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Review

Translational therapies for multiple system atrophy: Bottlenecks and future directions

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ABSTRACT

Over the last decade a prominent amount of studies in preclinical transgenic models of multiple system atrophy (MSA) has been performed. These studies have helped understand mechanisms downstream to the α-synuclein oligodendroglial accumulation relevant to human MSA. However, the successful translation of the preclinical outcomes into a clinical trial has failed. Looking back, we can now identify possible confounders for the failure. Biomarkers of disease progression are mostly missing. Early diagnosis and initiation of therapeutic clinical trials is limited. The need of both proof-of-concept as well as clinically relevant preclinical study designs with clinically relevant timing and preclinical readouts is identified as a must in our translational efforts for MSA to date. Finally, improved clinical study designs with improved enrollment criteria, and measurement outcomes are warranted on the way to finding the successful therapeutic approach for MSA. This review provides an overview of experimental studies and clinical trials for MSA and the lessons learned over the last decade towards the identification of the cure for MSA.

Multiple system atrophy (MSA) is an α-synucleinopathy with a very aggressive course and poor prognosis. It is less common as compared to Parkinson's disease (PD), but due to its fast progression after clinical diagnosis and the limited availability of symptomatic amelioration, MSA represents a serious health and social problem. The disease lacks efficient treatment and poses a great challenge to translational research at present.

1. Diagnostic limitations

MSA presents with a variable set of non-motor and motor symptoms that makes the early diagnosis difficult. Classically, based on the current diagnostic criteria (Gilman et al., 2008), MSA is diagnosed clinically with partial degree of certainty (possible or probable) only when motor symptoms occur (Fanciulli and Wenning, 2015). However, the motor symptoms are usually preceded by a set of non-motor features including urogenital dysfunction, orthostatic hypotension, REM sleep behavior disorder (RBD) that may seem unspecific but indicate a much earlier disease onset. The efforts to identify early body fluid-, tissue-, or imaging biomarkers are yet insufficient to support the early diagnosis of MSA before the onset of parkinsonism or cerebellar symptoms (Jellinger and Wenning, 2016). Therefore, the first bottleneck in the successful identification of translational therapies for MSA remains the difficulty to provide early diagnostic markers and markers of disease progression.

2. Therapeutic target definition in MSA – unresolved etiology and candidate downstream disease mechanisms

What is the trigger of MSA? A single study to date provides evidence for mutations in the COQ2 gene linked to MSA in Japanese families (The Multiple-System Atrophy Research Collaboration, 2013). However, these mutations were not found to play a role in other cohorts of MSA patients (Sharma et al., 2014; Ogaki et al., 2014; Chen et al., 2015) proposing a possible population-specific predisposition. Genome-wide association studies and estimates of heritability fail to confirm a strong role of genetic predisposition as a prominent risk factor for MSA (Sailer et al., 2016; Federoff et al., 2015). Alternatively, environmental and epigenetic factors have been suggested to link to higher risk of developing MSA (Nicholl et al., 1999; Vanacore et al., 2000; Vanacore, 2005; Vanacore et al., 2005; Sturm and Stefanova, 2014). However, both the genetic analyses and the epidemiological studies in MSA suffer a major limitation related to the low number of sample sets of well-characterized patients. Therefore, the outcomes of these studies may differ or even show contradictory results due to a low statistical power and poor design. In summary, genetic targets for therapies of MSA at this stage remain undefined, while epigenetic factors are insufficiently studied.

The main neuropathological hallmark which serves the final post-mortem diagnosis of MSA, are the glial cytoplasmic inclusions (GCIs). GCIs are ectopic aggregates of fibrillar α-synuclein (α-syn) together with other components in the cytoplasm of oligodendrocytes in the

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Table 1
Functional phenotype in experimental MSA models with α-synuclein pathology.

Model	Survival	Motor symptoms (onset)	Cardio-vascular autonomic dysfunction (onset)	Urogenital dysfunction (onset)	REM sleep behavior disorder (onset)	Respiratory dysfunction (onset)	Preserved olfaction	Symptom progression
MBP-α-syn mice								
Line 29[a]	< 6 mo	YES (2–4 mo)	na	na	na	na	na	Aggressive
Line 1[b]	Normal	YES (6–12 mo)	NO	na	na	na	na	Slow
CNP-α-syn mice[b]	Normal	YES (7–9 mo)	na	na	na	na	na	Slow
PLP-α-syn mice[b]	Normal	YES (6–12 mo)	YES (5 mo)	YES (2 mo)	YES (2 mo)	YES (13 mo)	YES	Slow
AAV-MBP								
Rat	na	YES (3–6 mo)	na	na	na	na	na	Slow
Non-human primate	na	na	na	na	na	na	na	na
AAV-Olig001								
Rat	na	na	na	na	na	na	na	na
Non-human primate	na	na	na	na	na	na	na	na

[a] High levels of human α-syn overexpression.
[b] Intermediate levels of human α-syn overexpression; na - not assessed. (Shults et al., 2005; Yazawa et al., 2005; Stefanova et al., 2005; Stefanova et al., 2007; Krismer et al., 2013; Boudes et al., 2013; Kuzdas et al., 2013; Stefanova et al., 2013; Flabeau et al., 2014; Fernagut et al., 2014; Bassil et al., 2017b; Mandel et al., 2017; Hartner et al., 2016).

MSA brain (Papp et al., 1989; Spillantini et al., 1998; Wenning et al., 2008). α-syn has been shown to form aggregates also in the neuronal cytoplasm in affected neuronal circuits, however these neuronal inclusions show different properties as compared to classical Lewy bodies (Cykowski et al., 2015).

The reason for the unique pattern of α-syn accumulation in MSA remains to date greatly speculative. Currently, two major theories exist – one suggesting that a primary oligodendrogliopathy is the reason for the ectopic GCI formation (Wenning et al., 2008), and the second proposing the existence of disease-specific α-syn species and distinct protein assemblies which may explain the specific pathology and phenotypes in α-synucleinoapthies (Peelaerts et al., 2015; Melki, 2015).

The idea of possible primary oligodendroglial dysfunction is supported by the observation that p25α relocation from myelin to the soma and aggregation in the cytoplasm of MSA oligodendrocytes may precede the aggregation of α-syn and the formation of the classical GCIs (Song et al., 2007). However, it remains unclear how this event is triggered.

Another unresolved mystery of MSA pathogenesis which may be linked to a primary oligodendrogliopathy in this disorder, is the source of α-syn in GCIs. It is considered that α-syn is a neuronal protein that is not expressed in mature oligodendrocytes (Miller et al., 2005; Solano et al., 2000). A recent study which applies laser dissection microscopy to provide a more precise characterization of the SNCA mRNA expression in healthy and MSA oligodendroglia suggests that α-syn expression might be present in these cells and even show a tendency towards increase in MSA brains (Asi et al., 2014). However, these results contradict reports suggesting that the expression level of α-syn mRNA is unchanged in MSA post-mortem samples (Ozawa et al., 2001). Respectively, if the latter is true, the protein degradation rather than the production of α-syn may be disturbed in oligodendrocytes and trigger the GCI pathology. Currently, experimental indirect evidence supports this hypothesis (Schwarz et al., 2012; Pukass et al., 2015; Stefanova et al., 2012b) but the data from post-mortem studies in MSA brains confirming its validity is limited (Tanji et al., 2013; Langerveld et al., 2007;Miki et al., 2016).

Finally, the hypothesis of α-syn inclusion spreading linked to distinct α-syn strains is currently widely discussed and studied in MSA as well as in other α-synucleinopathies. The principle possibility of α-syn transfer from neurons to oligodendrocytes has been experimentally suggested in an AAV-α-syn overexpressing rat model of PD receiving rat oligodendroglial grafts in the striatum (Reyes et al., 2014). However, α-syn aggregates have not been detected in striatal grafts in MSA transgenic mice overexpressing α-syn in oligodendrocytes (Stefanova et al., 2009). A study by Peelaerts and co-workers suggested that the transfer of α-syn to oligodendrocytes may be dependent on the type of recombinant α-syn strains inoculated in the rodent brain (Peelaerts et al., 2015). The ability of α-syn derived from MSA brains to trigger aggregate spreading was shown in A53T transgenic mouse model of PD (Watts et al., 2013;Prusiner et al., 2015), however this study failed to demonstrate α-syn aggregation in oligodendrocytes. Furthermore, “a prion transmission of neurological disease”, as claimed by Prusiner and co-workers in relation to MSA, has been observed only in genetically modified transgenic mice overexpressing the A53T mutation of α-syn, but not in wild type animals (Watts et al., 2013; Prusiner et al., 2015). These results suggest that only a specific condition of the host brain but not the MSA α-syn species per se may trigger disease transmission.

In summary, the role of α-syn pathology in the pathogenesis of MSA is unequivocal, but its exact origin and genesis as well as the role of preceding oligodendroglial dysfunction remain unresolved and warrant further studies. It is possible that both, propagation from neurons to oligodendrocytes as well as oligodendroglial expression of α-syn may contribute to the formation of GCIs. However, at present there is insufficient evidence to claim the existence of “MSA prions” and label MSA a prion disease.

3. Animal models of MSA - advantages and limitations

A key problem and major limitation in modelling MSA to date is the limited knowledge on the initiation of the disease process. Over the years, transgenic models overexpressing human α-syn in oligodendrocytes using different promoters have been a valuable tool to identify downstream mechanisms of disease progression in MSA. Each of these models shows different degree of functional deterioration (Table 1) and MSA-like neuropathology (Table 2). The myelin basic protein (MBP)-α-syn mouse presents with prominent demyelination which is α-*syn*-dose dependent and leads to secondary neuronal loss in neocortex and axonal degeneration in striatum (Shults et al., 2005). The 2′,3′-Cyclic-nucleotide 3′-phosphodiesterase (CNP)-α-syn transgenic mouse suggested the role of endogenous α-syn accumulation in axons that may lead to secondary axonal degeneration affecting predominantly the cortex and the spinal cord (Yazawa et al., 2005). The proteolipid protein (PLP)-α-syn transgenic mouse suggests a leading role of microglial activation resulting in selective striatonigral degeneration (SND)