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Basic Science

Extracellular matrix-regulated neural differentiation of human multipotent marrow progenitor cells enhances functional recovery after spinal cord injury

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Abstract

BACKGROUND CONTEXT: Recent advanced studies have demonstrated that cytokines and extracellular matrix (ECM) could trigger various types of neural differentiation. However, the efficacy of differentiation and in vivo transplantation has not yet thoroughly been investigated.

PURPOSE: To highlight the current understanding of the effects of ECM on neural differentiation of human bone marrow-derived multipotent progenitor cells (MPCs), regarding state-of-art cure for the animal with acute spinal cord injury (SCI), and explore future treatments aimed at neural repair.

STUDY DESIGN: A selective overview of the literature pertaining to the neural differentiation of the MSCs and experimental animals aimed at improved repair of SCI.

METHODS: Extracellular matrix proteins, tenascin-cytotactin (TN-C), tenascin-restrictin (TN-R), and chondroitin sulfate (CS), with the cytokines, nerve growth factor (NGF)/brain-derived neurotrophic factor (BDNF)/retinoic acid (RA) (NBR), were incorporated to induce transdifferentiation of human MPCs. Cells were treated with NBR for 7 days, and then TN-C, TN-R, or CS was added for 2 days. The medium was changed every 2 days. Twenty-four animals were randomly assigned to four groups with six animals in each group: one experimental and three controls. Animals received two (bilateral) injections of vehicle, MPCs, NBR-induced MPCs, or NBR/TN-C-induced MPCs into the lesion sites after SCI. Functional assessment was measured using the Basso, Beattie, and Bresnahan locomotor rating score. Data were analyzed using analysis of variance followed by Student-Newman-Keuls (SNK) post hoc tests.

RESULTS: Results showed that MPCs with the transdifferentiation of human MPCs to neurons were associated with increased messenger-RNA (mRNA) expression of neuronal markers including nestin, microtubule-associated protein (MAP) 2, glial fibrillary acidic protein, βIII tubulin, and NGF. Greater amounts of neuronal morphology appeared in cultures incorporated with TN-C and TN-R than those with CS. The addition of TN-C enhanced mRNA expressions of MAP2, βIII tubulin, and NGF, whereas TN-R did not significantly change. Conversely, CS exposure decreased

FDA device/drug status: Not applicable.

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MAP2, βIII tubulin, and NGF expressions. The TN-C-treated MSCs significantly and functionally repaired SCI-induced rats at Day 42. Present results indicate that ECM components, such as tenascins and CS in addition to cytokines, may play functional roles in regulating neurogenesis by human MPCs.

CONCLUSIONS: These findings suggest that the combined use of TN-C, NBR, and human MPCs offers a new feasible method for nerve repair. © 2014 Elsevier Inc. All rights reserved.

Keywords: Chondroitin sulfate; Extracellular matrix; Human multipotent progenitor cells; Neurogenesis; Tenascin-cytotactin; Tenascin-restrictin

Introduction

Classically, mature neurons were thought to lack the capacity to proliferate or respond to either acute or chronic pathologic changes. However, in 1992, Reynolds and Weiss [1] isolated multipotential stem cells from the striatum of the adult mouse brain and succeeded in differentiating these cells into neurons and astrocytes in vitro. This raised the possibility of repairing central nervous system neurons. However, subsequent work demonstrated that only very few sites, such as the hippocampus and ventricular and subventrical zones [2,3], can recruit neural stem cells, which generally appear in the resting state and do not significantly aid in repairing severe neural defects. Exogenic or allogenic progenitor cells are required to serve as seed cells for the repair of neural lesions. Of these candidates, adult bone marrow-derived multipotent progenitor cells (MPCs) were especially attractive as bone marrow harvesting is associated with fewer ethical debates than the use of embryonic cell sources. Moreover, it has been long established that the MPCs are multipotent and act as precursors of various mesoderm-type cells such as osteoblasts, chondrocytes, and adipocytes in cultivation [4].

Several attempts have been made to induce neuronal transdifferentiation from mammalian and human MPCs. Intravenous transplantation of labeled MPCs resulted in the wide distribution and differentiation of these cells in bone marrow, muscles, spleen, kidneys, lungs, liver, endothelium, and brain tissues, which demonstrated the transdifferentiation potential of the MPCs [5–7]. Neuroprogenitor cells were triggered in the brain from mouse bone marrow [8] and rat hematopoietic stem cells [9]. Transdifferentiation of MPCs to neural lineages was reported to be spontaneously induced after removing the basic fibroblast growth factor and epidermal growth factor signals [10–12]; however neural differentiation can be promoted using neurotrophic-3 (NT-3), platelet-derived growth factor, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), retinoic acid (RA), sonic hedgehog, and α-secretase-cleaved fragment of the amyloid precursor protein [13,14].

The extracellular matrix (ECM) has been suggested to modulate the differentiation of embryonic stem cells [15]. For example, Type IV collagen, laminins, and fibronectin were shown to guide neurite extension on differentiated neuron cells [16–19]. Conversely, exposure to chondroitin sulfate (CS) resulted in the inhibition of axon outgrowth [20]. Another ECM molecule, tenascin restrictin (TN-R), was also shown to induce the formation of microprocesses along neurites and enlarged growth cones of chick tectal neurons [21,22]. Tenascin-cytotactin (TN-C), highly expressed in the subventricular zone, generates a stem cell ''niche'' that acts to orchestrate neural stem cell development in mice [23,24]. Among transdifferentiation studies, most have been conducted with animal cells [25–28] and some with human MPCs [29,30].

Previous study reported that the local transplantation of hNSC improved the functional recovery of animals with spinal cord injury (SCI) [31]. The MPC was also considered a candidate for SCI [32,33] Advantages of MPCs used in the repair of SCI include the ease of isolation, low immunogenicity, a potential increase of cell proliferation, and some degree of differentiation. However, there is still a clinical demand to achieve more complete neuronal differentiation using a human in vitro study. The purpose of the present research was to investigate the ECM effects on neuronal transdifferentiation of human bone marrow-derived MPCs and confirm its potential to regenerate the spinal cord. The effects of TN-R, TN-C, or CS together with cytokines including NGF/BDNF/RA (NBR) were evaluated using immunocytochemistry and a reverse transcriptase polymerase chain reaction (RT-PCR) in vitro, followed by a cell therapy in rats after an SCI.

Materials and methods

Subjects

Consenting bone marrow donors were selected from the patients admitted to the Orthopedic Section of Taipei Municipal Chung-Hsin Hospital (Taipei, Taiwan). None had endocrine disease or was receiving hormone replacement therapy. Bone marrow was obtained from a femur fracture site by proximal femur aspiration during surgical treatment procedures.

Isolation, cultivation, and identification of MPCs

Multipotent progenitor cells were isolated and expanded from human bone marrow as described previously [34]. They were mixed with sodium-heparin and diluted with five volumes of phosphate-buffered saline. The cell suspension was fractionated on a Percoll gradient (40% initial density,

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