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Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

Immunotherapy for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia worldwide. In AD the normal soluble amyloid β (sAβ) peptide is converted into oligomeric/fibrillar Aβ. The oligomeric forms of Aβ are thought to be the most toxic, while fibrillar Aβ becomes deposited as amyloid plaques and congophilic angiopathy, which serve as neuropathological markers of the disease. In addition the accumulation of abnormally phosphorylated tau as soluble toxic oligomers and as neurofibrillary tangles is a critical part of the pathology. Numerous therapeutic interventions are under investigation to prevent and treat AD. Among the more exciting and advanced of these approaches is vaccination. Active and passive Immunotherapy targeting only Aβ has been successful in many AD model animal trials; however, the more limited human data has shown much less benefit so far, with encephalitis occurring in a minority of patients treated with active immunization and vasogenic edema or amyloid-related imaging abnormalities (ARIA) being a complication in some passive immunization trials. Therapeutic intervention targeting only tau has been tested only in mouse models; and no approaches targeting both pathologies concurrently has been attempted, until very recently. The immune approaches tried so far were targeting a self-protein, albeit in an abnormal conformation; however, effective enhanced clearance of the disease associated conformer has to be balanced with the potential risk of stimulating excessive toxic inflammation. The design of future more effective immunomodulatory approaches will need to target all aspects of AD pathology, as well as specifically targeting pathological oligomeric conformers, without the use of any self-antigen.

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia globally, affecting approximately 36 million people currently and ~115 million by 2050 [1]. The associated costs are enormous, being estimated in the USA alone to be ~$200 billion in 2013. Presently available treatments have minimal, or no, effect on the course of disease. The neuropathology of AD consists of the accumulation of amyloid β (Aβ) as amyloid plaques and congophilic amyloid angiopathy (CAA), as well as the accumulation of aggregated, phosphorylated tau as neurofibrillary tangles [2]. The most toxic species of Aβ and aggregated tau are thought to be oligomeric, with both of these pathologies spreading via extracellular soluble

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oligomers, which under some conditions have been shown to use a "prion-like" mechanism [3–5]. Aβ and tau oligomers, as well as amyloid plaques and NFTs share many structural and biophysical properties, such as a high β-sheet content, resistance to proteolytic degradation and neuronal toxicity. It has also been shown that Aβ and tau related pathology can, under some conditions, "seed" or propagate each other [5].

At least in mouse models, immunotherapy has shown great effectiveness in preventing the development of both AD and prion diseases [6,7]. Numerous novel therapeutic strategies are being developed to potentially treat AD, with active and passive immunization being among the most advanced approaches [8–12]. Certainly in AD Tg mouse models Aβ directed immunization has been spectacularly successful using a wide variety of methods. However, translating these results effectively and without toxicity in humans has been challenging. Significant unanswered questions remain for the current and future human trials. What is the best design of a vaccine? What is the best target? How can autoimmune toxicity be avoided? When should therapy start? Also a key issue which needs to be addressed is the simultaneous targeting of both amyloid β (Aβ) and tau related pathology, as well as targeting the most toxic oligomeric forms of aggregated Aβ and tau.

2. Pathogenesis of Alzheimer's disease

The pathological hallmarks of AD are the accumulation of extracellular Aβ as neuritic plaques and congophilic angiopathy, as well as the intracellular accumulation of abnormally phosphorylated tau in the form of neurofibrillary tangles (NFTs). Missense mutations in APP or in the presenilin genes PRES 1 and 2 cause early onset, familial forms of AD (FAD) affecting $<$1% of AD patients [13,14]. The most common form of AD is sporadic and late-onset. The dominant theory for the causation of AD has been the amyloid cascade hypothesis [15–17]. This updated theory currently suggests that accumulation of Aβ peptides particularly in a highly toxic oligomeric form is the primary pathogenic driver, that downstream leads to tau hyperphosphorylation, NFT formation and ultimately to synaptic and neuronal loss. A number of proteins may actively promote the conformational transformation of soluble Aβ and stabilize pathological oligomeric conformers. Examples of such proteins in AD include apolipoprotein E (apo E), especially its E4 isoform [18], $\propto$1-antichymotrypsin (ACT) [19] or C1q complement factor [20,21]. In their presence, the formation of Aβ fibrils in a solution of water-soluble Aβ is much more efficient [18,19]. These "pathological chaperone" proteins have been found histologically and biochemically in association with fibrillar Aβ deposits but not in preamyloid aggregates which are not associated with neuronal loss [22]. An important event in the pathomechanism of AD is thought to be reaching a critical concentration of water-soluble Aβ and/or chaperone proteins in the brain, at which point the conformational change occurs. This in turn leads to formation of Aβ aggregates, initiating a neurodegenerative cascade. In sporadic AD this may be related to any combination of an age-associated impaired clearance from the brain, and/or influx into the CNS of Aβ circulating in the serum [15]. Extensive evidence supports the amyloid cascade hypothesis in FAD patients and in models of FAD: (1) Inherited forms of AD linked with mutations in the APP gene or in the PRES1 or 2 genes are associated with changes in APP processing that favor over production of sAβ or production of more aggregation prone forms of sAβ such as Aβ1-42 [23]. (2) Down's syndrome, where there is an extra copy of the APP gene due to trisomy 21, is associated with AD related pathology at a very early age [24,25]. (3) In transgenic and other models of co-expressed amyloid β and tau, amyloid β oligomer formation precedes and accentuates tau related pathology, consistent with the hypothesis that NFT formation is downstream from Aβ aggregation [26–29]. (4) In transgenic mouse models of mutant APP over-expression (where there is no tau pathology) therapeutic prevention and/or removal of Aβ is associated with cognitive benefits in experimental mice [26,30,31]. Importantly, in transgenic mouse models of both mutant APP and tau over-expression (with both amyloid and tau related pathology) prevention of Aβ pathology leads to both amelioration of cognitive deficits and tau related pathology [32–34]. However, evidence proving that Aβ is central in the common late-onset sporadic form of AD is more limited: (1) A correlation has been shown between biochemically extracted Aβ peptides species from sporadic AD brains with cognitive decline [35]. (2) Isolated Aβ peptide dimers/oligomers from sporadic AD brains have been documented to impair synaptic structure and function [36]. (3) Aβ extracted from sporadic AD patients has been shown to induce amyloid deposits when injected into transgenic mice [5,37]. Potential conflicting evidence to the amyloid cascade hypothesis comes from the autopsy data from the initial human active vaccination trial, which is further discussed below. Post-mortem analysis was available from nine subjects in the active immunization arm [38]. All these individuals showed a considerable degree of plaque removal and reduced Aβ load compared to comparable non-immunized controls. Despite this, there were no differences between placebo and active immunization groups in terms of long-term survival outcome, time to severe dementia and in outcome measures such as ADAS-Cog, MMSE or DAD. This might have been related to the immunization having begun too late in the disease process [9,15]; alternatively, one can use this data to suggest that the amyloid cascade hypothesis is an oversimplification. A number of investigators have suggested alternative theories, whereby accumulation of aggregated, toxic forms of Aβ and tau are dual pathways both downstream from a common upstream pathogenic deficit (which remains to be identified) [39–41]. In either of these scenarios it is essential for immunotherapy to address both of these pathologies to be highly effective in clinically symptomatic AD. In this review we will summarize the preclinical and clinical data for both Aβ and phosphorylated tau reduction immunotherapeutic approaches.

3. Active immune therapy targeting Aβ in humans

Initial studies supporting immunotherapy for AD showed that anti-Aβ antibodies could inhibit Aβ peptide fibrillization, disaggregate pre-formed fibrils and prevent cell culture based neurotoxicity [42,43]. This lead to Schenk et al. to use full length, aggregated Aβ1-42 for active immunization with Freund's adjuvant to demonstrate that this could reduce plaque burden in an AD Tg model, without obvious toxicity [44]. Subsequent trials of active vaccination of AD Tg mice with Aβ1-42 or Aβ homologous peptides co-injected with Freund's or alum adjuvants also demonstrated striking reduction in Aβ deposition, as well as prevention of cognitive impairments [26,30,45–49] (see Table 1). The predominant epitope from these active immunizations was mainly located in the first 15 amino acids of the Aβ peptide, with studies demonstrating that the generated anti-Aβ antibodies were able to label amyloid plaques on human AD brain sections. Similar effects on Aβ load and behavior were demonstrated in AD Tg mice by peripheral injections of anti-Aβ monoclonal antibodies indicating that the therapeutic effect of the vaccine is based primarily on eliciting a humoral response [26,30,50,51]. In these initial preclinical studies no toxicity was evident in the treated mice; however, some investigators suggested that use of non-fibrillogenic, non-toxic Aβ homologous peptides along with approaches that stimulate primarily humoral, Th-2 immunity, in contrast to a primary Th-1 cell mediated response might reduce