Abstract 937

TREM2 ENGAGEMENT BY A NOVEL MONOCLONAL ANTIBODY ATTENUATES EXPERIMENTAL ALZHEIMER'S DISEASE

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Topic: β-Amyloid Diseases: Alzheimer´s Disease (AD), Prodromal AD, Cerebral Amyloid Angiopathy (CAA), Down Syndrome (DS) & Mild Cognitive Impairment (MCI) / Drug Development, Clinical Trials and Trial Design / A3.a immunotherapy

Authors: M. Fassler, M. Rappaport, J. George; Israel

Aims

To understand what is the role for TREM2 engagement with a novel monoclonal antibody in attenuating degeneration in transgentic alzheimer's disease models.

Methods

In this study we elaborate a thorough production of a novel monoclonal antibody targeting a unique epitope in the extracellular domain of TREM2, that binds and engages both its soluble and membrane bound forms. The mAb activation of trem2 expressing cells was tested in a number of immunoassays. Flow cytometry was used to measure beta amyloid cellular uptake and proliferation. Cognitive phenotype in various AD models was tested after systemic treatment using a variety of behavioral assessment methods such as Morris water maze and novel object recognition.

Results

By engaging membrane bound TREM2, the selected antibody was shown to promote their cellular proliferation, uptake of oligomeric beta amyloid/apoptotic neurons and activation in a Syk and Akt dependent manner. The antibody was shown to avidly bind soluble TREM2 in the CSF from AD patients and blunted the proinflammatory program driven by its intracerebral injection. Upon in vivo treatment, the antibody was shown to improve cognitive function in experimental amyloidopathy and taupathy models and to facilitate plaque associated microglial coverage and activation.

Conclusions

In conclusion, we describe a novel monoclonal antibody targeting membrane bound and soluble TREM2, that improves cognitive function in amyloidopathy and tauopathy models of alzheimer's disease by inducing microglial activation and attenuating chronic neuroinflammation. Thus, TREM2 engagement and activation may represent a promising therapeutic modality in patients with AD.