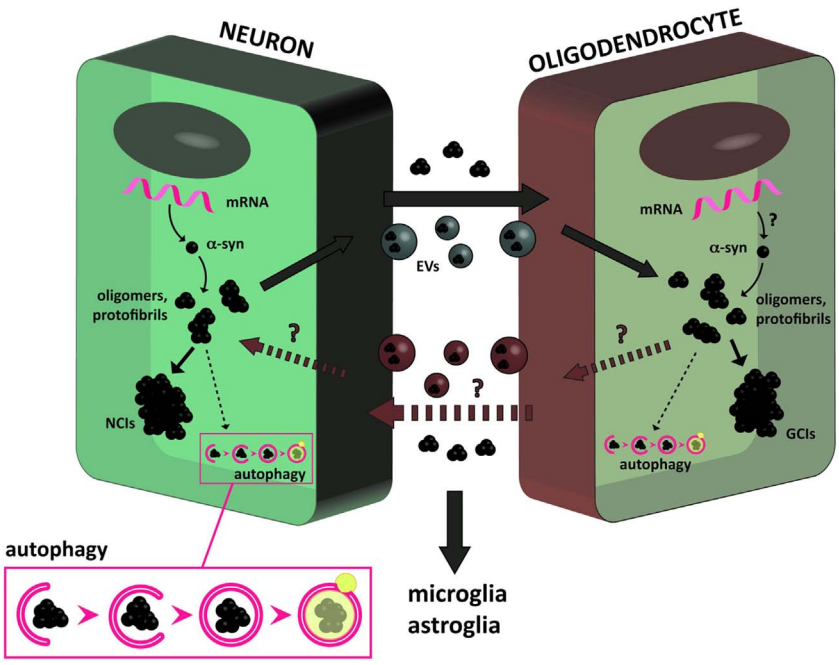

Fig. 1. Neuropathology of MSA and cell-to-cell propagation of α-syn. It is believed that in MSA oligodendrocytes accumulate α-syn after a process of propagation from neurons or other oligodendroglial cells. Increased expression and/or reduced α-syn clearance in neurons may stimulate the accumulation 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.

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 oligodendrocytes 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 neuroinflammation (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 synucleinopathies (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 synucleinopathies (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