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Research Report

Bone marrow stromal cell transplantation for treatment of sub-acute spinal cord injury in the rat

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ABSTRACT

Bone marrow stromal cells (BMSCs) have been studied as effective transplants for the treatment of spinal cord injury (SCI). Our previous study showed that BMSCs infused into the cerebrospinal fluid (CSF) exhibited distinct effects on the recovery of acute SCI. The present study examined the effects of BMSCs in sub-acute SCI (2 weeks post-injury) by transplanting them directly into the lesion. The spinal cord was crush-injured at the Th8-9 level in rats, and 2 weeks later, cultured BMSCs (5×10^5) derived from GFP-transgenic rats of the same strain were transplanted into the lesion. Tissue repair and nerve regeneration were examined by immunohistochemistry and electron microscopy. GFP-labeled BMSCs survived as cell assemblies in the spinal cord for 1-2 weeks after transplantation. The dorsal side of BMSC assemblies in the spinal cord usually showed an expanded GFAP-negative, astrocyte-devoid area, in which extracellular matrices including collagen fibrils were deposited. Numerous regenerating axons associated with Schwann cells grew out through such astrocyte-devoid extracellular matrices. Ascending (CGRP-containing) and descending (5HT- and TH-containing) axons were included in these regenerating axons. Regenerated axons were myelinated by Schwann cells beyond 2 weeks post-transplantation. Cavity formation was reduced in the cell transplantation group. Locomotory behavior assessed by the BBB scale improved to 9.8 points in the cell transplantation group, while it was to 5.5-5.7 in the control. BMSC transplantation into lesions of advanced SCI has markedly beneficial effects on tissue repair and axonal outgrowth, leading to improved locomotion in rats.

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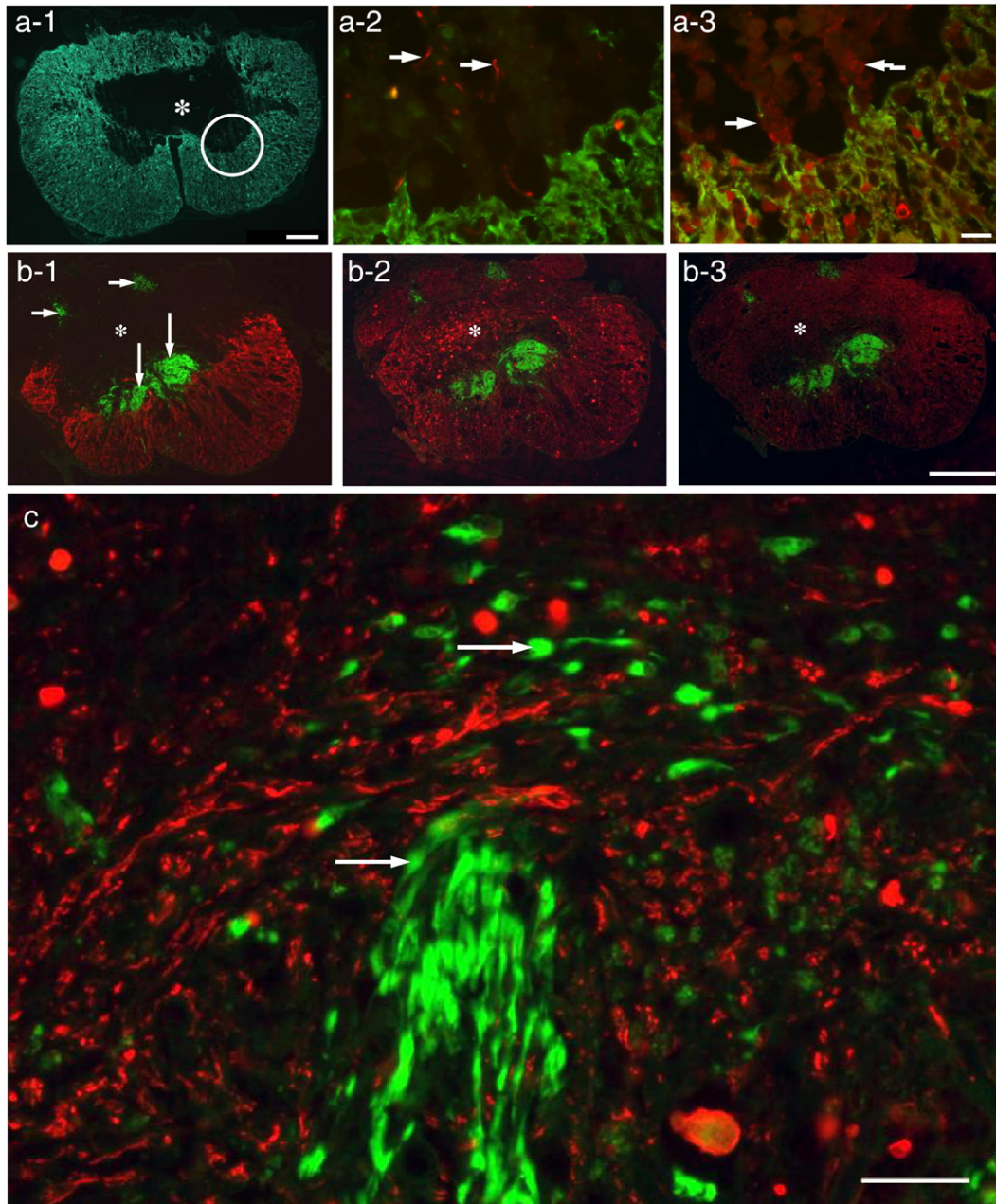


Fig. 1 – Spinal cord before cell transplantation (2 weeks after crush injury) (a-1, 2, and 3), and 1 week after BMSC transplantation (b-1, 2, 3, and c). a-1. GFAP-immunohistochemistry of the section from the epicenter of the lesion before transplantation. Sections were stained with FITC-labeled anti-mouse IgG antibody for GFAP. There is a cavity (asterisk) in the center of the spinal cord, and astrocytes (green) surround the cavity. Astrocyte scar is not distinct on the border of the cavity. Scale: 200 μm . a-2. Double-staining for GFAP (green) and neurofilaments (red) of the section adjacent to a-2. The area corresponding to the circle in a-1 was enlarged. Axons were stained by Cy-3-labeled anti-rabbit IgG antibody. Some axons (arrows) are associated with oligodendrocytes as shown in a-3. a-3. Double-staining for GFAP (green) and GST- π (red) of the section adjacent to a-1. The area corresponding to the circle in a-1 was enlarged. Oligodendrocytes were stained by Cy-3-labeled anti-rabbit IgG antibody. Short cell strands of oligodendrocytes (arrows) extend into the cavity, without accompanying astrocyte processes. No distinct astrocyte scar was formed. Scale: 20 μm (a-2 and 3). b-1. BMSC transplantation. GFP-transgenic BMSCs (green) are located as cell assemblies (long arrows) in the center of the spinal cord. Astrocytes immunostained by Cy-3-labeled antibody (red) are seen in the ventral part of the spinal cord, while the dorsal side (asterisk) of the BMSC assemblies is devoid of GFAP immunoreactivity. Small BMSC clusters (short arrows) are also seen at the periphery of the spinal cord. b-2. Immunohistochemistry for neurofilaments of the section adjacent to b-1. Numerous axons stained by Cy-3-labeled antibody (red) are seen in the astrocyte-devoid area (asterisk) of the spinal cord. b-3. Immunohistochemistry for GST- π of the section adjacent to b-2. No distinct staining for oligodendrocytes is found in the astrocyte-devoid area (asterisk) of the spinal cord. Scale: 500 μm (b-1, 2 and 3). c. Higher magnification of the astrocyte-devoid area of the section obtained from the same series of sections (b-1, 2, and 3), but at the different level from them. Immunohistochemistry for neurofilaments. Abundant axons (red) are found around engrafted BMSCs (green, arrows) in the astrocyte-devoid area of the spinal cord. Scale: 50 μm .

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