BMC Proceedings

Poster presentation

An in vitro model of central nervous system infections and regeneration: neuronal stem cells as regenerative therapies in bacterial meningitis

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from Infectious diseases of the nervous system: pathogenesis and worldwide impact
Paris, France. 10–13 September 2008

Published: 23 September 2008

BMC Proceedings 2008, **2**(Suppl 1):P26

This abstract is available from: http://www.biomedcentral.com/1753-6561/2/S1/P26

Bacterial meningitis is a devastating disease with high mortality rates of up to 25% leading to life-long disabilities in up to 50% of the survivors. Brain injury caused by bacterial meningitis prominently affects the cortex and hippocampus a brain region involved in learning and memory function. In experimental bacterial meningitis hippocampal injury is characterized by apoptotic cell death of neuronal stem cells and/or their progeny in the subgranular zone of the dentate gyrus, which is responsible for neurogenesis, and therefore potentially well equipped for brain repair.

Multipotency and the capacity for continuous self-renewal of embryonic stem cells make them attractive candidates for cell-replacement studies. We are systematically developing an in vitro system to study brain regeneration in bacterial meningitis.

Here we used a co-culture model of long-term hippocampal slice cultures from postnatal rats (P4–5) and embryonic stem/progenitor cells from the subventricular zone (E14–17) to evaluate the potential of transplanted cells to survive and to integrate into organotypic hippocampal slice cultures for therapeutic approaches. To this end, we grafted chemically labelled embryonic-derived stem/progenitor cells into organotypic hippocampal slices in the region of the dentate gyrus. Cells were allowed to grow in such co-culture conditions with the addition of epidermal (EGF) and basic fibroblast growth factor (bFGF). The survival and integration of grafted cells was examined on cryosections of organotypic slice cultures by using immunohistochemistry.

Sections showed movement and neurite outgrowth of subventricular cells into the dentate gyrus at day 7 after engraftment. In the presence of bFGF and EGF embryonic derived stem/progenitor cells were able to differentiate and to mature into neurons.

In conclusion, we demonstrated that embryonic derived stem/progenitor cells are well suited for subsequent migration, proliferation, differentiation and integration into organotypic slice cultures in vitro and may thus hold promise for regenerative therapies in patients after bacterial meningitis.