

Adult stem cells and spinal cord injury treatment

Jesse Owens Ph.D.

By now almost everyone has heard a lot about “stem cells” and their potential in treating a variety of medical problems, including spinal cord injury. Much of the publicity and controversy has been in regard to embryonic stem cells and their potential for developing into any tissue within the adult body. These cells may literally become lifesavers in the future, but there are a couple of thorny problems that are generated by the use of cells from a human embryo. The issue most of us have heard about is the ethical problem of using a human embryo for spare parts even if it means enhancing the life of an existing person. That is not the only problem limiting the use of the cells for therapeutic purposes. The amazing plasticity of these cells is what makes them so promising; but also so dangerous. In some animal trials embryonic stem cells not only developed into the desired tissue but also produced abnormal growths containing unwanted body parts like teeth and hair.

The ability to restrict the growth of these cells to a specific desirable tissue is a very active area of research. Restricted development and differentiation of embryonic stem cells has already been accomplished in a small number of cases, such as the directed development of motor neurons in rats. The issues mentioned above are not trivial to overcome. I, and many other scientists, believe that it will some time before embryonic stem cells will become a safe and useful tool in restorative or regenerative medicine in humans. This assessment might sound a bit discouraging for those of us who seek a treatment for spinal cord injury in the near future, if there appeared to be no alternative. Fortunately, in the past few years “adult” stem cells from bone marrow have been shown to possess amazing potential for healing, or assisting in the healing in a wide array of tissues, including the spinal cord.

Before I describe the use of adult stem cells from bone marrow in CNS treatment let me give you a bit of history about these cells. There are a number of different types of blood cells and some of them are replenished on a regular basis. The fact that bone marrow contains stem cells has been known for many years. Under most normal circumstances the stem cells are sequestered within the marrow and do not come into contact with the rest of the body as does the blood itself. Bone marrow contains two major types of stem cells: those that give rise to the cells found in the circulating blood, and those which can differentiate into a variety of other cell types including cells found in the spinal cord and brain.

One of the factors that has aided in the study of these cells is that they are relatively easy to isolate and culture in a petri dish. When bone marrow cells are placed on a plastic dish many of the stem cells stick to the plastic and the others wash off. This is a fortuitous quality of the cells that has greatly enhanced the ability to readily obtain them and study them, even from human donors. In addition to directly removing them from bone marrow, techniques have been developed in humans to stimulate the stem cells in the

marrow to proliferate and spill out into the blood stream. Stem cells can then be harvested directly from the blood, which is much less invasive than bone marrow biopsies.

As the scientific world started focusing on the potential of stem cells in general, a few curious investigators started examining the developmental plasticity of the bone marrow stem cells by either isolating them and exposing them to various growth factors in the culture dish, or marking them so they could be identified later and injecting them into animals to see if they gave rise to other types of cells. This is about the time the disagreements began regarding the capacity of these cells to differentiate into other types of tissue. In one beautiful study at the University of Minnesota rat embryos had a single adult stem cell placed within the embryo and the animal was then allowed to develop. In these studies the implanted stem cell possessed a molecular marker that permitted the localization of the cell's progeny in the adult animal's tissues. Remarkably, it appeared that the single stem cell had given rise to a big variety of different cells types within the adult animal. This experiment left little doubt about the plasticity of these cells if they were placed within an embryo, but what about placing adult stem cells in a fully developed animal? Would those cells give rise to different cells types as well? Researchers at Stanford addressed this question by injecting a single adult stem cell into adult animals and then examined the animal thoroughly to determine if there were any appreciable numbers of "transdifferentiated" cells in the host tissue. They found almost none! So where does the truth lie, can these adult stem cells develop into other cells types in the adult or not.

A likely explanation for these seemingly contradictory results is that the animals in the Stanford experiment were lacking a critical signal needed to induce the appearance of bone marrow stem cell markers on other types of tissue. The animals were all healthy and did not have any injured tissue. Injury and active inflammation appear to be a key signal for these cells to attempt repair or to differentiate into a specialized cell type. Many different publications now support the idea that bone marrow stem cells which have been injected into the blood stream or directly into tissue need to sense that an injury has occurred in order to home to the damaged tissue and exert a healing influence.

The list of experiments that have been done with these cells is growing rapidly as the scientific and medical world unravels their tremendous potential for healing damaged tissue.

So what about the use of the cells in the treatment of CNS injury? A few years ago experimental animals had the blood flow to one side of the brain temporarily blocked which caused the equivalent of a stroke in humans. Subsequently, bone marrow stem cells were injected into the blood stream of some of the animals. Those which received the stem cells recovered markedly more than the others. When the investigators examined the brain they found that the stem cells had crossed the blood brain barrier and had taken up residence in the brain. More recently others have demonstrated that after spinal cord injury the stem cells can not only cross the blood brain barrier and zero in on the damaged region, but can produce some new neurons, secrete helpful substances such as neurotrophic factors, and re-myelinate axons which became denuded as the result of

injury. The experiments described above were performed on acutely injured animals, but recent findings for the laboratory of Dr. Giles Plant in Australia indicate that these cells may have a role in the treatment of chronic spinal cord injury as well.

There is ongoing controversy as to how these cells exert their healing influence. Some experiments suggest that the stem cells find an injury site and secrete helpful substances, or actually turn into different cell types as needed. Others studies clearly demonstrate that the stem cells fuse with stressed cells and apparently reprogram their DNA to tolerate the stress or convert them to a more juvenile state of differentiation. Which of the scenarios is correct? The jury is still out, but it may be that the cells perform their magic by all three mechanisms.

Some of the most important advantages of using of these cells are:

1. They can be obtained from the individual who is to receive treatment without excessively traumatic surgery.
2. If they are obtained from the patient and transplanted back into the patient there will be no problem with tissue rejection
3. They appear to have a great deal of innate wisdom as to how to repair the spinal cord. This should greatly increase the speed that we could bring this type of therapy to human patients.
4. Since the stem cells can cross the blood brain barrier we could deliver the cells repeatedly through the blood stream instead of surgically invading the CNS multiple times
5. We may find that it is possible to use the stem cells as a vehicle to carry useful agents into the damaged region of the spinal cord by way of the blood. This has already been demonstrated for delivery to the brain.

This is indeed an exciting time to be working in the field of central nervous system repair. In future installments I will describe other agents which may help produce a meaningful treatment for damaged spinal cords.

Klein, S and Svendsen, CN (2005) Stem cells in the injured spinal cord:reducing the pain and increasing the gain. *Nature Neuroscience*, 8:3 pg.258-259.

Sykova, E. and Jendelova, P. (2005) Magnetic and resonance tracking of implanted adult and embryonic stem cells in the brain and spinal cord. *Ann. N.Y. Acad.Sci.* 1049:146-160.

Kamada, T. et al. (2005). Transplantation of bone marrow stromal cell-derived schwann cells promotes axonal regeneration and functional recovery after complete transaction of the adult rat spinal cord. *J. Neuropathol. Exp. Neurology*, 64:1, pg 37-46