

Application of microglia to possible cell therapy for Alzheimer's disease

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Abstract

According to the amyloid cascade hypothesis, aggregation of β -amyloid ($A\beta$) in senile plaques is an early event in Alzheimer's disease (AD); therefore, inhibition of $A\beta$ deposition, and removal of $A\beta$ from the brain are important goals for AD prevention and treatment. Since microglia/macrophages have the ability to phagocytose $A\beta$, the therapeutic use of these cells has attracted our attention for the treatment of AD. We injected β -amyloid peptide $A\beta_{1-42}$ ($A\beta_{42}$) into the left hippocampus of rats. Microglia were labeled with superparamagnetic iron oxide (Resovist) and then transplanted into either the lateral ventricle or the carotid artery. T2-weighted magnetic resonance imaging (MRI) revealed significant signal changes attributable to the Resovist-containing microglia that gathered in $A\beta_{42}$ -injected areas. Histochemistry demonstrated that Resovist-positive microglia accumulated around the $A\beta$ deposits and internalized some of the $A\beta_{42}$ peptide. The resultant amounts of $A\beta_{42}$ injected into the rat hippocampus were then measured with and without microglial transplantation into the lateral ventricle. Although the amounts of $A\beta_{42}$ were gradually reduced, even in control rats, the reduction was significantly promoted by the transplantation. Thus, Resovist-labeled exogenous microglia can migrate from the lateral ventricle to the $A\beta_{42}$ -injected site and phagocytose $A\beta_{42}$. This study suggested that these microglia/macrophages could promise a bright future as therapeutic tools for AD. *Tottori J. Clin. Res.* 2(1), 142-147, 2009

Key words: Alzheimer's disease, β -amyloid, microglia, magnetic resonance imaging, cell therapy

Introduction

Senile plaques and neurofibrillary tangles are hallmarks of AD. According to the amyloid cascade hypothesis, aggregation of $A\beta$ in senile plaques is an early event in AD^{1, 2)}; therefore, inhibition of $A\beta$ deposition and removal of $A\beta$ from the brain are important goals for the prevention and treatment of AD²⁾. Several potential methods have been proposed for the removal of $A\beta$ deposits, including vaccination³⁾, sequestration^{4, 5)}, gene therapy⁶⁾ and cell therapy^{7, 8)}.

Akiyama and McGeer⁹⁾ demonstrated that the

reduction in senile plaques occurred in cortical areas affected by incomplete ischemia in AD. In those areas, $A\beta$ fragments were detected in activated microglia. These findings suggested that exogenous microglia might be of therapeutic use in AD if they could be delivered into the brain through an area where there was a breakdown of the blood-brain barrier (BBB).

MR tracking of exogenous microglia

For such cell therapeutics, it is very important to non-invasively monitor the administered cells; h-