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PRECLINICAL STUDIES

Human Umbilical Cord Blood Monocytes, but not Adult Blood Monocytes, Rescue Brain Cells from Hypoxic–Ischemic Injury: Mechanistic and Therapeutic Implications

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ABSTRACT 1

Introduction

Human umbilical cord blood (CB) mononuclear cells (MNC) are being tested in clinical trials to treat hypoxic–ischemic (HI) brain injuries. Although early results are encouraging, mechanisms underlying potential clinical benefits are not well understood.

Objective

To explore these mechanisms further, we investigated how CB cells are protective in hypoxic–ischemic insults compared with adult peripheral blood (PB) cells and what specific subpopulation of cells mediates the protection.

Methods

We used mouse brain organotypic slice cultures on membrane inserts and exposed these to oxygen and glucose deprivation (OGD) to mimic the hypoxic–ischemic condition. We then treated the brain slices with cells from CB or PB. Subpopulations of cells were purified by magnetic-activated cell sorting.

Results

We found that CB-MNCs protected neurons from OGD-induced death and reduced both microglial and astrocyte activation, whereas PB-MNC failed to affect either outcome. We also found protection was largely mediated by factors secreted by CB-MNC. To determine if a specific cell type among the diverse cell subpopulations of CB-MNC mediated these protective activities, we assayed the protective activities of CB-MNC depleted of various cell types in the OGD-shocked brain slice culture system. We found that only removal of CB CD14+ monocytes abolished neuroprotection. Furthermore, positively selected subpopulations of CB-MNC CD14+ cells, but not purified PB-CD14+ cells, efficiently protected neuronal cells from death and reduced glial activation following OGD. Gene expression microarray analysis demonstrated that, compared with PB-CD14+ monocytes, CB-CD14+ monocytes overexpressed several secreted proteins with the potential to protect neurons. Differential expression of five candidate effector molecules (chitinase 3-like protein-1, inhibin-A, interleukin-10, matrix metalloproteinase-9, and thrombospondin-1) was confirmed by Western blotting and immunofluorescence.

Discussion

Our findings suggest that CD14+ monocytes are the cells in CB-MNC products that protect brain tissue from HI and that specific secretory proteins expressed by these cells may mediate this protection.