Microglia function in Alzheimer’s disease: studying human primary cells

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The Netherlands

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Microglia function in Alzheimer's disease: studying human primary cells

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Research Abstract

Alzheimer’s disease (AD) is the most common form of dementia in elderly and is characterized by beta-amyloid (Abeta) aggregates forming plaques in the brain and neurofibrillary tangles. Abeta-oligomers in particular, cause neurotoxicity and cell death in AD brains. Abeta plaques in the AD brain are surrounded by activated microglia which implies an important role for these cells in the progression of AD. Therefore, microglia can be an interesting therapeutic target for AD but so far, no promising microglial therapies have been developed yet.
It has been suggested that defects in synapses have a central role in age-associated changes in the central nervous system. Synapses are especially vulnerable to damage and age-related synaptic dysfunction is thought to precipitate neurological degeneration in neurodegenerative diseases such as AD.
Early in postnatal development neurons generate more synaptic connections than those that are retained in the adult brain tissue. Recently, it has been shown that microglia are mediators of synaptic pruning in the developing brain. Also in the adult brain, microglia may play a role in synaptic remodeling and plasticity. One of the factors involved in synaptic pruning by microglia was shown to be CX3CL1 which is exclusively expressed by neurons and its receptor is CX3CR1which is expressed by microglia in the brain. Interestingly, in several transgenic mouse models of AD, CX3CR1 deficiency ameliorated Abeta deposition by altering microglial activation and promoting microglial phagocytosis. The hypothesis of the proposed study is therefore that in the AD brain microglia phagocytize more synapses, thereby inducing problems with neuronal communication. Since cognitive functioning is dependent on synapse density in the brain, abnormal microglia pruning can therefore be involved in reduced synapse density and thereby affect cognitive functioning leading to dementia in AD.
Our specific objectives are to specifically isolate microglia from post-mortem AD and control brain tissue and to elucidate their role in Abeta degradation and synaptic pruning, to study if Abeta oligomer uptake by microglia is brain region specific, to determine whether uptake of synaptic vesicles altered in control microglia compared to AD microglia and we will study if synaptic pruning by primary microglia altered upon Abeta uptake. Novel techniques to isolate microglia from post-mortem human brain tissue will be used which enables us to culture these cells and analyse their efficiency to take up and degrade Abeta. We will isolate human primary cells and study different microglia subtypes since we found in mouse models for AD that different microglia subtypes, the CD11b and CD11c positive microglia, are involved in the pathology of AD.
Since Abeta oligomers are very unstable and either can disintegrate into smaller species or aggregate to larger oligomeric species and insoluble fibrils, we will use novel stable Abeta 1-42 oligomers.
To determine the role of microglia in synaptic pruning in AD, we aim to set up a technique to isolate synaptosomes from human brain tissue. In addition, we will develop several co-culture models for human primary microglia and neurons based on existing models using rodent cells.
The knowledge that is generated through the proposed project will help us in understanding the role of microglia in AD in uptake of Abeta oligomers and synaptic pruning. This will contribute to the development of new treatment strategies to relief the plaque burden and synaptic loss in AD patients. This is important for the treatment of AD since cognitive functioning is dependent on synapse density in the brain.

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