Alzheimer’s Disease: Molecularly Based Immunotherapeutics

Alzheimer’s Disease (AD) is a neurodegenerative disorder characterized by the deposition of amyloid protein in areas of the brain that are important for memory and cognition. This deposition is thought to be an important component of the pathology of AD. Due, in part, to the aging baby boomer population, AD is beginning to approach epidemic proportions in the industrialized world such as in the United States; it is estimated that by the year 2025, there will be approximately 22 million cases of AD worldwide, with at least 10 million being in the U.S. alone. Such a large number of AD patients will have the potential to cripple the health care system. These onerous predictions underscore the necessity for the development of effective therapies for AD.

During the last 2 years, an exciting novel technology that may combat AD has generated considerable interest: an experimental vaccine that targets the β-amyloid protein within the amyloid plaque in the brains of patients suffering from AD. In the summer of 1999, Schenk et al. at Elan Pharmaceuticals in San Francisco published a provocative study in which the β-amyloid peptide (Aβ) component of the amyloid precursor protein (APP), when used as a vaccine, was able to induce significant antibody responses with a concomitant decrease in Aβ accumulation in the brain of a transgenic mouse model for AD (Schenk et al., 1999). A subsequent paper by their group demonstrated that the decrease in amyloid burden after vaccination was mediated by anti-Aβ-specific antibodies. This conclusion was drawn because the passive administration of an anti-AB monoclonal antibody to these transgenic mice resulted in the decrease in Aβ levels in the brains (Bard et al., 2000), indicating the important role of antibodies in mediating the biologic activity of the vaccine. Two subsequent papers that contributed significantly to the field were published in December of 2000. Both reports, one of which was from our group, demonstrated the ability of the Aβ peptide vaccine to protect transgenic AD mice from functional memory deficits (Morgan et al., 2000; Janus et al., 2000). These studies were important in that they demonstrated that this vaccine could positively impact, not only the AD-like histopathologic effects, but also the AD-like behavioral phenotype found in APP transgenic mouse models of amyloid deposition.

This special issue of DNA and Cell Biology presents a compilation of papers dealing with some of the immunologic and molecular aspects of vaccine development against AD. The initial paper is an overview by Schenk et al. of the immunization strategies being employed against AD. This review is particularly relevant in light of the recent report by Elan Pharmaceuticals and Wyeth-Ayerst Research on the safety and immunogenicity of a Aβ vaccine in human clinical trials. The second article, authored by Loring and colleagues, provides an extensive summary of the immunization strategies being employed against AD. This review is particularly relevant in light of the recent report by Elan Pharmaceuticals and Wyeth-Ayerst Research on the safety and immunogenicity of a Aβ vaccine in human clinical trials. The primary epitope for antibody responses was demonstrated to reside in the N-terminal portion of the Aβ peptide. Such findings have implications for the design of future vaccine trials. In addition, the T lymphocyte helper 2 nature of the antibody responses was demonstrated, as was the fact that peptide vaccination results in significant anti-peptide T-cell proliferative activity.

The paper by Wilcock et al. correlates several features of histopathology in APP + PS1 mice as a function of different number of vaccinations. Importantly, this study demonstrated that the number of vaccinations of mice with the Aβ peptide influenced antibody titers, microglial activation, and the Aβ load in the appropriate areas of the brain. Again, this study has important implications for the development of clinical vaccine preparations. Finally, the contribution by Arendash et al. to this special issue examines task specificity and correlations between Aβ deposition and spatial memory. The study indicated that behavioral protection conferred by long-term Aβ vaccination is task specific, with the preservation of hippocampus-associated working memory tasks most likely to occur.
It is clear from many of the studies presented in this special issue that vaccines utilizing the Aβ peptide can induce functionally beneficial anti-Aβ antibody responses in several transgenic mouse models of AD. There are several mechanisms that have been proposed as to how anti-Aβ antibodies may mediate their effects on decreasing brain Aβ burden as well as protecting against memory deficits. The mechanisms are diagrammatically summarized in the accompanying figures. These hypothetical mechanisms are: (1) binding of anti-Aβ antibodies to the fibrillar form of Aβ with activation of Fc receptor-mediated phagocytosis (Fig. 1); (2) dissolution of preformed fibrillar Aβ plaques by anti-Aβ antibodies with a shift of the equilibrium of the Aβ molecule to the monomeric form (Fig. 2); and (3) binding of vaccine-induced anti-Aβ antibodies to circulating plasma Aβ, resulting in greater Aβ efflux from the brain down its concentration gradient (Fig. 3). There is evidence for each mechanism in the articles published here. The data presented by Solomon strongly support the dissolution of preformed aggregates by antibodies. The changes in soluble and serum Aβ reported by Vehmas et al. argue for a peripheral mechanism of action, while the correlations between microglia activation and reduced Aβ accumulation found by Wilcock et al. are consistent with Fc receptor-mediated phagocytosis. This is a microcosm of what is brewing into a significant controversy in this rapidly expanding field. It is critical to recognize that none of these mechanisms is mutually exclusive, and all may be working in concert to achieve benefit in APP transgenic mice. We can only hope they will be as effective in human populations.

Irrespective of what mechanism or mechanisms ultimately are shown to be important, the success of Aβ peptide vaccines in transgenic mouse models of AD has opened up an exciting door for potentially novel preventatives and therapies for human AD. Elan Pharmaceuticals have recently reported on a Phase I safety trial of their Aβ vaccine (AN-1792). It was shown to be safe in patients and immunogenic in terms of the production of antibodies. The results of Phase II trials, to be shortly, will be eagerly awaited. In the meantime, important mechanistic as well as other information can be garnered from studies with murine and other models. The contributors to this special issue are at the forefront of these important studies.

REFERENCES


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