The interaction of complement system with abeta-binding liposomes: towards engineering of safer vesicles for the management of alzheimer's disease

A pathological hallmark of Alzheimer's disease (AD) is accumulation of beta amyloid (Aβ) plaques in the brain, and the reduction of Aβ is considered a primary therapeutic target. Peripheral treatments with molecules that have high affinity for Aβ can reduce the level of Aβ in the brain through the proposed 'sink effect'. Such approaches can further benefit with engineered nanoparticles bearing multiple binding sites for Aβ, where sequestered plasma Aβ will be routed to hepatic and splenic macrophages for destruction. This approach could potentially reduce or prevent brain amyloidosis and is currently under investigation. A promising example is sphingomyelin/cholesterol liposomes with bilayer incorporated phosphatidic acid (PA), which exhibits affinity for beta amyloid (Aβ)40 and 42 peptides. From the safety issue, liposomal infusion, however, often induces acute IgE-independent pseudoallergic responses, which are believed to be secondary to activation of the complement system. Accordingly, we have examined the effect of liposomal size and PA content on generation of a wide range of complement activation products in sera of healthy individuals and those of AD patients with a fully functional complement system. Complement activation was not significant with 5 mol% PA-containing liposomes of 150 nm in size, while abeta-binding affinity was maintained. Complement activation, however, proceeds with larger vesicles bearing 5 mol% PA. These and liposomes with higher PA contents (regardless of their size) activated complement exclusively via the alternative pathway, with likely involvement of anti-phospholipid antibodies in some cases. These antibodies are mostly of IgM class that can trigger alternative pathway activation following binding of factor B to C3b deposited on their F(ab) portion. We are currently assessing complement activation by other abeta-binding liposomes and following interaction with beta amyloid peptides and aggregates. These findings will contribute towards rational design of immunologically safe Aβ-binding vesicles for the management of AD.

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Organisations: University of Milan - Bicocca, University of Copenhagen
Contributors: Andersen, A. J., Hashemi, S. H., Galimberti, G., Re, F., Masserini, M., Moghimi, S. M.
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