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# The role of transcriptional control in multiple system atrophy

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ABSTRACT

Multiple system atrophy (MSA) is an α-synucleinopathy that is clinically characterized by varying degrees of parkinsonian, autonomic, and cerebellar features. Unlike other α-synucleinopathies such as Parkinson's disease, MSA is unique in that the principal α-synuclein lesions, called glial cytoplasmic inclusions, occur in oligodendroglia rather than neurons, with significantly more α-synuclein accumulating in MSA brain compared with Parkinson's disease. Although well defined clinically, the molecular pathophysiology of MSA has barely been investigated. In particular, there have been no systematic studies of the perturbation of the brain transcriptome during the onset and progression of this disease. Interestingly, measurements of α-synuclein gene (*SNCA*) expression in MSA brain tissue have not revealed overexpression of this gene in oligodendroglia or neurons. It has therefore become clear that other genes and gene networks, both directly as noncoding RNAs or through protein products, contribute to the accumulation of the α-synuclein protein in the brain. This review provides a summary of current developments in the investigation of the transcriptional causes of MSA and outlines perspectives for future research toward the elucidation of the molecular pathology of MSA-specific neurodegeneration.


## 1. Introduction

α-Synucleinopathies comprise a group of neurodegenerative disorders, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) (Fellner and Stefanova, 2013; Ferrer, 2001; Halliday et al., 2011; Jellinger, 2003). The major pathologic hallmark of α-synucleinopathies is the aggregation of the protein α-synuclein throughout the brain; in PD and DLB these aggregates occur primarily in the neurons and are known as Lewy bodies and Lewy neurites, in MSA α-synuclein aggregation occurs in oligodendroglia and are known as glial cytoplasmic inclusions (GCIs).

α-Synuclein aggregation is thought to be a key event in the pathogenesis of α-synucleinopathies; however, the exact molecular mechanisms of pathogenesis have not been elucidated (Wakabayashi and Takahashi, 2006). The gene encoding human α-synuclein (*SNCA*) is located on chromosome 4q21.3-q22 (Campion et al., 1995), and 4 protein isoforms have been identified: α-synuclein 140, α-synuclein 126, α-synuclein 112, and α-synuclein 98 (Beyer and Ariza, 2013; Ma et al., 2013; McLean et al., 2000). Studies have shown that point mutations at the A30P, E46K, G51D, and A53T sites of α-synuclein 140 as well as the phosphorylation of serine at the 129 position are responsible for the development of PD (Kiely et al., 2013; Kosaka, 1978; Ma et al., 2013; Zarranz et al., 2004). Importantly, multiplications of the whole gene are also pathogenic for PD (Lesage and Brice, 2009). The expression of α-synuclein 98 is upregulated in PD and DLB patients (Beyer et al., 2008), whereas high expression of α-synuclein 112 is observed in DLB patients, suggesting that α-synuclein 112 might play a role in the pathogenesis of DLB (Beyer, 2006). In contrast to PD, *SNCA* gene multiplications do not occur in MSA, and there is no evidence of increased messenger RNA (mRNA) for the major species α-synuclein 140 (Asi et al., 2014; Jin et al., 2008; Miller et al., 2005; Ozawa et al., 2001). This suggests different pathogenic mechanisms between these α-synucleinopathies.

## 2. The role of glia in α-synucleinopathies

Glia is an umbrella term for a number of different cell types present in the brain including astrocyglial (or astrocytes), oligodendroglial (or oligodendrocytes), and microglial (Fellner and Stefanova, 2013; Halliday and Stevens, 2011). In a healthy brain, glial cells play an important support role throughout the brain providing an insulating myelin sheath around axons and metabolic and structural support for neurons. Evidence is emerging, suggesting that glial cells play a crucial role in a variety of α-synucleinopathies (Fellner et al., 2011; Halliday and Stevens, 2011). Initial injury or infection causes

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microglial and astroglial cells to be activated (Nimmerjahn et al., 2005; Wilhelmsson et al., 2006). Activated microglia and astroglia undergo morphologic changes, releasing trophic and inflammatory factors; additionally, activated microglial cells remove dead or apoptotic cells processes that are vital for neuron survival (Nimmerjahn et al., 2005; Wilhelmsson et al., 2006). However, in chronic diseases, astroglia, and microglia can become over activated leading to neurotoxicity and increased tissue damage after the release of proinflammatory cytokines, reactive oxygen species, and nitric oxide (Dean et al., 2010; Deshpande et al., 2005).

In neuronal α-synucleinopathies such as PD, α-synuclein aggregation occurs primarily in neurons but also features α-synuclein accumulation in astroglial cells (Braak et al., 2007; Wakabayashi et al., 2000). It is speculated that astroglia play a major role in PD by releasing inflammatory agents at the site of injury and recruiting microglial cells (Fellner and Stefanova, 2013). The microglial cells then become over activated leading to the production of proinflammatory agents, followed by oxidative stress, hence accelerating neuronal cell death (Zhang et al., 2005). It is not thought that oligodendroglia play a role in neuronal α-synucleinopathies. In the oligodendroglial α-synucleinopathy MSA, the initial site of α-synuclein accumulation is in the oligodendroglia cells. This results in the compromised function of these cells resulting in demyelination of axons and overall a lack of neuronal support. Activated astroglia at the site attract microglia through the release of proinflammotry cytokines, and oxidative stress promotes neuronal death (Fellner and Stefanova, 2013).

These models are not without controversy. Different studies have reported conflicting results on the functions of glial cells in α-synucleinopathies (Stefanis, 2012), suggesting that glial cells might participate in more than one pathogenic process and that their dominant function corresponds to their local environmental changes, such as neuroinflammation. Furthermore, other research groups have suggested that astroglia are not activated during some α-synucleinopathies (Mirza et al., 2000; Vila et al., 2001). This is further confounded by glial cells well-documented positive effects on compromised neuronal cells. The complex role of glia in α-synucleinopathies warrants further investigation in neurodegenerative diseases.

## 3. Multiple system atrophy

MSA is a sporadic neurodegenerative disorder characterized by varying combinations of parkinsonism, cerebellar ataxia, and autonomic failure (Gilman et al., 2008; Lu et al., 2013). Prevalence rates range from 1.9 to 4.6/100,000, and the mean age at disease onset is approximately 55 years (O'Sullivan et al., 2008). The incidence rate is approximately 0.6 cases per 100,000 persons (Vanacore et al., 2001). The mean survival time after diagnosis of MSA is 9 years (Donadio et al., 2010). It is a rapidly progressing disease, and patients may be confined to a wheelchair after only a few years from diagnosis (Watanabe et al., 2002). Studies have shown that males are more susceptible to this disease than females, with ratios ranging from between 1.4: 1 to 1.9: 1 (Wenning et al., 2004). Two significant pathologic features that characterize MSA are GCIs and neuronal intranuclear inclusions, both of which are composed of α-synuclein (Nakayama et al., 2012). However, the precise function and regulation of α-synuclein in MSA is yet to be determined. Further, extensive myelin (forming a myelin sheath around axons in white matter) damage is present in the brains of MSA patients (Matsuo et al., 1998; Probst-Cousin et al., 1998).

MSA is further categorized into 2 subtypes based on clinical phenotypes (Gawel et al., 2012; Umoto et al., 2012). Patients who present predominantly with parkinsonian symptoms are classified as MSA with parkinsonism (MSA-P), and patients who present predominantly with a cerebellar syndrome are classified as MSA with cerebellar signs (MSA-C) (Gilman et al., 2008; Kawai et al., 2008; Nicoletti et al., 2006). The primary pathologic differences between the 2 subtypes are based on the sites of neuronal loss and GCI accumulation (Tong et al., 2010). In MSA-C patients, the loss of neurons occurs primarily in the basis pontis, inferior olives, and cerebellar cortex, this is coupled with white matter (WM) degeneration of the middle cerebellar peduncle (Lu et al., 2013; Minnerop et al., 2010). The main differentiating pathology in MSA-P is the progressive degeneration of putaminal neurons (Sato et al., 2007), significantly affecting basal ganglia circuits involved in the regulation of motor pathways. Further, MSA-P is characterized by progressive akinesia and rigidity and a poor response to levodopa therapy (Wenning et al., 2004). The prevalence of MSA-P and MSA-C varies in different parts of the world: subtype C has been reported to be more prevalent than subtype P in the Japanese population (65%–67% vs. 33%–35%), whereas subtype P is more prevalent in Europe (63% vs. 34%) and North America (60% vs. 13%, with 27% of cases unclassified) (Multiple-System Atrophy Research Collaboration, 2013).

## 4. α-Synuclein and MSA

As mentioned previously, the etiology of MSA is an increase in the brain level and accumulation of α-synuclein, a small, natively unfolded protein that accounts for as much as 1% of the total protein in the soluble cytosolic brain fraction (Bisaglia et al., 2009; Uversky, 2007). Monomeric α-synuclein exists in the presynaptic termini in equilibrium between free and membrane-bound states (McLean et al., 2000). Approximately 15% of α-synuclein is membrane bound (Lee et al., 2002), suggesting that the protein may regulate vesicular release and/or turnover and other synaptic functions in the central nervous system (Clayton and George, 1999; Lavedan, 1998; Ueda et al., 1993). Mutation and/or environmental changes may reduce the capability of α-synuclein to recognize proper binding partners. For instance, the presence of $Al^{3+}$ and $Cu^{2+}$ may induce structural perturbation (Paik et al., 1997, 1999), and point mutations at A30P, E49K, and A53T were shown to reduce protein hydrophobicity (Li et al., 2001), thus leading to the formation of nonfunctional and deadly aggregates (Uversky, 2007). In addition, the interaction between α-synuclein and β-III tubulin in the transgenic mouse model and the nitration of α-synuclein tyrosine residues are critical for the formation of insoluble protein complexes that progressively accumulate in neurons (Ischiropoulos and Beckman, 2003; Nakayama et al., 2012; Souza et al., 2000). These accumulated α-synuclein complexes lead to neuronal dysfunction (Nakayama et al., 2009). However, according to studies GCIs usually contain full-length and C-terminally truncated α-synuclein; the latter, truncated α-synuclein, is more prone to fibrillate than the full-length protein in vitro (Gai et al., 1998; Murray et al., 2003; Serpell et al., 2000; Uversky, 2007). Research has also shown that phosphorylation of α-synuclein at serine 129 promotes fibril formation in vitro, possibly by altering the confirmation of the C terminus of α-synuclein (Fujiwara et al., 2002).

Studies using animal models have not only demonstrated that the expression of lipid and membrane transport genes are associated with α-synuclein expression but have also stated that changes in membrane fluidity and in cellular fatty acid uptake and metabolism are consequences of either the overexpression or homozygous deletion of *SNCA* in a neuronal cell line (Castagnet et al., 2005; Golovko et al., 2005; Scherzer et al., 2003; Sharon et al., 2003).

Alternative splicing is a versatile and widespread post-transcriptional mechanism for the generation of multiple mRNAs from a single transcript (Beyer, 2006; McLean et al., 2000; Mills and Janitz, 2012). The α-synuclein-encoding gene *SNCA* undergoes complex splicing events, including in-frame deletion (the deletion of one