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# Towards translational therapies for multiple system atrophy

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ABSTRACT

Multiple system atrophy (MSA) is a fatal adult-onset neurodegenerative disorder of uncertain etiopathogenesis manifesting with autonomic failure, parkinsonism, and ataxia in any combination. The underlying neuropathology affects central autonomic, striatonigral and olivopontocerebellar pathways and it is associated with distinctive glial cytoplasmic inclusions (GCIs, Papp-Lantos bodies) that contain aggregates of α-synuclein. Current treatment options are very limited and mainly focused on symptomatic relief, whereas disease modifying options are lacking. Despite extensive testing, no neuroprotective drug treatment has been identified up to now; however, a neurorestorative approach utilizing autologous mesenchymal stem cells has shown remarkable beneficial effects in the cerebellar variant of MSA. Here, we review the progress made over the last decade in defining pathogenic targets in MSA and summarize insights gained from candidate disease-modifying interventions that have utilized a variety of well-established preclinical MSA models. We also discuss the current limitations that our field faces and suggest solutions for possible approaches in cause-directed therapies of MSA.



**Contents**



*Abbreviations:* MSA, multiple system atrophy; MSA-P, parkinsonian variant of MSA; MSA-C, cerebellar variant of MSA; α-Syn, alpha-synuclein; SND, striatonigral degeneration; OPCA, olivopontocerebellar atrophy; GCI, (oligodendro-)glial cytoplasmic inclusions; UMSARS, unified MSA rating scale; wt, wild type; tg, transgenic; PLP, proteolipid protein; MBP, myelin basic protein; CNP, 2′,3′-cyclic-nucleotide 3′-phosphodiesterase; SN, substantia nigra.

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## 1. Introduction

Multiple system atrophy is an adult onset, fatal, neurodegenerative disease, presenting with autonomic failure, parkinsonism, and cerebellar ataxia in different combinations. The mean age of disease onset is ~57 years and survival after disease onset lies between six and nine years (Stefanova et al., 2009a). The prevalence is 1.9–4.9/100,000 and the incidence is 3/100,000/year in the population over 50 years, MSA therefore meets orphan disease status (Orpha number: ORPHA102) (Wenning and Stefanova, 2009). Depending on the predominant motor presentation MSA is mainly classified into a parkinsonian variant (MSA-P) reflecting underlying striatonigral degeneration (SND) and a cerebellar variant (MSA-C) resulting from olivopontocerebellar atrophy (OPCA). As illustrated in Fig. 1, the degeneration of the MSA-P-, MSA-C- and autonomic failure-associated regions can appear in different combinations and different severities. There is no current evidence to suggest that pathogenesis differs in MSA-P and MSA-C based on overlapping neuropathologies including GCI deposition (Ubhi et al., 2011). MSA-P accounts for 60% of patients in the Western hemisphere whereas MSA-C appears to be predominant in East-Asian countries such as Japan (Watanabe et al., 2002; Wenning et al., 1994a). However, also other subtypes that do not fit to this classification have been described such as minimal-change MSA or MSA with disease duration that widely exceeds the usual survival time of 6–9 years after disease onset (Piao et al., 2001; Wenning et al., 1994b). In addition to progressive motor impairment, most MSA patients develop features of autonomic failure including orthostatic hypotension and urogenital disturbances such as increased frequency, enhanced urgency, incontinence and/or retention associated with male erectile dysfunction and female genital hyposensitivity. Especially in early disease stages, MSA-P might often be mistaken for PD and genetic or secondary late-onset ataxias may be labeled as MSA-C due to similarities in disease presentation (Gilman et al., 2008). A definite diagnosis requires the finding of oligodendrogliopathy at autopsy, which is characterized by alpha-synuclein (α-Syn)-positive glial cytoplasmic inclusions (GCIs, Papp-Lantos bodies) throughout the central nervous system (CNS), and the presence of neurodegenerative changes consistent with SND, OPCA and autonomic degeneration of predominantly central origin (Trojanowski and Revesz, 2007). Consensus diagnostic guidelines for possible, probable and definite MSA have been proposed and validated (Gilman et al., 1998, 2008). So far there is no cure available for this disease and symptomatic therapies are limited (Wenning and Stefanova, 2009). Therefore there is a strong need to further investigate the mechanisms of neurodegeneration and find interventional treatment options. Here we review the progress over the last decade in defining pathogenetic targets of MSA and the effects of candidate neuroprotective and neurorestorative interventions utilizing the growing number of *in vitro* and *in vivo* MSA models. This work has led to several clinical trials and there is hope that an effective intervention could be identified in the near future.

## 2. Etiology

The etiology of this fatal disease remains to be further investigated, however, there is evidence that it is caused by a combination of genetic predisposition and environmental influences. Single nucleotide polymorphisms (SNPs) at the SNCA locus coding for α-Syn have been identified and patients with SNCA duplications and triplications have been found to manifest clinical and pathological features that are similar to those seen in MSA (Al-Chalabi et al., 2009; Fuchs et al., 2007; Scholz et al., 2009). Recently, Holton and colleagues reported a G51D mutation in the SNCA locus and described mixed pathological features of PD and MSA suggesting that investigation of this mutation could help in discovering the exact mechanisms of α-Syn malfunction (Kiely et al., 2013). However, the connection between the SNCA locus and MSA could not be confirmed in an independent genome wide association study (Sailer, 2012).

Genetic forms of MSA appear to be very rare (Hara et al., 2007; Wullner et al., 2004, 2007). A recent study of autosomal recessive MSA families from Japan reports mutations in the COQ2 gene which encodes an enzyme essential for the biosynthesis of

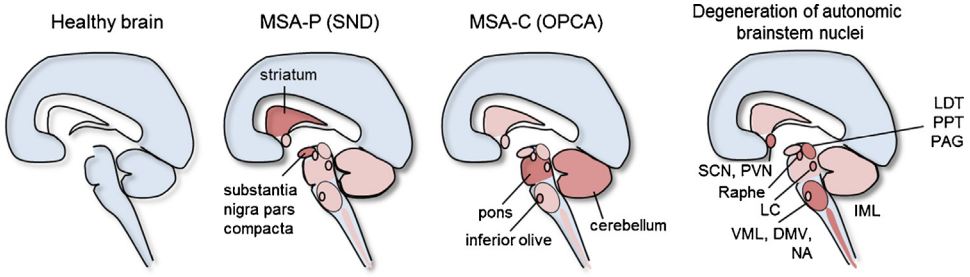


**Fig. 1.** Neuropathology underlying MSA-P, MSA-C and autonomic failure in MSA. Striatonigral degeneration is the underlying pathology of MSA-P, olivopontocerebellar atrophy occurs in MSA-C and degeneration of autonomic brainstem nuclei plays a role for characteristic autonomic failure in MSA patients. SND, striatonigral degeneration; OPCA, olivopontocerebellar atrophy; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus; LC, locus coeruleus; VML, ventrolateral medulla; DMV, dorsal motor nucleus of the vagus; NA, nucleus ambiguus; IML, intermediolateral column of the thoracic spinal cord; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus; PAG, periaqueductal gray.

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