*Experimental Neurobiology*
Vol. 18, pages 19~25, June 2009

# Topographical Propagation of α-synuclein Pathology in Parkinson's Disease: Phenomenology and Hypothetical Mechanism

Minsuk Hyun and Seung-Jae Lee*

Department of Biomedical Science and Technology, IBST,
Konkuk University, Seoul 143-701, Korea

## ABSTRACT

Parkinson's disease is an age-related, slowly progressing neurodegenerative disorder characterized by abnormal deposition of aggregated α-synuclein in neuronal cell bodies (Lewy bodies) and neurites (Lewy neurites), as well as in glia. Based on semiquantitative assessment of Lewy pathologies in autopsy samples, a staging system was proposed indicating a highly predictable sequence of pathological progression. This staging system implicates a propagation of α-synuclein aggregation throughout the brain with an ascending pattern from lower brain stem to neocortex. The underlying mechanism for the pathological propagation is unknown. However, the recent discoveries on the secretion of neuronal α-synuclein and subsequent uptake of the protein by neighboring cells propose an interneuronal transmission of α-synuclein aggregates as a novel mechanism for the spread of Lewy pathology in PD. Elucidation of this mechanism is likely to identify novel therapeutic strategies that halt the progression of PD.

**Key words:** lewy body, protein aggregation, exocytosis, endocytosis

## INTRODUCTION

Parkinson's disease (PD) is a common age-related neurodegenerative disorder, first described by English physician James Parkinson. Clinically, PD is primarily defined by motor symptoms, such as muscle rigidity, resting tremor, and bradykinesia (Fahn and Sulzer, 2004). However, PD also shows a spectrum of non-motor symptoms, ranging from central nervous system dysfunctions (dementia, cognitive impairment, psychiatric disorders, loss of olfaction, etc.) to various autonomic dysfunctions (oily skin, urinary incontinence, weight loss, etc.) (Poewe, 2007). Pathological features of PD include the loss of dopaminergic neurons in substantia nigra and the occurrence of α-synuclein immunoreactive inclusion bodies, called Lewy bodies (LBs) and Lewy neurites (LNs), in the remaining neurons (Forno, 1996). Lewy pathology is not limited to PD, but also found in a variety of neurological disorders, including dementia with LBs (DLB) and the LB variant of Alzheimer's disease, which are now collectively referred to as synucleinopathies (Hardy and Gwinn-Hardy, 1998). Lewy pathology in PD and other synucleinopathies generally shows wide spread patterns affecting various regions of the brain. Recently, Braak and colleagues proposed

*To whom correspondence should be addressed.
TEL: 82-2-450-4166, FAX: 82-2-447-5683
e-mail: sjlee@konkuk.ac.kr
Received December 23, 2008
Accepted for publication June 10, 2009

a staging system for assessing the progression of PD pathology, based on their observation that α-synuclein-positive Lewy pathology shows a predictable sequence of pathological progression throughout the brain (Braak et al., 2003). In this review, we will summarize the current knowledge on the pathological progression in PD, and propose a hypothesis for the underlying mechanism of the progression based on the recent discoveries in extracellular α-synuclein.

## CLINICAL OVERVIEW OF PD

In PD, although not all patients display identical symptoms with identical progression, common motor symptoms of PD show a characteristic pattern of progression (Alves et al., 2005; Jankovic, 2008). The early motor symptoms include bradykinesia, tremors, postural deformities, and decreased facial expression (Jankovic, 2008). Bradykinesia, which refers to slowness of movement, is most commonly seen in PD patients. It is marked as a basal ganglia disorder, and renders slowness in daily-life activities and reaction times. Rest tremor, one of the common and easily recognized symptoms of PD, is present in the distal part of an extremity. As the disease progresses to more severe forms, the symptoms on one side of body begin to encroach on the other. More advanced PD patients show poor-balance ability, difficulty in initiating movements, and more severe rigidity. PD patients also show non-motor symptoms; autonomic dysfunction features from orthostatic hypotension, sweating dysfunction, sphincter dysfunction to erectile dysfunction; sleep disorders, especially the REM sleep disorder; cognitive and psychiatric abnormalities such as depression, apathy, anxiety, hallucination, and dementia (Poewe, 2007). Like the motor symptoms, the severity of the non-motor symptoms in PD patients tend to show progressive characteristics; the average MMSE score, which measures the state of cognitive condition, of PD patients showed a linear trend of decline from Braak stages 3 to 6 (Fig. 1).

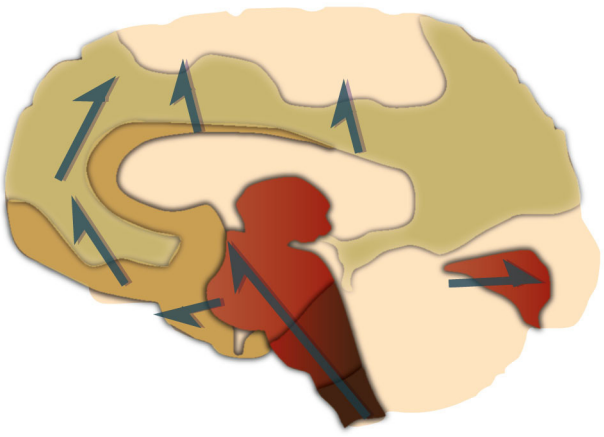

**Fig. 1.** Propagation of α-synuclein pathology with an ascending pattern. The Lewy pathology starts in the dorsal motor nucleus and progresses, via substantia nigra and mesocortex, eventually to the neocortex. The intensity of the shading indicates the severity of the pathology (adopted from (Braak et al., 2004)).

## TOPOGRAPHICAL PROGRESSION OF LEWY PATHOLOGY

PD pathology is characterised by α-synuclein inclusions: LBs and LNs (Braak et al., 2003). While the mechanisms of lesion development are not yet understood, autopsy studies by Braak and colleagues showed α-synuclein deposition in various brain regions following a predictable and systematic progression pattern (Braak et al., 2002; Braak et al., 2003) (Fig. 1). Brain samples from potential PD patients, presumably representing the earliest PD pathology, showed confined lesions in the two sites: the dorsal motor nucleus of the vagus nerve and the olfactory bulb (Braak et al., 2006). No more than a few LBs and LNs were found in the vagus nerve at this stage (Braak Stage 1). As the Lewy pathology in the dorsal motor nucleus worsens along the progression of the PD, this pathological feature then spreads to the upper brainstem nuclei. This upward tendency from dorsal motor nucleus to brainstem, however, is initially restricted to the boundary of the pontine tegmentum (Braak Stage 2). When the pathological features approach to Braak stage 3, the midbrain and forebrain show disease-related alterations. In this stage, the upward progression from dorsal motor nucleus crosses the limit of the pontine tegmentum and encroaches on the substantia nigra. At the same time, previous damages in the lower brain worsen. Pathological progression after this point overlaps with AD pathology. Inclusion bodies start to appear in the transition zone between the allocortex and

the neocortex, which corresponds to the antero-medial temporal mesocortex. Specifically, numerous LBs were found in high order sensory organs such as entorhinal region and amygdala (Braak Stage 4). Sometime at this point, it is thought that PD is clinically manifested. After mesocortex, the pathology finally spreads to neocortex, with the clinical symptoms fully developed. Pathology of neocortex first appears in the prefrontal and high sensory area, and is later shown in the premotor and first order sensory association areas (Braak Stage 5 and 6). Although some studies reported the cases that did not comply with the Braak staging of PD pathology (Parkkinen et al., 2005; Parkkinen et al., 2008), this staging system has been confirmed by a number of autopsy studies (Jellinger, 2003; 2004).

## PD AND α-SYNUCLEIN

Even though the cause of PD is largely unknown, both environmental and genetic factors are thought to contribute to the development of the disease. Since 1997, several mutations have been identified in familial cases of the disease (Farrer, 2006). The first of such mutations was identified in the gene encoding neuronal protein α-synuclein; two additional autosomal dominant missense mutations and several gene multiplication mutations in the same gene have been identified in familial PD afterwards. The link between α-synuclein and PD was further strengthened by the finding that fibriliar aggregates of this protein are the major component of LBs and LNs in sporadic PD (Spillantini et al., 1998). Biochemical analyses indicated that α-synuclein may form amyloid fibrils that are similar to the aggregates found in LBs (Conway et al., 2000). Furthermore, all the α-synuclein missense mutations accelerated the aggregation of the protein (Cookson, 2005). The role of α-synuclein aggregation in neurodegeneration was demonstrated when overexpression of wild type and mutant α-synuclein led to neuronal loss and LB-like inclusion formation in animal models (Maries et al., 2003).

α-synuclein is a member of the synuclein family which also includes β-synuclein and γ-synuclein (George, 2001). Human α-synuclein consists of 140 amino acids and is characterised by highly conserved amphipathic N-terminal regions with seven repeats of the KTKEGV consensus motif and highly variable acidic C-terminal regions (Cookson, 2005). This protein also contains a central hydrophobic non-amyloid-β component (NAC) domain, through which amyloidogenic intermolecular interaction might occur (Giasson et al., 2001). Biological function of α-synuclein is not completely understood. However, its localization in the presynaptic nerve terminals and its ability to bind to lipid membranes indicate its role in neural transmission (Iwai et al., 1995; Davidson et al., 1998). Subtle, but significant changes in neurotransmission and synaptic vesicle recycling have been found in α-synuclein knock-out mice (Abeliovich et al., 2000; Cabin et al., 2002; Liu et al., 2004; Yavich et al., 2004). The knockout studies also suggested its role in fatty acid metabolism (Castagnet et al., 2005; Golovko et al., 2005). Other studies suggested that α-synuclein has characteristics of molecular chaperones (Kim et al., 2000; Souza et al., 2000).

## EXOCYTOSIS OF α-SYNUCLEIN

Despite the fact that α-synuclein is typically a cytosolic protein, a small amount of this protein is constitutively secreted from various types of cells, including primary neurons (El-Agnaf et al., 2003; Lee et al., 2005; Sung et al., 2005). Although the mechanism of the secretion is not well understood, translocation of the protein into vesicles and subsequent exocytosis appear to be the primary mechanism responsible for the secretion of α-synuclein (Lee et al., 2005). The identity of the vesicles is unknown as yet. However, electron microscopy and density gradient ultracentrifugation experiments showed that the vesicles containing α-synuclein have morphologies and sedimentation properties similar to the dense core vesicles (Lee et al., 2005). The critical questions to be addressed include how the α-synuclein proteins to be secreted are selected and what are the vesicles involved and how the exocytosis is regulated.

Analyses of human cerebrospinal fluid (CSF) and blood plasma confirmed the presence of extracellular α-synuclein, suggesting that the secretion of α-synuclein occurs in human (Borghi et al., 2000; El-Agnaf et al., 2003). Although whether the level of extracellular α-synuclein changes in disease is

embroiled in controversy (Borghi et al., 2000; El-Agnaf et al., 2003; Lee et al., 2006; Tokuda et al., 2006), measurement using the ELISA specific for oligomeric forms of α-synuclein showed that oligomeric α-synuclein levels in blood plasma and postmortem CSF from PD patients have elevated significantly compared to control group (El-Agnaf et al., 2006).

Since only a small amount of cellular α-synuclein is translocated and secreted through vesicles with the majority of the proteins remain in the cytoplasm, vesicle entry of this protein must be a selective process. Although the mechanism of this selection is unknown, our recent study suggests that misfolded/damaged proteins are preferentially translocated into vesicles and subsequently discarded from cells by exocytosis (Lee et al., unpublished data). The accumulation of misfolded α-synuclein in specific vesicle populations predicts the aggregation of this protein within the vesicles. In fact, α-synuclein aggregation preferentially occurs in vesicles, and these aggregates are exocytosed from cells (Lee et al., 2005). Although physiological and pathological functions of extracellular α-synuclein is still in mystery, its potential role in the initiation and progression of PD has been proposed from its ability to induce neuronal death in culture and neuroinflammatory responses from glial cells (Zhang et al., 2005; Klegeris et al., 2006; Su et al., 2007; Thomas et al., 2007; Klegeris et al., 2008; Lee, 2008).

## HYPOTHETICAL MECHANISM OF PATHOLOGICAL PROPAGATION IN PD

PD is a progressive disease with its pathology beginning and advancing in a highly predictable sequence throughout the CNS (Braak et al., 2003). Given the consistent progression pattern, it may not be unreasonable to consider the possibility of progressive propagation of pathogenic events through the affected areas. How the pathogenic events are propagated is unknown. One possible mechanism for the propagation might involve a spatial progression from one brain region to another of the factors that affects the basic physiology of neurons and surrounding glial cells. Alternatively, the pathological process, such as α-synuclein aggregation, might directly propagate from affected neurons to adjacent neurons or to distant neurons through synaptic connections. The latter possibility was recently supported by the studies showing the neuron's ability to take up extracellular α-synuclein (Sung et al., 2001; Ahn et al., 2006; Lee et al., 2008b). Extracellular α-synuclein aggregates are taken up by the receptor-mediated endocytosis, followed by endosomal trafficking and lysosome-mediated breakdown (Lee et al., 2008b). Both neuronal and glial cells are capable of this endocytic internalization and degradation of α-synuclein aggregates (Lee et al., 2008a). Although the normal fate of the internalized α-synuclein appears to be the lysosomal degradation, following the prolonged exposure to extracellular α-synuclein aggregates, the internalization of these aggregates may cause the accumulation of the protein in LB-like inclusion forms (Lee et al., unpublished data). During the accumulation of these aggregates, the externally derived aggregates interact with the intrinsic cytoplasmic α-synuclein, suggesting a seeding-induced amplification of the aggregates (Lee et al, unpublished data). These studies provide strong experimental evidence for direct cell-to-cell propagation of α-synuclein aggregates.

Propagation of pathogenic events by exogenous pathogens has been well documented in prion disorders. In prion disorders, pathogenic prion aggregates can "infect" cells and nucleate the polymerization of normal cellular proteins (Caughey, 2000). Alzheimer's disease may be operated by a similar pathogenic propagation mechanism. Administration of brain homogenates prepared from Alzheimer's patients or a transgenic mouse model of the disease caused earlier and more severe plaque pathology and neurodegeneration in an animal model of AD (Meyer-Luehmann et al., 2006). Although no such experiments have been performed in models of PD, secretion of α-synuclein aggregates into the extracellular space and subsequent uptake of these proteins by adjacent neurons implicate interneuronal transmission of α-synuclein aggregates and the prion-like aggregate seeding, which may constitute the mechanistic basis for the pathological propagation (Fig. 2). This hypothetical mechanism may also explain the recent findings of host-to-graft propagation of α-synuclein inclusions

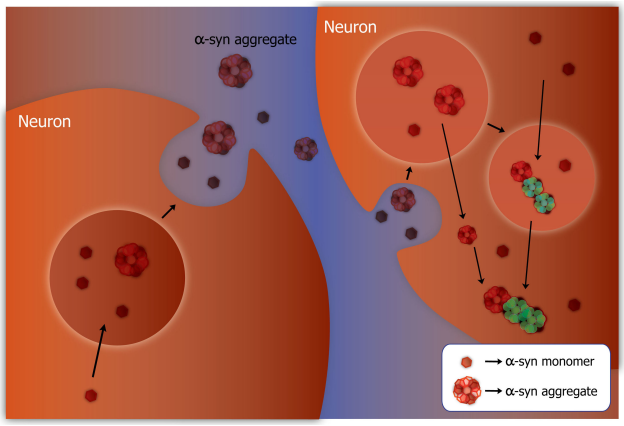


**Fig. 2.** Hypothesis for the propagation of Lewy pathology through neuron-to-neuron transmission of α-synuclein aggregates. Secreted α-synuclein aggregates are transmitted to adjacent neurons and may be amplified by the seeded polymerization mechanism.

in long term mesencephalic transplants in PD patients (Kordower et al., 2008; Li et al., 2008). However, how the internalized α-synuclein aggregates interact with the intrinsic α-synuclein proteins and whether the aggregates can be amplified by this mechanism remain to be addressed. These questions should be addressable using the transgenic animal models and tissue culture models expressing human α-synuclein.

## CONCLUSION

PD is a chronic disease with progressive manifestation of a wide spectrum of symptoms, which may be attributed to damages of various regions in CNS as well as in autonomic nervous system. Analyses of autopsied brains showed a highly predictable pattern of α-synuclein pathology progression. Recent advances in α-synuclein biology enabled us to formulate a testable hypothesis for the mechanism of direct cell-to-cell propagation of α-synuclein aggregates. The proposed mechanism involves interneuronal transmission and seeded amplification of α-synuclein aggregates, reminiscent of prion propagation (Fig. 2). This mechanism provides an entirely novel way of looking at the progress of the disease and permits the identification of new therapeutic targets. The new model proposed in the paper may also explain some of the unexpected, yet significant, experimental findings, such as the protective effects of α-synuclein immunization in a transgenic mouse model (Masliah et al., 2005). Validation of this hypothetical model provides the critical basic knowledge that will allow the mechanistic approaches to the immunization therapy in the future. Finally, the model proposed here may amount to one of the fundamental principles that are commonly applied to neurological diseases, including Alzheimer's disease, which also feature spatiotemporal progression of protein pathologies.

## ACKNOWLEDGMENTS

We would like to thank Jihee Kim for graphic works. This work was supported by a grant from the Brain Research Center of the 21st Century Frontier Research Program (M103KV010021-06K2201-02110), by the Diseases Network Research Program (2007-04303), and by the Korea Science and Engineering Foundation grant (R01-2007-000-20200-0) funded by the Korea government(Ministry of Education, Science and Technology).

## REFERENCES

Abeliovich A, Schmitz Y, Farinas I, Choi-Lundberg D, Ho WH, Castillo PE, Shinsky N, Verdugo JM, Armanini M, Ryan A, Hynes M, Phillips H, Sulzer D and Rosenthal A (2000) Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron* 25:239-252.

Ahn KJ, Paik SR, Chung KC and Kim J (2006) Amino acid sequence motifs and mechanistic features of the membrane translocation of alpha-synuclein. *J Neurochem* 97: 265-279.

Alves G, Wentzel-Larsen T, Aarsland D and Larsen JP (2005) Progression of motor impairment and disability in Parkinson disease: a population-based study. *Neurology* 65: 1436-1441.

Borghi R, Marchese R, Negro A, Marinelli L, Forloni G, Zaccheo D, Abbruzzese G and Tabaton M (2000) Full length alpha-synuclein is present in cerebrospinal fluid from Parkinson''s disease and normal subjects. *Neurosci Lett* 287:65-67.

Braak H, Bohl JR, Muller CM, Rub U, de Vos RA and Del Tredici K (2006) Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov Disord* 21:2042-2051.

Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D and Rub U (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol* 249(Suppl. 3):III/1-5.

Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN

and Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24:197-211.

Braak H, Ghebremedhin E, Rub U, Bratzke H and Del Tredici K (2004) Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 318:121-134.

Cabin DE, Shimazu K, Murphy D, Cole NB, Gottschalk W, McIlwain KL, Orrison B, Chen A, Ellis CE, Paylor R, Lu B and Nussbaum RL (2002) Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha- synuclein. *J Neurosci* 22:8797-8807.

Castagnet PI, Golovko MY, Barcelo-Coblijn GC, Nussbaum RL and Murphy EJ (2005) Fatty acid incorporation is decreased in astrocytes cultured from alpha-synuclein gene-ablated mice. *J Neurochem* 94:839-849.

Caughey B (2000) Transmissible spongiform encephalopathies, amyloidoses and yeast prions: common threads? *Nat Med* 6:751-754.

Conway KA, Harper JD and Lansbury PT, Jr. (2000) Fibrils formed in vitro from alpha-synuclein and two mutant forms linked to Parkinson's disease are typical amyloid. *Biochemistry* 39:2552-2563.

Cookson MR (2005) The biochemistry of Parkinson's disease. *Annu Rev Biochem* 74:29-52.

Davidson WS, Jonas A, Clayton DF and George JM (1998) Stabilization of alpha-synuclein secondary structure upon binding to synthetic membranes. *J Biol Chem* 273:9443-9449.

El-Agnaf OM, Salem SA, Paleologou KE, Cooper LJ, Fullwood NJ, Gibson MJ, Curran MD, Court JA, Mann DM, Ikeda S, Cookson MR, Hardy J and Allsop D (2003) Alpha-synuclein implicated in Parkinson's disease is present in extracellular biological fluids, including human plasma. *Faseb J* 17:1945-1947.

El-Agnaf OM, Salem SA, Paleologou KE, Curran MD, Gibson MJ, Court JA, Schlossmacher MG and Allsop D (2006) Detection of oligomeric forms of alpha-synuclein protein in human plasma as a potential biomarker for Parkinson's disease. *Faseb J* 20:419-425.

Fahn S and Sulzer D (2004) Neurodegeneration and neuroprotection in Parkinson disease. *NeuroRx* 1:139-154.

Farrer MJ (2006) Genetics of Parkinson disease: paradigm shifts and future prospects. *Nat Rev Genet* 7:306-318.

Forno LS (1996) Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol* 55:259-272.

George JM (2001) The synucleins. *Genome Biol* 2002;3:reviews3002.1-reviews3002.6.

Giasson BI, Murray IV, Trojanowski JQ and Lee VM (2001) A Hydrophobic Stretch of 12 Amino Acid Residues in the Middle of alpha-Synuclein Is Essential for Filament Assembly. *J Biol Chem* 276:2380-2386.

Golovko MY, Faergeman NJ, Cole NB, Castagnet PI, Nussbaum RL and Murphy EJ (2005) Alpha-synuclein gene deletion decreases brain palmitate uptake and alters the palmitate metabolism in the absence of alpha-synuclein palmitate binding. *Biochemistry* 44:8251-8259.

Hardy J and Gwinn-Hardy K (1998) Genetic classification of primary neurodegenerative disease. *Science* 282:1075-1079.

Iwai A, Masliah E, Yoshimoto M, Ge N, Flanagan L, de Silva HA, Kittel A and Saitoh T (1995) The precursor protein of non-A beta component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron* 14:467-475.

Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 79:368-376.

Jellinger KA (2003) Alpha-synuclein pathology in Parkinson's and Alzheimer's disease brain: incidence and topographic distribution--a pilot study. *Acta Neuropathol* 106:191-201.

Jellinger KA (2004) Lewy body-related alpha-synucleinopathy in the aged human brain. *J Neural Transm* 111:1219-1235.

Kim TD, Paik SR, Yang CH and Kim J (2000) Structural changes in alpha-synuclein affect its chaperone-like activity in vitro. *Protein Sci* 9:2489-2496.

Klegeris A, Giasson BI, Zhang H, Maguire J, Pelech S and McGeer PL (2006) Alpha-synuclein and its disease-causing mutants induce ICAM-1 and IL-6 in human astrocytes and astrocytoma cells. *Faseb J* 20:2000-2008.

Klegeris A, Pelech S, Giasson BI, Maguire J, Zhang H, McGeer EG and McGeer PL (2008) Alpha-synuclein activates stress signaling protein kinases in THP-1 cells and microglia. *Neurobiol Aging* 29:739-752.

Kordower JH, Chu Y, Hauser RA, Freeman TB and Olanow CW (2008) Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nat Med* 14:504-506.

Lee HJ, Patel S and Lee SJ (2005) Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. *J Neurosci* 25:6016-6024.

Lee HJ, Suk JE, Bae EJ and Lee SJ (2008a) Clearance and deposition of extracellular alpha-synuclein aggregates in microglia. *Biochem Biophys Res Commun* 372:423-428.

Lee HJ, Suk JE, Bae EJ, Lee JH, Paik SR and Lee SJ (2008b) Assembly-dependent endocytosis and clearance of extracellular alpha-synuclein. *Int J Biochem Cell Biol* 40: 1835-1849.

Lee PH, Lee G, Park HJ, Bang OY, Joo IS and Huh K (2006) The plasma alpha-synuclein levels in patients with Parkinson's disease and multiple system atrophy. *J Neural Transm* 113:1435-1439.

Lee SJ (2008) Origins and effects of extracellular alpha-synuclein: implications in Parkinson's disease. *J Mol Neurosci* 34:17-22.

Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Bjorklund A, Widner H, Revesz T, Lindvall O and Brundin P (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med* 14:501-503.

Liu S, Ninan I, Antonova I, Battaglia F, Trinchese F, Narasanna A, Kolodilov N, Dauer W, Hawkins RD and Arancio O (2004) alpha-Synuclein produces a long-lasting increase in neurotransmitter release. *Embo J* 23:4506-4516.

Maries E, Dass B, Collier TJ, Kordower JH and Steece-Collier K (2003) The role of alpha-synuclein in Parkinson's disease: insights from animal models. *Nat Rev Neurosci* 4: 727-738.

Masliah E, Rockenstein E, Adame A, Alford M, Crews L, Hashimoto M, Seubert P, Lee M, Goldstein J, Chilcote T, Games D and Schenk D (2005) Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease. *Neuron* 46:857-868.

Meyer-Luehmann M, Coomaraswamy J, Bolmont T, Kaeser S,

Schaefer C, Kilger E, Neuenschwander A, Abramowski D, Frey P, Jaton AL, Vigouret JM, Paganetti P, Walsh DM, Mathews PM, Ghiso J, Staufenbiel M, Walker LC and Jucker M (2006) Exogenous induction of cerebral beta-amyloidogenesis is governed by agent and host. *Science* 313:1781-1784.

Parkkinen L, Kauppinen T, Pirttila T, Autere JM and Alafuzoff I (2005) Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Ann Neurol* 57:82-91.

Parkkinen L, Pirttila T and Alafuzoff I (2008) Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance. *Acta Neuropathol* 115:399-407.

Poewe W (2007) Dysautonomia and cognitive dysfunction in Parkinson's disease. *Mov Disord* 22(Suppl. 17):S374-S378.

Souza JM, Giasson BI, Lee VM and Ischiropoulos H (2000) Chaperone-like activity of synucleins. *FEBS Lett* 474:116-119.

Spillantini MG, Crowther RA, Jakes R, Hasegawa M and Goedert M (1998) alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. *Proc Natl Acad Sci U S A* 95: 6469-6473.

Su X, Maguire-Zeiss KA, Giuliano R, Prifti L, Venkatesh K and Federoff HJ (2008) Synuclein activates microglia in a model of Parkinson's disease. *Neurobiol Aging 29:1690-1701.*

Sung JY, Kim J, Paik SR, Park JH, Ahn YS and Chung KC (2001) Induction of neuronal cell death by Rab5A-dependent endocytosis of α-synuclein. *J Biol Chem* 276:27441-27448.

Sung JY, Park SM, Lee CH, Um JW, Lee HJ, Kim J, Oh YJ, Lee ST, Paik SR and Chung KC (2005) Proteolytic cleavage of extracellular secreted α-synuclein via matrix metalloproteinases. *J Biol Chem* 280:25216-25224.

Thomas MP, Chartrand K, Reynolds A, Vitvitsky V, Banerjee R and Gendelman HE (2007) Ion channel blockade attenuates aggregated alpha synuclein induction of microglial reactive oxygen species: relevance for the pathogenesis of Parkinson's disease. *J Neurochem* 100:503-519.

Tokuda T, Salem SA, Allsop D, Mizuno T, Nakagawa M, Qureshi MM, Locascio JJ, Schlossmacher MG and El-Agnaf OM (2006) Decreased alpha-synuclein in cerebrospinal fluid of aged individuals and subjects with Parkinson's disease. *Biochem Biophys Res Commun* 349:162 -166.

Yavich L, Tanila H, Vepsalainen S and Jakala P (2004) Role of alpha-synuclein in presynaptic dopamine recruitment. *J Neurosci* 24:11165-11170.

Zhang W, Wang T, Pei Z, Miller DS, Wu X, Block ML, Wilson B, Zhang W, Zhou Y, Hong JS and Zhang J (2005) Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. *Faseb J* 19:533-542.