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Amyloid immunization in Alzheimer's disease: do we promote amyloid scavenging at the cost of inflammatory degeneration?

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A large number of epidemiologic studies have indicated that the use of non-steroidal anti-inflammatory drugs (NSAIDs) may prevent or delay the clinical features of Alzheimer's disease (AD) [3,8,12]. The pharmacological activity of NSAIDs is generally attributed to the inhibition of cyclooxygenase (COX), a rate-limiting enzyme in the production of prostaglandins (PGs). However, the mechanism by which these anti-inflammatory drugs, influence the clinical progression of AD dementia and/or AD neuropathology has yet to be defined. Further, evidence has indicated that COX inhibitors may also prevent AD-type β amyloid (Aβ) neuropathology in experimental animals [6].

Interestingly, recent studies in murine models of AD have found that immunization with Aβ peptides can mitigate Aβ neuritic plaque pathology through the activation of the brains resident macrophages (microglia) [1,4,9,10]. Based on observations from these models, it has been demonstrated that either passive (intraperitoneal injection (IP) of pre-derived Aβ antibodies) or active (IP injection of Aβ peptides) immunization with Aβ can activate pro-inflammatory microglial cells through immunoglobulin receptor signaling, and result in the clearance and degradation of Aβ plaques [1,10]. This suggests a potential beneficial role for features of inflammation in AD. However, we note that the induction of proinflammatory cascades, e.g. microglial cytokine synthesis and generation of free radicals [5], is little understood and has been previously implicated in neuronal injury [13].

In humans, evidence has suggested that inflammation is integrally involved in the progression of AD dementia, and that separate segments of inflammatory cascades may play important and possibly independent roles in different phases of the disease. For example, the induction of several cytokine inflammatory mediators, particularly those generated by microglial activation such as IL-6 and TGF–β1, but not IL-1β, IL-1α, TNFα and β among others, are found to be elevated in the brain of severely demented AD cases and not in subjects at earlier stages of clinical AD [7]. Moreover, we have recently shown that the expression of the inducible form of COX, COX-2, is elevated in the brain of early AD dementia cases [2]. This information bears important implications to the development of anti-inflammatory strategies that diminish inflammatory neurodegeneration in the brain as a function of the clinical progression of AD dementia. But more importantly, it raises concern about the potential proinflammatory consequences of Aβ immunization as a therapeutic tool in AD. For example, if the induction of specific cytokines or other unknown microglial proinflammatory factors are integral to the process of microglial scavenging of Aβ plaques, the use of anti-inflammatory drugs that interfere with microglial cytokine activity may aberrantly impact immunization based Aβ plaque clearance. Further, if Aβ immunization induces/intensifies inflammation in patients clinically characterized by early stage AD dementia, this treatment may potentially, through the promotion of inflammatory neurodegeneration, lead to an acceleration of clinical dementia.

Indeed, if clinical studies to investigate anti-inflammatory drugs in combination with Aβ immunization are to be initiated, consideration of disease state and further elucidation of Aβ plaque clearance mechanisms are essential. For example, it may be possible that an *ideal* anti-inflammatory drug should be one that does not interfere with the select pro-inflammatory mediated scavenging of Aβ plaques by microglia, but does prevent the harmful pro-inflammatory responses associated with microglial activation (e.g. pro-oxidative conditions, superoxides generation). Further, data from a recent immunization study suggests that modifica-

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tion of the antigen employed in the immunization may alter the type of immune response produced [11]. It is currently unknown what profile of inflammation Aβ immunization will induce in the human brain, and we are encouraged by recent immunization safety studies that received positive review at the World Alzheimer Congress 2000. However, it is clear that a more extensive investigation of inflammatory cascades evoked by immunization induced plaque scavenging is clearly warranted before large-scale clinical studies may start in humans.

Although experimental evidence demonstrates that Aβ immunization in mice can result in the clearance of AD type Aβ plaques and modify behavior in the diseases progression [1,4,9,10], this may not be representative of outcomes with such measures in humans in different clinical stages of AD. Further, the multifaceted nature of AD neuropathology is composed of features currently not represented in animal models of the disease, such as neurofibrillary tangle pathology and neuronal loss, and thus cannot be considered in the framework of the apparent beneficial role of Aβ immunization therapy. For illustration, we recently reported that the elevation of the pro-inflammatory cytokine Il-6 in the brain of severely demented AD cases positively correlates with the level of neurofibrillary tangle pathology [7], thus it might not be unexpected that the select pro-inflammatory condition associated with Aβ immunization could positively influence Aβ plaque scavenging, but yield a very different influence upon neurofibrillary pathology.

Undoubtedly, recent immunization studies have conveyed much needed insight to the feasibility and consequences of manipulating Aβ load in the brain, but have not yet relayed sufficient validation of this therapy for use in human subjects. Thus we wish to raise concern to the possibility that while Aβ immunization strategies may succeed in the clearance of Aβ plaques, further understanding of immunization with regard to inflammation and other hallmarks of AD pathology is necessary before there is sufficient confidence that this treatment will not concurrently hasten the onset of the neuropathological features of AD dementia in humans.

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