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Investigation of Fc-receptor mediated phagocytosis on A β clearance *ex vivo*

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Immunotherapy is a promising approach for the treatment of Alzheimer's disease (AD). A β immunization as well as passive administration of A β antibodies into transgenic mice has been shown to induce clearance of amyloid plaques (the pathological hallmark of the disease), as well as cognitive improvement. A human trial of A β vaccination in AD, which had to be stopped due to symptoms of meningoencephalitis in 6% of the patients, provided some evidence for slower rates of cognitive decline in immunized patients compared to controls. In order to develop an effective and safe immunotherapeutic strategy in AD, it is of utmost importance to determine the mechanisms by which immunotherapy induces A β clearance and cognitive improvement. Two mechanisms of A β clearance have been proposed. The microglial hypothesis suggests that microglial cells are activated by antibodies that enter the brain and induce these cells to phagocytose amyloid, presumably via Fc-receptors. The peripheral hypothesis advocates a "sink" mechanism in which circulating antibodies bind A β in the periphery, causing an efflux of soluble A β from the brain to the blood due to a shift in equilibrium between insoluble and soluble A β . We believe that these mechanisms are not mutually exclusive and that both may contribute to A β clearance from the brain. In the present study, however, we focus on the potential role of Fc receptor mediated phagocytosis in the clearance of CNS amyloid. Fc γ RIIB negatively regulates Fc γ RI and Fc γ RIII-induced phagocytosis as much as 30-fold. Therefore, we developed an *ex vivo* assay to examine whether Fc γ RIIB-deficient microglia phagocytose A β (in the presence of specific anti-A β antibodies) more efficiently than wild-type microglia. We also use this assay to screen the efficacy of various monoclonal A β antibodies in stimulating the phagocytosis of amyloid. Our goal in these experiments is to better understand the role of microglia in antibody-induced clearance of A β , and thereby contribute to the eventual development of a safe treatment for AD.