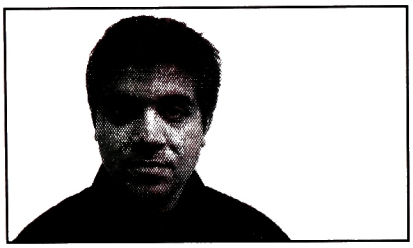
Remyelinating Damaged Nerves



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Christopher Reeve (1952 - 2004) once said, "We live in a time when the words impossible and unsolvable are no longer part of the scientific community's vocabulary. Each day we move closer to trials that will not just minimize the symptoms of disease and injury but eliminate them." Unfortunately Reeve passed away before the major breakthroughs in the field of central nervous system (CNS) nerve regeneration. Today, Reeve's words are a source of hope for millions of people around the world that suffer from illnesses that cause CNS nerve degeneration. Since the discovery that stem cells can serve as precursors for neuronal and glial cells researchers have been conducting many animals trials to see whether transplanting stem cell-derived neuronal and glial cells can induce the remyelination of degenerated nerves. Also, researchers are searching for alternative cells with stem cell properties that can be used to produce neuronal and glial cells. Researchers found that they are also able to produce neuronal and glial cells from bone marrow cells, which have stem cell like properties. Once injected, the neuronal and glial cells migrate to the damaged area in the CNS and remyelinate previously demyelinated areas, restoring some function to the damaged areas.

The CNS is a very delicate system consisting of numerous neuronal cells and their processes and several supporting cells called glial cells. Given that stem cells can differentiate into various neuronal and glial cells, scientists have been experimenting with injection of stem cells into the CNS to determine if remyelination occurs. However, before delving into research involving the CNS, one needs to have an understanding of CNS anatomy and physiology.

The CNS consists of the brain and the spinal cord, both of which are equipped with sensory and motor neurons and nerve fibers which allow for communication between the CNS and the rest of the body. Intact communication between the CNS and the body are essential for normal physiology (Carlson, 2004). There are nerve fibers termed axons which are very long, slender processes along which electric impulses (action potentials) are transmitted; these processes are typically surrounded by an insulation sheath or myelin. Myelinated axons conduct action potentials much faster than unmyelinated axons. Recent research on ion channels indicates that myelin sheaths regulate proper distribution and therefore function of channels participating in proper (fast and strong) transmission of action potentials (Carlson, 2004). Although the CNS has an inherent capacity to remyelinate previously demyelinated nerve fibers, persistent demyelination can have a severe impact on the myelination process (Blakemore et al., 2000). Multiple sclerosis, trauma and leucodystrophies can cause such demyelination.

Researchers believe there are two possible solutions to the problem of demyelination: to promote the production of cells with the capability to remyelinate, or to conduct research on animals with demyelination in the CNS by injecting differentiated neuronal and glial cells into the CNS. Once injected, the differentiated cells migrate to the lesion sites and remyelinate the demyelinated nerves to a certain extent (Blakemore et al., 2000). Many scientists believe the latter to be the next major breakthrough in the process of CNS regenerational recovery. Researchers have found that remyelination does occur and in some experiments remyelination occurred in up to 67% of demyelinating axons (Minodora et al., 2004). Researchers believe that the differentiated cells migrate to the region where the lesion has occurred and partially remyelinate the nerves, thus allowing for some function to return. A reason why not all demyelinated nerves are remyelinated is because the injected cells are unable to migrate to all areas of the lesion (Minodora et al., 2004). Generally, researchers transplant stem cells either directly into the brain or to the area in the spinal cord that has the lesion (Wu et al., 2002). Such is the case with Wu and others. (2004), who utilized a microsurgical operation to transplanted hippocampus-derived neurosphere cells into an injured spinal cord. However, Wu and his colleagues found that injecting stem cells directly into the lesion would be clinically unrealistic if the lesion covers a large area (Wu et al., 2002). Due to these discrepancies, Wu and colleagues have devised a new method of injecting the cells into the CNS. They have conducted experiments where they inject the cells for transplantation into the cerebrospinal fluid (CSF) in the fourth ventricle. The researchers found that the distribution of cells injected through the CSF were superficial as compared to these injected directly into the CNS. The injected cells were also able to survive in different regions of the CNS, and were able to migrate to the lesion area; once they reached the lesion the transplanted cells

remyelinated degenerated nerves (Wu et al., 2002).

Although researchers have been able to stimulate remyelination of injured spinal cord nerves in their experimental rats, there were major complications that arose in this process. When considering remyelination of nerves, most experiments fail rather than succeed due to the pathological changes that affect the CNS (Minodora, 2004). Another problem is that although the migration process and myelination do occur in most animals, very often it is incomplete. Age also seems to play a major role in the efficiency of myelination (Minodora, 2004). Minodora and colleagues have shown that older animals have a decreased chance of success and even if myelination of older animals does succeed the yield as compared with younger animals is much lower (Minodora, 2004). This observation is somewhat inconsistent with previous findings that the adult rat CNS has full potential of spontaneous remyelination after demyelinating injury, and indicates the need for more studies on spontaneous remyelination in animal models. The use of stem cells in research has been under tremendous scrutiny, so researchers have had little leeway in the experiments that they conduct. Despite these obstacles, research is rapidly moving forward.

As research has advanced in neuronal migration and demyelination, so has research into finding alternative cells with stem cell-like properties. Due to the legal implications dealing with stem cell usage, such substitute cells can be used as precursors for the production of neuronal cells. The discovery of bone marrow cell properties is an important advancement within surrogate cell research. Researchers have found that bone marrow cells can be differentiated into a variety of different cell lineages, including nerve cells (Akiyama, 2002). In various experiments conducted by Akiyama and colleagues, bone marrow cells were extracted from rats, which thereafter differentiated into neuronal cells, glial cells, as well as other cell lineages. This demonstrated that bone marrow cells have stem cell like properties (Akiyama et al., 2002).

Researchers such as Akiyama are now injecting substitute cells into rats with lesions in their CNS, using the same transplantation procedures as used with stem cell aggregate neuronal cells. They have found that when these cells are directly injected into a demyelinated nerve zone, they can cause partial remyelination (Akiyama , 2002). Akiyama and colleagues have also shown that transplanting bone marrow cells into rats with dysfunctional spinal cords restores function (Akiyama, 2002). Through subsequent autopsies, the researchers found that the pattern of remyelination occurring in their bone marrow injected model rats was similar to that of normal rats that are myelinated with oligodendrocytes (Akiyama, 2002).

Although bone marrow cell-induced myelination looks promising, there are several major concerns. First, the immune system of the rats may not accept the bone marrow cells, and may attack and destroy the injected cells before they are able to migrate to the damaged area. For this reason, Akiyama and colleagues have been using rats whose immune systems have been deactivated (Akiyama 2002). Another problem facing Akiyama's group is that the bone marrow cells remyelinate the damaged nerves at unpredictable levels, unlike stem-cell aggregate neuronal cells. This setback has brought into question the effectiveness of bone marrow aggregate neuronal cells in

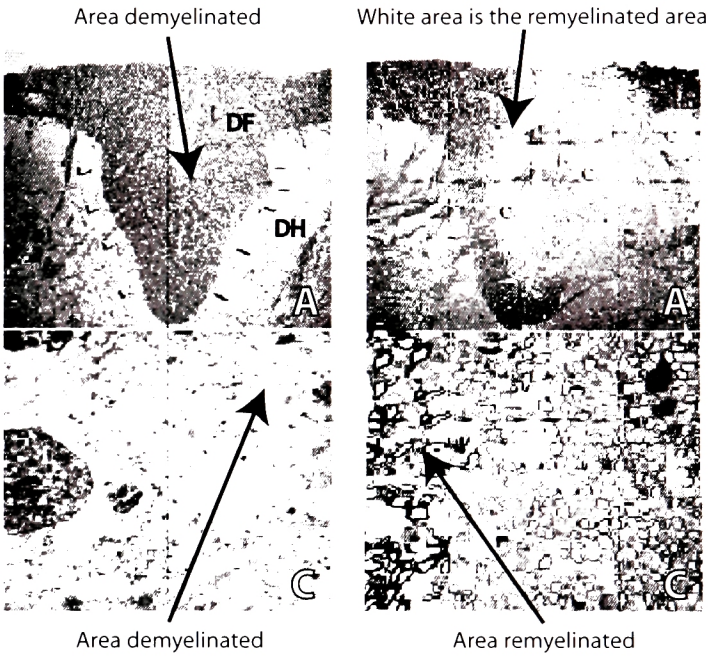

Figure 1: The two figures on the left are of a rat with a demyelinated area. The same area after injection shows remyelination of the cells (Akiyama, 2002).

remyelinating damaged areas (Akiyama, 2002). Although these issues have raised some concerns, the research is still in its initial stages.

Even though Christopher Reeve died before his dream of walking again was realized, there are millions of people whose lives could potentially be changed for the better in due time. Researchers have shown that CNS damage in experimental rats can partially be repaired by the injection of neuronal and glial cells that originated from stem or bone marrow cell aggregates. Although it seems that we are on the verge of a major breakthrough, there is still some time before human clinical trials can begin. M