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Multiple System Atrophy: Moving towards a Multi-mechanistic Hypothesis

Monica Federoff*

Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, USA

***Corresponding author:** *Monica Federoff, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, USA, E-mail: monica.federoff22@gmail.com*

With an estimated incidence of 3-4 per every 100,000 individuals among adults 50-99 years of age, Multiple System Atrophy (MSA) is a rare progressive neurodegenerative disease clinically characterized by the following trio: cerebellar ataxia, parkinsonism and autonomic dysfunction in conjunction with pyramidal signs [1-3].

MSA usually progresses over a 7-9 year period, with an average age of onset of 57 and affects both sexes equally [2,4]. Given our limited fund of knowledge regarding the genetics and biomarkers underlying MSA etiology, definitive diagnosis can only be verified upon pathological examination, in which one must confirm the presence of MSA's pathognomonic hallmark: alpha-synuclein-positive glial cytoplasmic inclusions (GCIs) [2,5].

While a few familial studies have revealed an underlying genetic component of MSA, it is currently classified as a sporadic disease [4,6]. As an etiologically and clinically complex disorder, MSA has been split into two distinct subtypes based on predominant clinical features and corresponding post-mortem examination: MSA-Cerebellar (C), MSA-parkinsonism (P), with frequency varying in a population-specific manner [1,7,8]. While MSA patients display marked neurodegenerative changes in the striatonigral and/or olivopontocerebellar structures of the brain with respect to subtype, there is extensive variation in the degree of degeneration, depicted by a broad spectrum of myelin pallor, gliosis and neuronal loss; hence, despite clinically and pathologically defined subtype characterization, the histopathological features among patients with MSA are quite heterogeneous [1].

In Kurt A. Jellinger's recent mini review entitled, "Pathogenesis of Multiple System Atrophy-Recent Developments," he discusses our current understanding of MSA etiopathogenesis according to the latest findings in the field. With respect to molecular pathophysiology, he reflects on perhaps the largest conundrum underlying GCI formation: how does alpha-synuclein ultimately end up in oligodendrocytes, despite its apparently neuronal site of origin?

A thorough analysis of MSA literature illustrates that many groups have garnered evidence for the most widely supported hypothesis: alpha-synuclein is derived from neurons but spreads to oligodendroglia. In 2012, Kisos et al. revealed that in the presence of elevated alpha-synuclein levels, either in the form of soluble oligomers or intracellular alpha-synuclein inclusions in neurons, neuronal secretion is enhanced within rat brains [9]. Specifically, it was demonstrated that rat oligodendroglial cells *in vitro* internalized alpha-synuclein from neuronal secretions in a time, concentration and clathrin-dependent fashion [9].

Furthermore, Rockenstein and colleagues utilized transgenic mice models to study heterozygous progeny. Among the parental mice, one expressed alpha-synuclein under an oligodendroglial-specific myelin-basic promoter and the other parental mouse expressed alpha-synuclein under a neuronal platelet derived growth factor promoter [10]. Studying the compound transgenic mice progeny demonstrated a "robust redistribution" of alpha-synuclein [8,10]. While the exact mechanism of action is unknown, Rockenstein and colleagues hypothesized that a direct "translocation" through the extracellular space occurred via cell-cell interactions, moving alpha-synuclein from neurons to neighboring oligodendrocytes [10].

Collectively, these data suggest a predilection for alpha-synuclein accumulation in oligodendroglia relative to the neurons in regions of the brain susceptible to MSA, resonating with classic pathophysiological changes seen in the disease [8,10]. Moreover, in 2014, Reyes *et al.* demonstrated that oligodendrocytes can successfully uptake recombinant alpha-synuclein and internalize it in vivo in mouse cortices [11]. Thus, while evidence for this mechanism is substantial, Jellinger discusses more recent findingswhich may suggest that several mechanisms occur in tandem.

Within the last two years, the discovery of alpha-synuclein's propagating and seeding abilitieshas been pivotal. Upon injection into rat brains, Peelaerts *et al.* portrayed that alpha-synuclein is capable of in vivo amplification. Secondly, intravenous injection of alpha-synuclein was shown to cross the blood brain barrier into the CNS. Upon scrutinizing strain type, the data suggests that oligomers, ribbons and fibrils formed by alpha-synuclein may harbor different levels of solubility and toxicity, as defined by distinctive histopathology and behavioral phenotypes manifested by rats [12]. Further, others have even suggested that alpha-synuclein be classified as a prion, capable of causing MSA and resonating with prion diseases like Creutzfeldt-Jakob Disease (CJD) and Kuru [13]. While evidence for the latter is insufficient at present, as we have no proof that MSA is indeed transmissible among humans, the propagation and seeding abilities of alpha-synuclein have been proven by multiple sources [12-16]. Collectively, these studies represent an important milestone in unraveling MSA pathophysiology and have since been incorporated into our evolving framework.

It has been suggested that specific MSA clinical subtypes, duration of disease, and disease severity are all associated with the

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quantitative distribution and density of GCIs in MSA cases [1]. While GCIs represent the pathological signature of MSA, the abnormal accumulation of alpha-synuclein has also been identified within neuronal cytoplasmic inclusions (NCIs), neuronal nuclei inclusions (NNIs), and within neurites of a minority of MSA affected brains. While these findings have not been the primary focus of MSA in previous molecular research, the potential role of NCIs, NNIs and neurites in the pathological process of MSA has warranted further investigation [1,17].

Within the last year, Cykowski *et al.* embarked on an extensive neuropathological investigation of MSA post-mortem brains and revealed that widespread neuronal inclusions were seen in most patients, in both disease-associated regions (i.e. substantia nigra), and several other non-disease associated regions (i.e. hypothalamus). Further, a hierarchal region specific susceptibility pattern was observed from neuronal inclusions. While this was unrelated to clinical phenotype, the severity of pathology was disease duration dependent. Moreover, interregional correlations between pathological neuronal and glial lesion burden were observed, hinting at possible overlapping disease mechanisms in distinct brain regions and the significance of NCIs and NNIs in MSA histopathology [18].

Further on this subject, Jellinger discusses the recent publication of a study investigating the immunohistochemistry underlying Minimal change MSA (MC-MSA), in which MC-MSA is defined as a subtype of MSA manifesting neuronal loss primarily in the substantia nigra and locus coeruleus [19]. Ling *et al.* identified a greater proportion of NCIs in the disease-associated regions (substantia nigra, caudate) of MC-MSA individuals than in MSA controls. As neuronal changes were demonstrated to be disease duration dependent by Cykowski and colleagues, this suggests that NCIs may be involved in the early disease process. Hence, their findings suggest that alpha-synuclein associated oligodendroglial pathology (i.e. GCIs) could result or possibly occur in parallel with neuronal dysfunction (i.e. NCIs) capable of causing clinical symptoms prior to neuron loss [18].

Newly identified knowledge of alpha-synuclein seeding properties and the potentially important role of NNIs and NCIs in MSA elicit the question: can alpha-synuclein be derived from oligodendrocytes and if so, is this transmissible to neurons? First, it is useful to reflect on the feasible nature of transmission between oligodendrocytes and neurons using a glial derived protein, TPPP. As a protein of great interest regarding MSA pathology, tubulin-polymerization-promoting protein (TPPP), also known as p25 alpha, functions in the stabilization of microtubules and the differentiation of oligodendrocytes [20]. Approximately ten years ago Baker *et al.* demonstrated the presence of TPPP located within neurons, suggesting a transmission from oligodendroglia to neurons [21,22]. This is particularly noteworthy, as we have substantial evidence that TPPP is closely involved in GCI formation in oligodendrocytes. Revisiting the transmission of alpha-synuclein, Asi *et al.* demonstrated in 2014 that alpha-synuclein mRNA is expressed in oligodendrocytes among MSA post-mortem brain tissue [22,23]. While we know alpha-synuclein is transcribed and translated in neurons, the possibility of glial cells transcribing alpha-synuclein is intriguing, as it suggests that some of the alpha-synuclein aggregates in oligodendrocytes may indeed originate from those cells, or may even be transmitted to neurons to form NNIs and NCIs.

While *in vitro*, *in vivo* and transgenic studies continue to elucidate molecular mechanisms driving MSA etiology and pathology, a singular, unifying molecular mechanism underpinning MSA has yet to be clarified. However, by acquiring information from recent studies and applying it to an evolving MSA pathophysiological framework, Jellinger and others among the MSA scientific community continue to fill in missing pieces to the puzzle [22]. As portrayed in Jellinger's mini review, a comprehensive analysis of MSA molecular etiopathogenesis may suggest a multi-mechanistic (vs. singular) hypothesis, in which several molecular processes occur simultaneously among both neuronal and glial cells to result in observed MSA pathology.

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