Multipotent Adult Progenitor Cell Therapy for Traumatic Brain Injury: Systemic Modulation of Microglia

Supinder Singh Bedi BS, MS, Ph.D.; Peter Walker MD; Shinil Shah; Fernando Jimenez; Chelsea Thomas; Philippa Smith; Robert Hetz; Jason Hamilton PhD; Robert W. Mays PhD; Charles S. Cox MD

Introduction

Traumatic brain injury (TBI) can cause cognitive, physical and behavioral deficits that are dependent on the severity and location of the injury. Immune responses are key regulators of TBI-induced alterations in the central nervous system (CNS). Microglia, a component of the immune response in the CNS are activated and become pro-inflammatory microglia (M1) after injury. In a rodent TBI model, we investigated interactions of multipotent adult progenitor cells [MAPC (Athersys, Inc)] and splenocytes to attenuate the immune response of microglia (pro to anti-inflammatory: M1 to M2) after TBI.

Methods

We utilized in vivo and in vitro techniques to characterize M2:M1. Antibodies CD 86 and CD 206 were used to assess the M2:M1 phenotype respectively using flow cytometry and immunohistochemistry.

Results

In vivo: MAPC treatment was administered 2 and 24 hr after injury. Microglia harvested 48 (2.1:1.3, $P<0.01$) and 120 hr (5.5:1.9, $P<0.01$) after injury showed a significant increase in the M2:M1 phenotype when compared to untreated microglia. In vitro: Isolated microglia were stimulated with Lipopolysaccharide (LPS). They were then incubated with supernatant derived from MAPC in direct contact with stimulated splenocytes. Seventy-two hours after the incubation, there was a significant increase in the M2:M1 phenotype when compared with LPS stimulated microglia alone (2.4:1.2, $P <0.01$) using flow cytometry. There was a significant increase in the M2 phenotype ($P < 0.05$), decrease in proliferation ($P < 0.01$) and an increase in M1 microglia apoptosis (2.5 fold, $P <0.05$).

Conclusions

The data indicate that there is a secreted soluble factor(s) due to the interactions between the spleen and MAPC, which modulates the microglia phenotype from M1 to M2. MAPC provides neuroprotection by causing M1 to undergo apoptosis. MAPC modulate the systemic inflammatory response, via the spleen, thereby significantly altering the M1 to M2 phenotype.

Learning Objectives

The overall objective is introduce the concept that 1)multipotent adult progenitor cells treatment for traumatic brain injury can systemically attenuate the harmful effects of pro-inflammatory microglia, and 2)they do this by modulating the M1 phenotype to M2 and also M1 apoptosis.

References

Walker PA, Shah SK, Jimenez F, Gerber MH, Xue H, Cutrone R, Hamilton JA, Mays RW, Deans R, Pati S, Dash PK, Cox CS, Jr. (2010) Intravenous multipotent adult progenitor cell therapy for traumatic brain injury: preserving the blood brain barrier via an interaction with splenocytes. Exp Neurol 225:341-352.

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