

Alzheimer's disease: A Commentary on Biofilms, Beta Amyloid and their Locations

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Abstract

The pathological study of brains affected by Alzheimer's disease (AD) has shown the presence of spirochetal infection. These bacteria produce a detectible biofilm as a defense mechanism, impenetrable by both the immune system and antibiotic medications. The failure of the innate immune system at the site of biofilm deposition ultimately leads to the pathognomonic beta-amyloid (A β) plaques of AD at the exact same location as visualized by immunological staining. Furthermore, recent studies show that senile plaques are partially composed of bacterial A β in addition to that of the host. The bacterial and neuropathology similarities continue with similar staining results using all of the following: silver impregnation techniques, green thioflavin S fluorescence, anti-A β PP, and anti-A β PP antibodies. TUNEL assay of senile plaques further support the DAPI visualization and in situ hybridization detection of bacterial DNA with extracellular DNA fragmentation that corresponds to spirochetal apoptosis in the plaque's biofilms, confirming the plaques are composed of spirochetes, A β , and biofilm. These significant similarities of biofilms and A β substantiate our hypothesis that amyloid of AD is located in the extracellular space.

Commentary

Recent studies have demonstrated pathologically that the brains of individuals stricken with Alzheimer's disease (AD) contain biofilms created by the spirochetes of dental bacteria and *Borrelia burgdorferi* [1,2]. These biofilms develop once a bacterial quorum is reached and are representative of the chronic infection that leads to the phenotype of AD [3]. The causal spirochetes of AD take approximately two years to accumulate the approximately 150 organisms necessary to create a quorum that can produce a single biofilm plaque as an encasing slime for noxious chemical and immunologic protection [2,4]. The biofilm is composed of curli fibers and amyloid fibers serving as a scaffolding for the polysaccharides, DNA, fatty acids, protein, dead cells, exporter cells, water channels, and spirochetes [2]. None of the commonly used antibiotics is able to penetrate this structured biofilm [2].

There is immunopathological evidence that the innate immune system, specifically Toll-like receptor 2 (TLR2), acts as the lynchpin to the neurodestruction of AD [2,5]. Due to the fact that TLR2 is unable to penetrate the spirochete biofilm, it ultimately attacks the surrounding host tissue. Additionally, Allen et al. combined pathology and immunopathology to demonstrate biofilm's co-localization with beta-amyloid (A) [5]. In a side-by-side 3D pathology presentation, A was visualized directly on the surface of the bacterial biofilms [6]. This superimposed imaging along with the proven co-localization demonstrates that the two materials are intrinsically linked as the building blocks of the hallmark pathologic plaques of AD [7].

The proposed pathway of the development of A shows the stepwise progression of spirochete infection, TLR2 activation of the myeloid differentiation D88 (MyD88) pathway, and the eventual production of the A byproduct as a result of the innate immune system's failure to exterminate the bacteria [7]. The antimicrobial A β produced from the conversion of amyloid precursor protein APP in the last step of the aforementioned pathway is produced in attempt to penetrate the

biofilm but, similarly to TNF α , which is likely attracted to the biofilm's curli fibers, it is unable to do so [4,5]. When A β is unable to penetrate the slime, it ultimately encompasses the biofilm causing a buildup that destroys the structure and function of the brain [2]. Rather than ridding the body of spirochetes, this pathway irreversibly damages the brain's neurocircuitry.

The pathway to A β is the same pathological progression as seen in neuro-syphilis: the same plaques, neurofibrillary tangles, A β , and Tau protein [2]. Thus, there is significant hope for bactericidal penicillin in concert with a biofilm dispersing agent to be a viable treatment option for the spirochetes of AD prior to their development into senile plaques [2].

Miklossy recently showed that A β and DNA are vital to both *in vivo* senile plaques as well as *in vitro* spirochetal biofilms [8]. The *in vivo* senile plaques of AD have not only shown the presence of A β but also bacterial DNA fragments as found in the biofilms created by *Borrelia in vitro* [8]. Immuno-electronmicroscopy and immune histochemical analysis found that amyloid beta precursor protein (A β PP) is expressed by spirochetes [9]. Furthermore, *Borrelia burgdorferi* was confirmed to contain amyloidogenic protein [10,11]. In Miklossy's most recent work, she also references numerous studies that demonstrate amyloidogenic protein as a previously overlooked part of many bacterial cellular envelopes [8]. Amyloidogenesis is described as "aggregation of soluble proteins into detergent-insoluble filamentous structures" [8]. The A β of AD is composed of both host and bacterial amyloid [8].

The staining of the biofilms and AD plaques has uncanny similarity. Senile plaques as well as *Borrelia burgdorferi* biofilms stain similarly with silver impregnation techniques, green thioflavin S fluorescence, anti-A β PP, anti-A β PP antibodies, and express the same silver-white fluorescence under UV light [8]. Senile plaques also contain *burgdorferi* specific antigens and antibodies [8]. *In vitro*, *Borrelia* biofilms, both adherent to cells and free floating in the media, exhibit

thioflavin S fluorescence and immunoprecipitation of A β [12]. TUNEL assay of senile plaques further support the DAPI visualization and *in situ* hybridization detection of bacterial DNA with extracellular DNA fragmentation that corresponds to spirochetal apoptosis in the plaque's biofilms, confirming the plaques are composed of spirochetes, A β , and biofilm [8].

Finally, to postulate an answer to the question if A β is intracellular or extracellular, we hypothesize that the amyloid is found in the extracellular space. We come to this conclusion for numerous reasons. First and most importantly, A β mirrors biofilm [8]. As a bacterial defense mechanism, biofilms are slimes produced in the extracellular space as an immune evasion strategy. Additionally, the microscopic studies suggest that the biofilms are free floating and adherent to, but not invading neighboring cells. Finally, A β has a large contribution of bacterial amyloid, which is a bacterial cell wall structure, suggesting its hardy extracellular nature. For concrete determination A β 's location we suggest further research be done on the topic.

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