

Using Stem Cells To Repair The Brain And Spinal Cord

The possibilities that stem cells bring to the medical field are truly amazing. And in the many different areas of medicine where stem cells bring hope, I am particularly impressed by the encouraging potential for stem cells to be used to repair the nervous system. In this paper, I am going to review some of the discoveries that have been made in the way of stem cells in three areas: paralysis, Lou Gehrig's disease, and Parkinson's Disease.

Paralysis

Although stem cells hold amazing promise for the treatment of paralysis, we are unable to say that paralysis will one day be a completely reversible disability. With respect to severe spinal cord injury, it may be that we will never have the ability to completely restore function. The problem is that with these severe injuries is not only that many different types of cells are destroyed, but, more importantly, that neurons—which transmit electrical signals between the brain and the body—are destroyed. “Getting these neurons to grow past an injury site and connect appropriately with their targets is extraordinarily difficult.” [1]

However, there is still hope for reversing paralysis because it is not always the result of a “severe” spinal cord injury. “In many spinal injuries, the spinal cord is not actually cut and at least some of the signal-carrying neuronal axons are intact. But the surviving axons no longer carry messages because cells called oligodendrocytes, which make the axons' insulating myelin sheath, are lost” [1]. This allows us to still have hope of greatly reducing the occurrence of permanent paralysis because, in animal studies, it has been shown that paralysis is reversible if it is caused by a deficient myelin sheath.

The first study to show this was published in July 1999. “Scientists took stem cells, manipulated them into neural cells and injected them into” rats that were born with a disease that prevents the myelin coating from forming around nerve cells [2]. The neural cells that the scientists created were able to “promote the growth” of the myelin covering. As a result, the nerve cells were able to function properly; “the treatment replaces the lost myelin but does not stop the disease” [2].

Another study in August of 2001 showed again that stem cells can be used to replace a lost or damaged myelin coating. In this study, scientists gave rats an injury that damaged the myelin sheath and then injected one group with stem cells that had been manipulated into “myelin coating cells” [3]. After six weeks, the myelin coating had grown back where it had been lost and the rats regained movement in their legs. Since a damaged myelin sheath is the cause of Christopher Reeve's paralysis, such a treatment could also mean that one day stem cells could reverse his paralysis. [3]

Lou Gehrig's Disease—Amyotrophic Lateral Sclerosis (ALS)

ALS is a degenerative disorder that

progressively destroys special nerves found in the spinal cord, known as motor neurons, that control movement. Patients with ALS develop increasing muscle weakness over months to years, which ultimately leads to paralysis and death. The cause is largely unknown, and there are no effective treatments. [1]

The approach being used to try to stop the progression and hopefully reverse the damage of ALS is to use stem cells to cause new motor neuron cells to grow. However it is important to note that the only reason it is possible to even think of doing this is because of the idea that the nervous system is able to generate new neurons. Ten years ago, it was thought that the adult nervous system did not have this ability; that dead neurons and other brain tissue could never be replaced by new tissue. However, evidence has entirely turned this thinking upside-down, and it is now a firm fact that the nervous system has a “regenerative capacity.” [1]

Currently, there are two methods that use this “new” regenerative capacity of the nervous system to treat disorders that affect it. The first method

is to grow differentiated cells in a laboratory dish that are suitable for implantation into a patient by starting with undifferentiated neural cells. The idea is either to treat the cells in culture to nudge them toward the desired differentiated neuronal cell type before implantation, or to implant them directly and rely on signals inside the body to direct their maturation into the right kind of brain cell. [1]

Currently, there are a “variety of stem cells that might be used for this task” [1].

Stem cells aren't as important to the other method that could repair the nervous system; it

relies on finding growth hormones and other “trophic factors”—growth factors, hormones, and other signaling molecules that help cells survive and grow—that can fire up a patient's own stem cells and endogenous repair mechanisms, to allow the body to cope with damage from disease or injury. [1]

It is also interesting to note that scientists speculate that it is possible that injecting stem cells—or, more accurately, manipulated stem cells that have become specialized—could produce positive results without the stem cells actually doing any work. It is believed that it is possible that the presence of these specialized stem cells could “turn on” the repair/growth mechanism of the nervous system, and that it is this reaction, by the nervous system, which creates the positive results that scientists see in experiments. Thus, after a study shows positive results after introducing specialized stem cells into the nervous system, further work must be done in order to verify that it is actually the stem cells themselves that are causing the desired results, rather than an “activated” mechanism of the nervous system.

At Johns Hopkins University, researchers “reported preliminary evidence that cells derived from embryonic stem cells can restore movement” in rats that had a disease which is the animal equivalent of ALS. The researchers exposed rats “to the Sindbis virus, which infects the central nervous system and

destroys the motor neurons in the spinal cord” and paralysis results [1]. And the next step was to inject specialized stem cells into the fluid surrounding the spinal cord and see if new neurons would be generated.

Because scientists have had difficulty sustaining stem cell lines derived from rat embryos, (rather, they used) embryonic germ cells...isolated from human fetal tissue in 1998. These cells can produce unchanged copies of themselves when maintained in culture, and they form into clumps called embryoid bodies. Under certain conditions, research has shown that the cells in the embryoid bodies begin to look and function like neurons when subjected to specific laboratory conditions [2]. The researchers had an idea that these embryoid body cells in their non-specialized state might become specialized as replacement neurons if placed into the area of the damaged spinal cord. [1]

In the experiment, the researchers selected embryonic germ cells that were barely differentiated and which displayed the molecular markers of neural stem cells. These stem cells were grown and then injected into the fluid surrounding the spinal cords of the paralyzed rats.

The response was impressive. Three months after the injections, many of the treated rats were able to move their hind limbs and walk, albeit clumsily, while the rats that did not receive cell injections remained paralyzed. Moreover, at autopsy the researchers found that cells derived from human embryonic germ cells had migrated throughout the spinal fluid and continued to develop, displaying both the shape and molecular markers characteristic of mature motor neurons. [1]

However, the hypothesis that specialized stem cells only spur the body to activate its own repair mechanisms cannot be forgotten. These researchers were “quick to caution... that they do not know for certain whether the treatment helped the paralyzed rats because new neurons took the place of the old, or because trophic factors from the injected cells facilitated the recovery of the rats’ remaining nerve cells” [1].

Parkinson’s Disease

Parkinson’s is a

progressive movement disorder that usually strikes after age 50. Symptoms often begin with an uncontrollable hand tremor, followed by increasing rigidity, difficulty walking, and trouble initiating voluntary movement. The symptoms result from the death of a particular set of neurons deep in the brain... These “nigro-striatal” neurons release the chemical transmitter dopamine... One of dopamine’s major roles is to regulate the nerves that control body movement. [1]

Currently, Parkinson’s is usually treated with a drug that, once it enters the brain, is converted into dopamine. This drug, levodopa, helps most patients at first but its side effects increase and its effectiveness decreases as time goes on. “This leaves Parkinson’s patients and their doctors fighting a long, uphill battle to balance medication with side effects to maintain function. In the end, many patients are utterly helpless” [1].

Like the other disorders of the central nervous system, methods being proposed to treat Parkinson’s include both “cell implantation and the trophic-factor strategies” [1]. Both of these approaches “are

promising,” however the cell implantation method is further along in development and the trophic-factor approach.

The idea behind the cell implantation method is simple: “implant cells into the brain that can replace the” dopamine-releasing neurons that are lost due to the disease [1]. However, despite the simplicity of the idea, the task is not easy. The first experiment along these lines, done with rats, was conducted in the 1970s; yet we still do not have a remedy for Parkinson’s. One of the barriers to successful tissue transplantation has been that “fully developed and differentiated dopamine neurons do not survive transplantation...so direct transplantation of fully developed brain tissue from cadavers, for example, is not an option” [1].

As some scientists work to improve direct tissue transplantation, others are hoping to use stem cells to create tissue that will successfully function as dopamine neurons after implantation into the brain. In order to accomplish this, these scientists must “find the right combination of growth factors and cell culture conditions to bring undifferentiated cells along in a culture dish to a point where they are committed to becoming dopamine neurons” [1]. Once scientists are able to do this, they can implant them into the brain and, if everything works, these almost fully-differentiated dopamine neurons will, once in the brain, finish growing and complete their differentiation. [1]

Also, if scientists are unable to manipulate stem cells so that they are “committed” to become dopamine neurons, there is another option: implanting “less-committed” stem cells into the brain. There is a possibility that “environmental signals in the brain (will) guide them into becoming” dopamine-releasing cells [1].

However, this second option is somewhat dangerous, since there is the risk that the implanted stem will not be “committed” enough and that they could grow into “unwanted cell types, such as muscle or bone, within the nervous system” [1]. Thankfully, it is not likely that we will have to face the risk that this second option brings, because Geron Corporation has announced that it “succeeded in directing human embryonic stem cells to become mature neural cells in laboratory culture, including cells that have the structural and chemical characteristics of dopamine neurons” [1].

Using Growth Factors To Treat Parkinson’s

Scientists are also searching for ways to activate the growth/repair mechanisms of the brain. There are two ways to do this, and one of them uses stem cells. In the first, scientists use stem cells from embryos or adults, but rather than trying to directly replace lost dopamine-neurons, these cells are instead “to turn on the body’s own repair mechanisms” [1]. The second method involves finding “drug treatments that help a patient’s own stem cells,” which can create new neurons, as well as to stimulate the repair mechanisms of the nervous system [1].

Although the cell implantation method is more developed than this approach, activating “trophic factors” still holds promise. In adult primates, stem cells are found in two parts of the brain. In the mid-1990s, it was discovered that stem cells in both of these areas “proliferate and migrate toward the site of the damage” when the brain is injured [1]. Right now, researchers are “trying to discover how far this response can go towards ameliorating” damage to the brain [1].

Along these lines, there has been some development of our understanding of the body’s repair mechanisms. Scientists are interested in a protein called transforming growth factor alpha (TGF α). It is “a natural peptide found in the body from the very earliest stages of embryonic development onward” and it “is important in activating normal repair processes in several organs, including liver and skin” [1]. Studies by James Fallon suggest that the growth/repair mechanism of the brain “may never be adequately triggered in a slowly developing degenerative disease like Parkinson’s and that providing more TGF α can turn it on” [1].

Specifically, Fallon found that TGF α injected into a healthy rat brain causes stem cells in (one of the two locations to) proliferate for several days, after which they disappear. But if the researchers make similar injections into rats in which they first damage the nigro-striatal neurons (the ones which release dopamine) with a toxin (which causes the animal-equivalent of) Parkinson’s Disease—two things happen. After several days of cell proliferation, Fallon observes what he calls a “wave of migration” of the stem cells to the damaged areas, where they differentiate into dopamine neurons. Most importantly, the treated rats do not show the behavioral abnormalities associated with the loss of the neurons. Whether the beneficial effect on symptoms is the result of the newly formed cells or some other trophic effect is not yet entirely clear. [1]

In conclusion, stem cells hold a terrific amount of promise for treating disorders of the central nervous system. And impressively, stem cells are also essential to some remedies that rely on the body’s own repair mechanisms. We are witnessing the beginning of a new era in medicine, and personally, I can’t wait to see the cures that come from it.

Bibliography

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