sAPPα Enhances the Transdifferentiation of Adult Bone Marrow Progenitor

賴文福
Chen CW;Boiteau RM;Lai WF;Barger SW;Cataldo AM

摘要

Abstract

The remediation of neurodegeneration and cognitive decline in Alzheimer's Disease (AD) remains a challenge to basic scientists and clinicians. It has been suggested that adult bone marrow stem cells can transdifferentiate into different neuronal phenotypes. Here we demonstrate that the a-secretase-cleaved fragment of the amyloid precursor protein (sAPPα), a potent neurotrophic factor, potentiates the nerve growth factor (NGF)/retinoic acid (RA) induced transdifferentiation of bone marrow-derived adult progenitor cells (MAPCs) into neural progenitor cells and, more specifically, enhances their terminal differentiation into a cholinergic-like neuronal phenotype. The addition of sAPPa to NGF/RAstimulated MAPCs resulted in their conversion to neuronal-like cells as evidenced by the extension of neurites and the appearance of immature synaptic complexes. MAPCs differentiated in the presence of sAPPα and NGF/RA exhibited a 40% to as much as 75% increase in neuronal proteins including NeuN, β;-tubulin III, NFM, and synaptophysin, compared to MAPCs differentiated by NGF/RA alone. This process was accompanied by an increase in the levels of choline acetyltransferase, a marker of cholinergic neurons, compared to those of GABAergic and dopaminergic neuronal subtypes. MAPCs immunpositive for sAPP&a were identified within the septohippocampal system of transgenic PS/APP mice injected intravenously with sAPPa-transfected MAPCs and found in close proximity to the cerebral vasculature. Given that in AD cholinergic neurons are severely vulnerable to neurodegeneration and that the levels of sAPPa are significantly reduced, these findings suggest the combined use of sAPPα and MAPCs offers a new and potentially powerful therapeutic strategy for AD treatment.