Immunotherapy of neurodegenerative diseases

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Abeta immunotherapy can clear brain beta-amyloid, reduce tau-related neuropathology, and restore the morphology of previously damaged neurons both in experimental animals and in patients with Alzheimer's disease (AD). Moreover, Abeta immunotherapy can promote the survival of newly born neurons in the dentate gyrus of transgenic mice expressing Adcausing mutations resulting in longer dendrites with more complex arborization as compared to untreated controls, and in functional integration of matured neurons in hippocampal circuits. In human patients with AD, immunotherapy reduced hippocampal amyloid load, and it corrected neurite curvature ratios suggesting morphologic recovery of neurites. The improvement of neurite curvature ratio also occurred in the vicinity of remaining amyloid plaques, and amyloid removal was associated with a reduction in PHF1 tau suggesting a reduction of hyperphosphorylated tau whereas tau misfolding and aggregation might be more resistant to Abeta immunotherapy. Together, the converging experimental and neuropathological evidence suggests a strong potential for neuronal plasticity and repair in AD following Abeta removal by immunotherapy. More than 10.000 patients are currently included in more than 40 ongoing clinical immunotherapy trials. A large majority of patients is participating in passive immunotherapy trials using monoclonal antibodies against various domains of Abeta. Besides safety, tolerability, cognition and ADL, outcome measures include analyses of CSF and plasma levels of biomarkers including Aß and tau. Innovative trial designs measuring clearance rates of CSF Aß as well as brain amyloid load are emerging, and are accepted by the health authorities. So far, antibody-based immunotherapy has been safe despite challenges relating to vasogenic edema, and a skin lesion in one actively vaccinated patient. The immunotherapy-related potential for neuronal plasticity and repair may depend heavily on the time window during immunotherapy is initiated, because damage downstream of the initial toxic events could well progress even in the absence of Abeta after a certain point of now return on the path to neuronal death has been reached. Therefore, early detection by imaging of beta-amyloid followed by preventive removal of brain betaamyloid may be an important option for the secondary prevention of dementia in the future.