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COMMENTARY

# SENILE PLAQUES AND NEUROFIBRILLARY TANGLES: THE CONCURRENT LESIONS OF ALZHEIMER'S DISEASE

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ALZHEIMER'S disease (AD) is diagnostically and pathologically characterized by the concurrent presence of senile plaques (SP) and neurofibrillary tangles (NFT) (13), however, the reason why these two lesions are invaryingly present in AD is unknown. The preceding article by Trojanowski and co-workers expresses the view that concurrence is due to dependence (21). Whereas such interdependence between the lesions was proposed in the earliest studies of AD (reviewed in 22), and NFT develop all of the defined features of SP (12), several factors have made acceptance of SP/NFT co-dependence problematic. For instance, amyloid deposition occurs in the absence of NFT (2,8), and mutations in the amyloid precursor protein directly link to AD (6).

These apparent paradoxes make the simplicity of amyloid independence the most appealing. However, if one allows that the two different forms of SP may have distinct modes of formation (i.e., diffuse SP with little cellular abnormality and neuritic SP with abundant dystrophic neurites and glial reaction), it is apparent that one finds neuritic SP, the type related to dementia, only in the presence of NFT. Indeed, chronological studies indicate that diffuse SP are the first pathological marker and that NFT and neuritic SP occur together at a later time (2,8). Whether amyloid in the form of diffuse SP initiates further changes is unclear, however, it is clear that the cognitive and pathological markers of AD only occur with the co-occurrence of NFT and neuritic SP (10) that result in synaptic loss and consequent cognitive decline (9). Therefore, whereas the actual deposition of amyloid-β may be unrelated to NFT it is becoming increasingly apparent that in Alzheimer's disease neuritic SP and NFT are inexorably linked. This codependence of the lesions is supported by several findings.

1. Temporal correlation: In AD, Down syndrome and normal aging neuritic SP are coincidental with NFT (2,8).
2. Morphological intermediates between NFT and SP are seen as extracellular NFT which invariably contain the defining traits of SP (i.e., amyloid, dystrophic neurites, microglia and astroglia, and the same molecular deposits) (11,12).
3. The dystrophic neurites of neuritic SP but not diffuse SP, invariably contain the same abnormal filaments found in NFT (3).
4. The precursor protein of amyloid contains a β-sheet conformation-dependent binding site for τ protein, the major subunit of NFT (14,20). Furthermore, the interaction of τ with β-protein precursor promotes fibrillogenesis (5).
5. The dystrophic neurites of SP show membrane disruptions releasing β-protein precursor to the extracellular space suggesting a possible role in extracellular amyloid-β deposition of SP (15).
6. Implantation of PHF into the brain results in amyloid deposition (17).
7. Familial AD cases with mutation of the β-protein precursor gene show both amyloid deposition and NFT (7).

One particularly interesting aspect of the article by Trojanowski et al. (21) is that only stabilized/polymerized τ is able to elicit amyloid-β deposition since normal τ was only effective following treatment with $AlCl_3$ (16). PHF-τ did not require stabilization by aluminum suggesting that PHF-τ is intrinsically more stable. Whereas the increased number of phosphate moieties associated with PHF-τ might account for this increased stability, another possibility are the post-translational advanced glycation end products associated with PHF-τ that would stabilize PHF-τ through the formation of protein crosslinks (19,23).

The presence of NFT in the absence or virtual absence of amyloid in subacute sclerosing encephalitis and Guam-dementia complex suggests that NFT may be one of several responses to neuronal insult and not specific for amyloid-β. The finding that amyloid-β is produced normally by many types of cells (18) and the relative lack of neurodegeneration associated with diffuse SP

suggests that factors in addition to amyloid-β are required for a neuritic SP to form. Yet, the difference does not lie in amyloid-β because diffuse SP have amyloid-β fibrils (4) just as neuritic SP. However, diffuse SP do not show the substantial loss of synapses (9) and decreased neurite density observed in neuritic SP (1; personal observation). Neurodegeneration in the area where a SP will form could provide both neuronal factors as well as stimulate glial reactivity that promote amyloid-β deposition and potentiate neurodegeneration. This could lead to a positive feedback loop in which amyloid-β deposition contributes to neurodegeneration which itself promotes more amyloid-β deposition.

Taken together with the preceding discussion, one can conclude that while amyloid-β deposition as diffuse SP and NFT are independent lesions, in AD the development of neuritic SP and NFT are inexorably linked. Furthermore, in AD the presence of NFT and neuritic SP yields synergy between these two pathological processes. Importantly, such pathological synergy could utilize the connectivity of the brain to spread and lead to a disruption of that connectivity reflected by synapse loss. We would suggest that interrupting the synergistic interaction between NFT and amyloid-β might interrupt the progression of AD.

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