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Preface

Spinal cord Regeneration

It has long been believed that the spinal cord cannot regenerate once severed. However, transplantation studies over the last 2-3 decades have demonstrated that nerve fibers in the spinal cord have the ability to regenerate after injury if they are provided with an appropriate environment through which to extend.

Various kinds of cell or tissue have been examined as transplants, including Schwann cells, macrophages, embryonic tissues, olfactory ensheathing cells, choroid plexus ependymal cells, and ES cells. Among them, bone marrow stromal cells (BMSCs) have been regarded as the most promising cell in terms of clinical application, because they are markedly effective for axonal regeneration in the spinal cord, and, in addition, they have, unlike other cells, the unique advantage of being used as an autograft.

The ultimate purpose of a regeneration study using cell transplantation is that the cells under study can finally be applied in clinical cases. In this sense, cells associated with ethical and immunological problems and/or a tumorigenic tendency are unsuitable to be studied for cell transplantation. Those cells have no possibility to be used as transplants in clinical application. Transplantation studies using such cells cannot be categorized as "regeneration studies."

Cell transplantation has long been studied with the expectation that transplanted cells can be integrated into the host tissue, and finally differentiate into neural cells which will serve as sources of new neurons or scaffolds of growing axons. The typical study based on this concept is neural stem cell transplantation, in which implanted cells are expected to differentiate into neurons or glial cells that are subsequently integrated into the host spinal cord tissue, serving to promote axonal regeneration. However, BMSCs produce a distinct effect even if they are not integrated into the host tissue after transplantation.

After many trials using several kinds of cell including neural stem cells, we came, at present, to the conclusion that BMSCs are the most promising cells as transplants for spinal cord regeneration. Our recent studies showed that BMSCs, regardless of whether they were applied directly into the lesion or indirectly through the cerebrospinal fluid via the 4^{th} ventricle, enhanced the outgrowth of regenerating axons and improved locomotion.

Immunohistochemistry demonstrated that numerous regenerating axons traversed the spinal cord lesion. Electron microscopy showed that these regenerating axons were surrounded by Schwann cells and extended through connective tissue matrices composed of collagen fibrils. The behavior of rats was markedly improved from 0-4 points (control) to 10-12 on the BBB scale. The implanted BMSCs did not function as a scaffold for the growing axons, because they disappeared from the spinal cord within 2 weeks after

transplantation. There was no finding suggesting that astrocytes were associated with regenerating axons within the lesion.

These findings indicate that regenerating axons in the spinal cord extend through the connective tissue environment, as in the case of peripheral nerve regeneration. The fact that regenerating axons are surrounded by Schwann cells indicates that they are peripheral nerves in nature.

It has long been believed that the connective tissue is no good for the repair of CNS injury, because it triggers formation of astrocyte scars in CNS lesions. However, our study indicate that the limited intrinsic connective tissue formation without astrocyte scar following the spinal cord injury is not inhibitory, but promoting to the growth of regenerating axons in the spinal cord.

This consideration will revolutionize the old concept of spinal cord regeneration, and introduce a new trend to the cell transplantation study in the spinal cord injury.

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