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Review

Intraneuronal Aβ accumulation and origin of plaques in Alzheimer's disease

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Abstract

Plaques are a defining neuropathological hallmark of Alzheimer's disease (AD) and the major constituent of plaques, the β-amyloid peptide (Aβ), is considered to play an important role in the pathophysiology of AD. But the biological origin of Aβ plaques and the mechanism whereby Aβ is involved in pathogenesis have been unknown. Aβ plaques were thought to form from the gradual accumulation and aggregation of secreted Aβ in the extracellular space. More recently, the accumulation of Aβ has been demonstrated to occur within neurons with AD pathogenesis. Moreover, intraneuronal Aβ accumulation has been reported to be critical in the synaptic dysfunction, cognitive dysfunction and the formation of plaques in AD. Here we provide a historical overview on the origin of plaques and a discussion on potential biological and therapeutic implications of intraneuronal Aβ accumulation for AD.
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It was over a century ago that Alois Alzheimer admitted a 51-year-old patient, Auguste D., for progressive cognitive decline. Alzheimer's histopathological observations of her brain following her death a few years later led to his realization that he was observing a unique clinical-pathological process, that not long after was named Alzheimer's disease (AD). This was an era of major scientific advances in medicine, spurned by novel microscopic methods and the realization that specific biochemical and pathological processes characterized diverse diseases, including of the brain. Since microscopy was the major research method at the time, the detailed histological observations are unique and while increasingly forgotten can still provide insights today.

Investigators at the beginning of the last century were intrigued by the origin of the deposition of a "peculiar substance" (also called "miliary necrosis"), eventually termed plaques, that along with neurofibrillary tangles (NFTs) appeared to characterize presenile and senile dementia. Blocq and Marinesco first described plaques in 1892 in postmortem brains of chronic epileptics at a time when anticonvulsant medications were not yet available and patients with epilepsy were still routinely institutionalized. In 1898 Emil Redlich reported plaques in the brains of two patients with senile dementia, and because of their close association with astrocytes speculated that they may be derived from glia. Alzheimer's summary of his presentation in 1906 on the case of Auguste D. was published in 1907 and for the first time linked plaques and tangles with dementia. This 1907 report was brief, and it was in subsequent more detailed publications from Alzheimer's laboratory that speculations on the origin of plaques were discussed. Also in 1907, but subsequent to Alzheimer's initial report, Oskar Fischer working in a department headed by Arnold Pick in Prague, published his observations of plaques and tangles in more typical late onset "senile" dementia and speculated that the plaques he found in 12 of 16 postmortem brains from elderly subjects with dementia, but not in those from 45 elderly subjects without dementia, resulted from deposition of a foreign, presumably infectious, agent [21]. After laboriously staining for, but not finding, markers for infection in plaques, Fischer

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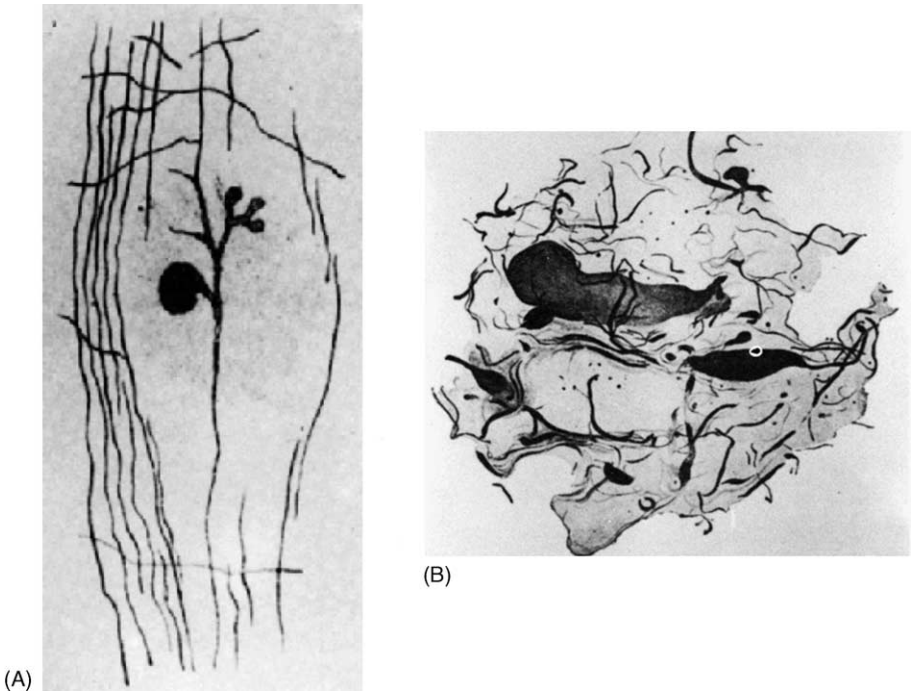

Fig. 1. Drawings of plaques by Fischer and Bonfiglio. (A) Drawing of a plaque by Oskar Fischer, who viewed plaques as deriving from dystrophic, degenerating neuronal processes. Legend in his paper from 1907: "Diversion of the fibrils, the central fibers arranged in an arch-like bow crossing over (not through) the plaques and with nodular formations. Other fibrils are not shown." (B) Drawing of a plaque by Bonfiglio. Legend from his paper in 1908: "Miliary foci of necrosis. Early stage with a neuron in the middle. A dense axonal plexus surrounding the neuron, with fusiform or roundish swelling phenomena."

altered his view the following year, suggesting instead that plaques derived from degenerating neuronal processes. In detailed drawings Fischer depicted swollen dystrophic neurites, forming club-shaped swellings, extending into plaques at different stages of plaque development (Fig. 1A). In 1908 Francesco Bonfiglio, an Italian scientist working in Alzheimer's laboratory, described the neuropathology of the second case of presenile dementia in which he deduced that plaques were derived from within neuronal cell bodies and their terminals: ". . .rather the alteration begins inside a neuron and in the nerve terminals which surround it and the amorphous central masses only observed in the final stage of the process are necrotic remnants of the neuron itself" (Fig. 1B) [7]. In 1910 Gaetano Perusini, another Italian scientist working with Alzheimer, described two cases of presenile dementia, including Alzheimer's original case Auguste D. in greater detail. He commented on the previously disparaging views for the origin of plaques and postulated that plaques initially evolved "*following* destruction of nervous tissue, in which pathological metabolic products of an as yet unknown kind are deposited" [65]. In 1911, Alzheimer in his most detailed description of cases with the disease bearing his name credited Fischer for extensive studies of plaques, also by calling them "Fischer's plaques" [3], and outlined the varying views of their possible origin but did not provide his own interpretation, possibly because he was aware that the tools to answer this question were not available.

1. Aβ in Alzheimer's disease

The isolation and biochemical characterization of Aβ from the vasculature [23] and parenchyma [55] of AD brain, and the subsequent cloning of the amyloid precursor protein (APP) [38], initiated the modern era of molecular biological studies on Aβ in the 1980s. Interestingly, a few early immunohistochemical studies with antibodies generated against the Aβ domain of APP found these to visualize not only plaques but also NFTs [54]. This staining was subsequently thought to be due to artifactual shared epitopes between Aβ and NFTs [1]. Moreover, emerging cell biological studies provided no support for an intraneuronal role for Aβ, since Aβ could not be found within cells. Aβ generation was thought to occur at the plasma membrane just prior to secretion, although there was evidence that the endosomal–lysosomal system was also involved [24,29]. The important publication of neuronal toxicity by the administration of Aβ to cultured primary neurons provided a compelling and unifying mechanism for extracellular Aβ pathogenesis in AD [87,88]. Secreted Aβ was thought to gradually increase in the extracellular space until it began aggregating to form insoluble β-pleated amyloid plaques, which in turn could propagate Aβ toxicity to surrounding neurons and their processes. Thus, the "extracellular Aβ toxicity" hypothesis for Aβ pathogenesis became dominant in the field. More recently, the extracellular toxicity hypothesis has been modified, since lower molecular weight Aβ oligomers and protofibrils, rather than Aβ fibrils,

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