Aggregation of Neurofilament and α-Synuclein Proteins in Lewy Bodies

Implications for the Pathogenesis of Parkinson Disease and Lewy Body Dementia

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The presence of Lewy bodies (LBs) in dopaminergic neurons of the substantia nigra pars compacta, as well as neuron loss and gliosis, is a diagnostic hallmark of Parkinson disease (PD), but LBs also are seen in other cortical and subcortical neurons of the PD brain.1,2 Additionally, LBs also occur in similar populations of neurons in the brains of patients with the classic clinical and pathological features of Alzheimer disease (AD).1,2 Furthermore, the presence of numerous cortical intraneuronal LBs, but only rare AD neurofibrillary tangles and senile plaques in the brains of patients with an AD-like dementia, defines a neurodegenerative disorder known as dementia with LBs (DLB).1,2 Ultrastructural examination of LBs has revealed masses of aggregated 7- to 25-nm-diameter filaments that appear similar to neurofilaments (NFs), but the precise molecular composition of LBs, including the abnormal filaments in these intracytoplasmic neuronal inclusions, remains to be clarified.1,2 Indeed, the biological significance of LBs, especially the role that they might play in the degeneration of neurons in LB disorders, is still enigmatic (Figure).

The recent report of a mutation in the α-synuclein gene in familial PD3 and the demonstration that α-synuclein, but not β-synuclein, is a major component of LBs in sporadic PD and DLB4 are likely to stimulate increased research on LBs and to prompt a reassessment of the role played by LBs in the pathogenesis of these disorders.5,6 Since the mutation described in familial PD leads to an alanine to threonine substitution at position 53 (A53T) in the α-synuclein protein, this mutation could alter the biophysical properties of α-synuclein, a poorly understood protein that is expressed primarily in neurons, where it is localized predominantly at axon terminals or synapses.5,6 Thus, the A53T mutation in α-synuclein could predispose this normally soluble protein to aggregate or interact aberrantly with other proteins (eg, NF subunits), leading to the formation of LBs and the degeneration of affected neurons in familial PD.5,6 Moreover, the report of the widespread presence of α-synuclein in perikaryal LBs and in dystrophic neuronal processes of sporadic PD and DLB brains1 is highly significant for understanding the pathogenesis of these disorders, because this finding implies that wild-type α-synuclein may aggregate, alone or with other proteins, into LBs and dystrophic neurites. Nonetheless, it remains to be determined if genetic or epigenetic factors might perturb the metabolism, solubility, or interactions of α-synuclein in sporadic PD and synuclein in dystrophic neurites. However, it is plausible that these lesions also could compromise the survival of affected neurons in these nonhereditary LB disorders.

Although insights into the composition of LBs have emerged slowly over the past 15 years, immunohistochemical studies have contributed a substantial amount of indirect information on the proteins found in LBs.1,2,7 Notably, NF subunits were among the first neuronal proteins detected in the LBs of PD brains,7 and epitope-mapping studies of cortical and subcortical LBs in the brains of patients with PD or DLB showed that protein domains spanning nearly the entire extent of each of the 3 NF subunits are present in these inclusions.8,9 Thus, it is plausible that NFs, the major class of neuronal intermediate filaments, are incorporated into LB fila-

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 nhiễm protein have been detected in LBs. However, many factors for the pathogenesis of LBs, a large number of other neurological alterations have developed support the notion that these protein may be trapped in LBs in a nonspecific manner, rather than being essential components of LBs.

To gain further insight into the pathology and etiology of LBs, methods for the purification and analysis of these inclusions from the brains of patients with DBL were developed, thereby allowing the generation of monoclonal antibodies to LB proteins. Notably, the findings of these studies have confirmed the presence of LBs and ubiquitin in LBs. These and other monoclonal antibodies raised to purified LBs should facilitate efforts to elucidate the biochemical composition of these neuronal inclusions, and this information could be used to determine how LBs form and whether they contribute to the degeneration of affected neurons in PD and DBL. Furthermore, anti-LB monoclonal antibodies could be used to develop assays for the early antemortem diagnosis of LB disorders by monitoring the levels of LB proteins in blood or cerebrospinal fluid. Although information on the biological consequences of LB formation is incomplete, the findings of studies of human LB disorders and transgenic mice in which NF-rich LB-like abnormalities have developed support the notion that these filamentous inclusions could lead to the death of affected neurons.

However, the refinement and use of methods for the purification and analysis of LBs isolated from postmortem brain tissue should accelerate efforts to dissect the building blocks of the filamentous proteins that aggregate in the dystrophic neurites detected by antibodies to α-synuclein. The long-term consequences of these pathological events could be the disconnection of the substantia nigra from the striatum and the disconnection of one cortical region from another. Accordingly, efforts to elucidate the pathological significance and the etiology of LBs may lead to improved strategies for the antemortem diagnosis of LB disorders, as well as to the development of novel therapeutic interventions for the treatment of PD and DBL.

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## REFERENCES

10. Ivatsubo T, Yamaguchi H, Fujimuro M, et al. Purification and characterization of α-synuclein with NFs leads to the abnormal accumulation of these proteins into pathological LBs and whether LBs compromise the function and viability of neurons in PD and DBL brains. Indeed, it is plausible that LBs might have a deleterious effect on neurons in several ways. For example, it is possible that the axons of nigral and cortical neurons might undergo a “dying back” process owing to (1) a disruption of perikaryal transport mechanisms by LBs that form in neuronal cell bodies or (2) a blockage of axonal transport by LB proteins that aggregate in the dystrophic neurites detected by antibodies to α-synuclein. The long-term consequences of these pathological events could be the disconnection of the substantia nigra from the striatum and the disconnection of one cortical region from another. Accordingly, efforts to elucidate the pathological significance and the etiology of LBs may lead to improved strategies for the antemortem diagnosis of LB disorders, as well as to the development of novel therapeutic interventions for the treatment of PD and DBL.

Schematic summary of the spectrum of familial and sporadic Lewy body (LB) disorders that may occur alone or in combination with other diseases, such as Alzheimer disease (AD). Little is known about genetic and environmental risk factors (indicated by the question marks) for Parkinson disease (PD) or dementia with LBs (DLB), but a mutation in the α-synuclein gene has been identified in several kindreds with familial PD, and this mutation results in an alanine to threonine substitution at position 53 in the α-synuclein protein. Current data suggest that α-synuclein and neurofilament (NF) proteins are major constituents of LBs in PD and DBL.

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<tr>
<th>Genetic Factors (α-Synuclein Mutation, ?)</th>
<th>Epigenetic Factors (Toxins, ?)</th>
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