CELL AND TISSUE TRANSPLANTATION INTO THE ADULT BRAIN pdf

1: Neural stem cell | biology | www.enganchecubano.com

1. Ann N Y Acad Sci. ; Cell and tissue transplantation into the adult brain. [No authors listed] PMID: [PubMed - indexed for MEDLINE].

Stem Cell Transplant for Cancer Types of Stem Cell Transplants for Cancer Treatment In a typical stem cell transplant for cancer very high doses of chemo are used, sometimes along with radiation therapy , to try to kill all the cancer cells. This treatment also kills the stem cells in the bone marrow. Soon after treatment, stem cells are given to replace those that were destroyed. These stem cells are given into a vein, much like a blood transfusion. Over time they settle in the bone marrow and begin to grow and make healthy blood cells. This process is called engraftment. There are 2 main types of transplants. They are named based on who gives the stem cells. The stem cells come from the same person who will get the transplant. The stem cells come from a matched related or unrelated donor. Autologous stem cell transplants In this type of transplant, your own stem cells are removed, or harvested, from your blood before you get treatment that destroys them. Your stem cells are removed from either your bone marrow or your blood, and then frozen. This kind of transplant is mainly used to treat certain leukemias , lymphomas , and multiple myeloma. Getting rid of cancer cells in the stem cells saved for autologous transplants A possible disadvantage of an autologous transplant is that cancer cells may be collected along with the stem cells and then later put back into your body. Another disadvantage is that your immune system is the same as it was before your transplant. This means the cancer cells were able to escape attack from your immune system before, and may be able to do so again. This may be called purging. A possible downside of purging is that some normal stem cells can be lost during this process. This may cause your body to take longer to start making normal blood cells, and you might have very low and unsafe levels of white blood cells or platelets for a longer time. This could increase the risk of infections or bleeding problems. Another treatment to help kill cancer cells that might be in the returned stem cells involves giving anti-cancer drugs after transplant. The stem cells are not treated. After transplant, the patient gets anti-cancer drugs to get rid of any cancer cells that may be in the body. This is called in vivo purging. The need to remove cancer cells from transplanted stem cells or transplant patients and the best way to do it is being researched. Tandem transplants double autologous Doing 2 autologous transplants in a row is known as a tandem transplant or a double autologous transplant. In this type of transplant, the patient gets 2 courses of high-dose chemo, each followed by a transplant of their own stem cells. All of the stem cells needed are collected before the first high-dose chemo treatment, and half of them are used for each transplant. Usually, the 2 courses of chemo are given within 6 months. The second one is given after the patient recovers from the first one. Tandem transplants are most often used to treat multiple myeloma and advanced testicular cancer. Because this involves 2 transplants, the risk of serious outcomes is higher than for a single transplant. Tandem transplants are still being studied to find out when they might be best used. Sometimes an autologous transplant followed by an allogeneic transplant might also be called a tandem transplant. Allogeneic stem cell transplants Allogeneic stem cell transplants use cells from a donor. This is sometimes called a MUD matched unrelated donor transplant. Transplants with a MUD are usually riskier than those with a relative who is a good match. Blood taken from the placenta and umbilical cord of newborns is a newer source of stem cells for allogeneic transplant. Called cord blood, this small volume of blood has a high number of stem cells that tend to multiply quickly. But there are often not enough stem cells in a unit of cord blood for large adults, so most cord blood transplants done so far have been in children and smaller adults. Researchers are now looking for ways to use cord blood for transplants in larger adults. One approach is to find ways to increase the numbers of these cells in the lab before the transplant. Another approach is the use of the cord blood from 2 infants for one adult transplant, called a dual-cord-blood transplant. A third way cord blood is being used is in a mini-transplant see below. Other strategies to better use cord blood transplants are being actively studied. Pros of allogeneic stem cell transplant: The donor stem cells make their own immune cells, which could help kill any cancer cells that remain after high-dose treatment. This is called the graft-versus-cancer effect. Other advantages are that the donor can often be asked to donate more stem cells or even white blood cells if needed, and stem cells from

healthy donors are free of cancer cells. Cons to allogeneic stem cell transplants: This is called graft-versus-host disease. There is also a very small risk of certain infections from the donor cells, even though donors are tested before they donate. A higher risk comes from infections you had previously, and which your immune system has had under control. These infections may surface after allogeneic transplant because your immune system is held in check suppressed by medicines called immunosuppressive drugs. Such infections can cause serious problems and even death. Allogeneic transplant is most often used to treat certain types of leukemia , lymphomas , multiple myeloma , myelodysplastic syndrome , and other bone marrow disorders such as aplastic anemia. Mini-transplants non-myeloablative transplants For some people, age or certain health conditions make it more risky to wipe out all of their bone marrow before a transplant. Your doctor might refer to it as a non-myeloablative transplant or mention reduced-intensity conditioning RIC. The goal is to kill some of the cancer cells which will also kill some of the bone marrow , and suppress the immune system just enough to allow donor stem cells to settle in the bone marrow. This makes it especially useful for older patients and those with other health problems. Rarely, it may be used in patients who have already had a transplant. Mini-transplants treat some diseases better than others. They may not work well for patients with a lot of cancer in their body or people with fast-growing cancers. Also, although side effects from chemo and radiation may be less than those from a standard allogeneic transplant, the risk of graft-versus-host disease is the same. This procedure has only been used since the late s and long-term patient outcomes are not yet clear. There are lower risks of some complications, but the cancer may be more likely to come back. Ways to improve outcomes are still being studied. Studies have looked at using an allogeneic mini-transplant after an autologous transplant. This is another type of tandem transplant being tested in certain types of cancer, such as multiple myeloma and some types of lymphoma. The autologous transplant can help decrease the amount of cancer present so that the lower doses of chemo given before the mini-transplant can work better. And the recipient still gets the benefit of the graft-versus-cancer effect of the allogeneic transplant. Syngeneic stem cell transplants â€" for those with an identical sibling This is a special kind of allogeneic transplant that can only be used when the patient has an identical sibling twin or triplet â€" someone who has the exact same tissue type. An advantage of syngeneic stem cell transplant is that graft-versus-host disease will not be a problem. Also, there are no cancer cells in the transplanted stem cells, as there might be in an autologous transplant. Every effort must be made to destroy all the cancer cells before the transplant is done to help keep the cancer from coming back. This technique is most often used in children, usually with a parent as the donor, though a child can also donate to a parent. Researchers are continuing to learn new ways to make haploidentical transplants more successful. Where do stem cells come from? Bone marrow from you or someone else The bloodstream peripheral blood â€" from you or someone else Umbilical cord blood from newborns Bone marrow Bone marrow is the spongy liquid tissue in the center of some bones. It has a rich supply of stem cells, and its main job is to make blood cells that circulate in your body. The bones of the pelvis hip have the most marrow and contain large numbers of stem cells. For this reason, cells from the pelvic bone are used most often for a bone marrow transplant. Enough marrow must be removed to collect a large number of healthy stem cells. A large needle is put through the skin on the lower back and into the back of the hip bone. The thick liquid marrow is pulled out through the needle. This is repeated until enough marrow has been taken out. The harvested marrow is filtered, stored in a special solution in bags, and then frozen. Peripheral blood Normally, not many stem cells are found in the blood. But giving shots of hormone-like substances called growth factors to stem cell donors a few days before the harvest causes their stem cells to grow faster and move from the bone marrow into the blood. For a peripheral blood stem cell transplant, the stem cells are taken from blood. A special thin flexible tube called a catheter is put into a large vein in the donor and attached to tubing that carries the blood to a special machine. The machine separates the stem cells from the rest of the blood, which is returned to the donor during the same procedure. This takes several hours, and may need to be repeated for a few days to get enough stem cells. The stem cells are filtered, stored in bags, and frozen until the patient is ready for them. The stem cells travel to the bone marrow, engraft, and then start making new, normal blood cells. Umbilical cord blood A large number of stem cells are normally found in the blood of newborn babies. The cord blood is frozen until needed. A cord blood transplant uses blood that

normally is thrown out after a baby is born. A possible drawback of cord blood is the smaller number of stem cells in it.

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2: Cell and tissue transplantation into the adult brain.

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In healthy adult laboratory animals, progenitor cells migrate within the brain and function primarily to maintain neuron populations for olfaction the sense of smell. Pharmacological activation of endogenous neural stem cells has been reported to induce neuroprotection and behavioral recovery in adult rat models of neurological disorder. Clinical and animal studies have been conducted into the use of stem cells in cases of spinal cord injury. One pair of reports of identical baseline characteristics and final results, was presented in two publications as, respectively, a patient randomized trial and as a subject observational study. Other reports required impossible negative standard deviations in subsets of people, or contained fractional subjects, negative NYHA classes. A university investigation, closed in without reporting, was reopened in July However, the immune system is vulnerable to degradation upon the pathogenesis of disease, and because of the critical role that it plays in overall defense, its degradation is often fatal to the organism as a whole. Diseases of hematopoietic cells are diagnosed and classified via a subspecialty of pathology known as hematopathology. The specificity of the immune cells is what allows recognition of foreign antigens, causing further challenges in the treatment of immune disease. Identical matches between donor and recipient must be made for successful transplantation treatments, but matches are uncommon, even between first-degree relatives. Research using both hematopoietic adult stem cells and embryonic stem cells has provided insight into the possible mechanisms and methods of treatment for many of these ailments. In this process, HSCs are grown together with stromal cells , creating an environment that mimics the conditions of bone marrow, the natural site of red-blood-cell growth. Erythropoietin , a growth factor , is added, coaxing the stem cells to complete terminal differentiation into red blood cells. Researchers are confident that the tooth regeneration technology can be used to grow live teeth in people. In theory, stem cells taken from the patient could be coaxed in the lab turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, and would be expected to be grown in a time over three weeks. The process is similar to what happens when humans grow their original adult teeth. Many challenges remain, however, before stem cells could be a choice for the replacement of missing teeth in the future. The group, led by Sheraz Daya , was able to successfully use adult stem cells obtained from the patient, a relative, or even a cadaver. Further rounds of trials are ongoing. In theory if the beta cell is transplanted successfully, they will be able to replace malfunctioning ones in a diabetic patient. In an adult, wounded tissue is most often replaced by scar tissue , which is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded fetal tissue, however, wounded tissue is replaced with normal tissue through the activity of stem cells. This method elicits a regenerative response more similar to fetal wound-healing than adult scar tissue formation. In , oogonial stem cells were isolated from adult mouse and human ovaries and demonstrated to be capable of forming mature oocytes. Human embryonic stem cells clinical trials Regenerative treatment models[edit] Stem cells are thought to mediate repair via five primary mechanisms: In addition, they have been found to secrete chemokines that alter the immune response and promote tolerance of the new tissue. This allows for allogeneic treatments to be performed without a high rejection risk. Researchers are able to grow up differentiated cell lines and then test new drugs on each cell type to examine possible interactions in vitro before performing in vivo studies. This is critical in the development of drugs for use in veterinary research because of the possibilities of species specific interactions. The hope is that having these cell lines available for research use will reduce the need for research animals used because effects on human tissue in vitro will provide insight not normally known before the animal testing phase. Rather than needing to harvest embryos or eggs, which are limited, the researchers can remove mesenchymal stem cells with greater ease and greatly reducing the danger to the animal due to noninvasive techniques. This allows the limited eggs to be put to use for reproductive purposes only. Spermatogonial stem cells have been harvested from a rat and placed into a mouse host and fully mature sperm were produced with the ability to produce viable offspring.

Currently research is underway to find suitable hosts for the introduction of donor spermatogonial stem cells. If this becomes a viable option for conservationists, sperm can be produced from high genetic quality individuals who die before reaching sexual maturity, preserving a line that would otherwise be lost. Accordingly, stem cells derived from bone marrow aspirates, for instance, are cultured in specialized laboratories for expansion to millions of cells. Research is underway to examine the differentiating capabilities of stem cells found in the umbilical cord, yolk sac and placenta of different animals. These stem cells are thought to have more differentiating ability than their adult counterparts, including the ability to more readily form tissues of endodermal and ectodermal origin. Stem-cell controversy There is widespread controversy over the use of human embryonic stem cells. This controversy primarily targets the techniques used to derive new embryonic stem cell lines , which often requires the destruction of the blastocyst. Opposition to the use of human embryonic stem cells in research is often based on philosophical, moral, or religious objections. On 23 January , the US Food and Drug Administration gave clearance to Geron Corporation for the initiation of the first clinical trial of an embryonic stem-cell-based therapy on humans. The trial aimed evaluate the drug GRNOPC1, embryonic stem cell -derived oligodendrocyte progenitor cells, on people with acute spinal cord injury. The trial was discontinued in November so that the company could focus on therapies in the "current environment of capital scarcity and uncertain economic conditions". Various clinical trials on MSCs have failed which used cryopreserved product immediately post thaw as compared to those clinical trials which used fresh MSCs. Misaligned breaks due to severe trauma, as well as treatments like tumor resections of bone cancer, are prone to improper healing if left to the natural process alone. Scaffolds composed of natural and artificial components are seeded with mesenchymal stem cells and placed in the defect. Within four weeks of placing the scaffold, newly formed bone begins to integrate with the old bone and within 32 weeks, full union is achieved. Stem cells have been used to treat degenerative bone diseases. The normally recommended treatment for dogs that have Leggâ€”Calveâ€”Perthes disease is to remove the head of the femur after the degeneration has progressed. Recently, mesenchymal stem cells have been injected directly in to the head of the femur, with success not only in bone regeneration, but also in pain reduction. This is important interest for those with reduced healing capabilities, like diabetics and those undergoing chemotherapy. These cells were injected directly into the wounds. Within a week, full re-epithelialization of the wounds had occurred, compared to minor re-epithelialization in the control wounds. This showed the capabilities of mesenchymal stem cells in the repair of epidermal tissues. These are often not found until after they have become worse because of the difficulty in visualizing the entire soft palate. This lack of visualization is thought to also contribute to the low success rate in surgical intervention to repair the defect. As a result, the horse often has to be euthanized. Recently, the use of mesenchymal stem cells has been added to the conventional treatments. After the surgeon has sutured the palate closed, autologous mesenchymal cells are injected into the soft palate. The stem cells were found to be integrated into the healing tissue especially along the border with the old tissue. There was also a large reduction in the number of inflammatory cells present, which is thought to aid in the healing process. Autologous stem cell based treatments for tendon injury, ligament injury, and osteoarthritis in dogs have been available to veterinarians in the United States since Over privately owned horses and dogs have been treated with autologous adipose-derived stem cells. The efficacy of these treatments has been shown in double-blind clinical trials for dogs with osteoarthritis of the hip and elbow and horses with tendon damage. Conventional therapies are very unsuccessful in returning the horse to full functioning potential. Natural healing, guided by the conventional treatments, leads to the formation of fibrous scar tissue that reduces flexibility and full joint movement. Traditional treatments prevented a large number of horses from returning to full activity and also have a high incidence of re-injury due to the stiff nature of the scarred tendon. Introduction of both bone marrow and adipose derived stem cells, along with natural mechanical stimulus promoted the regeneration of tendon tissue. The natural movement promoted the alignment of the new fibers and tendocytes with the natural alignment found in uninjured tendons. Stem cell treatment not only allowed more horses to return to full duty and also greatly reduced the re-injury rate over a three-year period. The embryonic stem cells were shown to have a better survival rate in the tendon as well as better migrating capabilities to reach all areas of damaged tendon. The overall repair quality was also higher,

with better tendon architecture and collagen formed. There was also no tumor formation seen during the three-month experimental period. Long-term studies need to be carried out to examine the long-term efficacy and risks associated with the use of embryonic stem cells. Horses and dogs are most frequently affected by arthritis. Natural cartilage regeneration is very limited and no current drug therapies are curative, but rather look to reduce the symptoms associated with the degeneration. Different types of mesenchymal stem cells and other additives are still being researched to find the best type of cell and method for long-term treatment. There has been a lot of success recently injecting mesenchymal stem cells directly into the joint. This is a recently developed, non-invasive technique developed for easier clinical use. Dogs receiving this treatment showed greater flexibility in their joints and less pain. Adipose and bone marrow derived stem cells were removed and induced to a cardiac cell fate before being injected into the heart. The heart was found to have improved contractility and a reduction in the damaged area four weeks after the stem cells were applied. Tissue was regenerated and the patch was well incorporated into the heart tissue. This is thought to be due, in part, to improved angiogenesis and reduction of inflammation. Although cardiomyocytes were produced from the mesenchymal stem cells, they did not appear to be contractile. Other treatments that induced a cardiac fate in the cells before transplanting had greater success at creating contractile heart tissue. These cells involved in the secondary damage response secrete factors that promote scar formation and inhibit cellular regeneration. Mesenchymal stem cells that are induced to a neural cell fate are loaded onto a porous scaffold and are then implanted at the site of injury. The cells and scaffold secrete factors that counteract those secreted by scar forming cells and promote neural regeneration. Eight weeks later, dogs treated with stem cells showed immense improvement over those treated with conventional therapies. Dogs treated with stem cells were able to occasionally support their own weight, which has not been seen in dogs undergoing conventional therapies. Peripheral nerves are more likely to be damaged, but the effects of the damage are not as widespread as seen in injuries to the spinal cord. Treatments are currently in clinical trials to repair severed nerves, with early success. Stem cells induced to a neural fate injected in to a severed nerve. Within four weeks, regeneration of previously damaged stem cells and completely formed nerve bundles were observed. Hematopoietic stem cells have been used to treat corneal ulcers of different origin of several horses. These ulcers were resistant to conventional treatments available, but quickly responded positively to the stem cell treatment. Stem cells were also able to restore sight in one eye of a horse with retinal detachment, allowing the horse to return to daily activities.

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3: Stem cells: What they are and what they do - Mayo Clinic

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Sign up now Stem cells: What they are and what they do Stem cells and derived products offer great promise for new medical treatments. Learn about stem cell types, current and possible uses, ethical issues, and the state of research and practice. Here are some answers to frequently asked questions about stem cells. What are stem cells? Under the right conditions in the body or a laboratory, stem cells divide to form more cells called daughter cells. These daughter cells either become new stem cells self-renewal or become specialized cells differentiation with a more specific function, such as blood cells, brain cells, heart muscle cells or bone cells. No other cell in the body has the natural ability to generate new cell types. Why is there such an interest in stem cells? Researchers and doctors hope stem cell studies can help to: Increase understanding of how diseases occur. By watching stem cells mature into cells in bones, heart muscle, nerves, and other organs and tissue, researchers and doctors may better understand how diseases and conditions develop. Generate healthy cells to replace diseased cells regenerative medicine. Stem cells can be guided into becoming specific cells that can be used to regenerate and repair diseased or damaged tissues in people. Stem cells may have the potential to be grown to become new tissue for use in transplant and regenerative medicine. Researchers continue to advance the knowledge on stem cells and their applications in transplant and regenerative medicine. Test new drugs for safety and effectiveness. Before using investigational drugs in people, researchers can use some types of stem cells to test the drugs for safety and quality. This type of testing will most likely first have a direct impact on drug development first for cardiac toxicity testing. New areas of study include the effectiveness of using human stem cells that have been programmed into tissue-specific cells to test new drugs. For the testing of new drugs to be accurate, the cells must be programmed to acquire properties of the type of cells targeted by the drug. Techniques to program cells into specific cells continue to be studied. For instance, nerve cells could be generated to test a new drug for a nerve disease. Tests could show whether the new drug had any effect on the cells and whether the cells were harmed. Where do stem cells come from? Researchers have discovered several sources of stem cells: These stem cells come from embryos that are three to five days old. At this stage, an embryo is called a blastocyst and has about cells. These are pluripotent ploo-RIP-uh-tunt stem cells, meaning they can divide into more stem cells or can become any type of cell in the body. This versatility allows embryonic stem cells to be used to regenerate or repair diseased tissue and organs. These stem cells are found in small numbers in most adult tissues, such as bone marrow or fat. Compared with embryonic stem cells, adult stem cells have a more limited ability to give rise to various cells of the body. Until recently, researchers thought adult stem cells could create only similar types of cells. For instance, researchers thought that stem cells residing in the bone marrow could give rise only to blood cells. However, emerging evidence suggests that adult stem cells may be able to create various types of cells. For instance, bone marrow stem cells may be able to create bone or heart muscle cells. This research has led to early-stage clinical trials to test usefulness and safety in people. For example, adult stem cells are currently being tested in people with neurological or heart disease. Adult cells altered to have properties of embryonic stem cells induced pluripotent stem cells. Scientists have successfully transformed regular adult cells into stem cells using genetic reprogramming. By altering the genes in the adult cells, researchers can reprogram the cells to act similarly to embryonic stem cells. This new technique may allow researchers to use reprogrammed cells instead of embryonic stem cells and prevent immune system rejection of the new stem cells. Researchers have been able to take regular connective tissue cells and reprogram them to become functional heart cells. In studies, animals with heart failure that were injected with new heart cells experienced improved heart function and survival time. Researchers have discovered stem cells in amniotic fluid as well as umbilical cord blood. These stem cells also have the ability to change into specialized cells. Amniotic fluid fills the sac that surrounds and protects a developing fetus in the uterus. Researchers have identified stem cells in samples of

amniotic fluid drawn from pregnant women to test for abnormalities â€” a procedure called amniocentesis. More study of amniotic fluid stem cells is needed to understand their potential. Why is there a controversy about using embryonic stem cells? Because human embryonic stem cells are extracted from human embryos, several questions and issues have been raised about the ethics of embryonic stem cell research. The National Institutes of Health created guidelines for human stem cell research in The guidelines define embryonic stem cells and how they may be used in research, and include recommendations for the donation of embryonic stem cells. Also, the guidelines state embryonic stem cells from embryos created by in vitro fertilization can be used only when the embryo is no longer needed. Where do these embryos come from? The stem cells are donated with informed consent from donors. The stem cells can live and grow in special solutions in test tubes or petri dishes in laboratories. Although research into adult stem cells is promising, adult stem cells may not be as versatile and durable as are embryonic stem cells. Adult stem cells may not be able to be manipulated to produce all cell types, which limits how adult stem cells can be used to treat diseases. Adult stem cells also are more likely to contain abnormalities due to environmental hazards, such as toxins, or from errors acquired by the cells during replication. However, researchers have found that adult stem cells are more adaptable than was first thought. What are stem cell lines and why do researchers want to use them? A stem cell line is a group of cells that all descend from a single original stem cell and are grown in a lab. Ideally, they remain free of genetic defects and continue to create more stem cells. Clusters of cells can be taken from a stem cell line and frozen for storage or shared with other researchers. What is stem cell therapy regenerative medicine and how does it work? Stem cell therapy, also known as regenerative medicine, promotes the repair response of diseased, dysfunctional or injured tissue using stem cells or their derivatives. It is the next chapter in organ transplantation and uses cells instead of donor organs, which are limited in supply. Researchers grow stem cells in a lab. These stem cells are manipulated to specialize into specific types of cells, such as heart muscle cells, blood cells or nerve cells. The specialized cells can then be implanted into a person. For example, if the person has heart disease, the cells could be injected into the heart muscle. The healthy transplanted heart muscle cells could then contribute to repairing defective heart muscle. Researchers have already shown that adult bone marrow cells guided to become heart-like cells can repair heart tissue in people, and more research is ongoing. Have stem cells already been used to treat diseases? Doctors have performed stem cell transplants, also known as bone marrow transplants. These transplants use adult stem cells or umbilical cord blood. Researchers are testing adult stem cells to treat other conditions, including a number of degenerative diseases such as heart failure. What are the potential problems with using embryonic stem cells in humans? For embryonic stem cells to be useful in people, researchers must be certain that the stem cells will differentiate into the specific cell types desired. Researchers have discovered ways to direct stem cells to become specific types of cells, such as directing embryonic stem cells to become heart cells. Research is ongoing in this area. Embryonic stem cells can also grow irregularly or specialize in different cell types spontaneously. Researchers are studying how to control the growth and differentiation of embryonic stem cells. Researchers continue to study how to avoid these possible complications. What is therapeutic cloning, and what benefits might it offer? Therapeutic cloning, also called somatic cell nuclear transfer, is a technique to create versatile stem cells independent of fertilized eggs. In this technique, the nucleus, which contains the genetic material, is removed from an unfertilized egg. The nucleus is also removed from the cell of a donor. This donor nucleus is then injected into the egg, replacing the nucleus that was removed, in a process called nuclear transfer. The egg is allowed to divide and soon forms a blastocyst. Some researchers believe that stem cells derived from therapeutic cloning may offer benefits over those from fertilized eggs because cloned cells are less likely to be rejected once transplanted back into the donor and may allow researchers to see exactly how a disease develops. Has therapeutic cloning in people been successful? However, in recent studies, researchers have created human pluripotent stem cells by modifying the therapeutic cloning process. Researchers continue to study the potential of therapeutic cloning in people.

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OBJECTIVE: To investigate the migration, proliferation, and differentiation of stem cells and neural progenitor cells (NPCs) from the adult human brain after transplantation into adult rodent brains. METHODS: Adult human NPCs were obtained from temporal lobe specimens removed because of medical intractable epilepsy.

Congenital disorders occur when the brain or spinal cord does not form correctly during development. Cancers of the nervous system result from the uncontrolled spread of aberrant cells. Degenerative diseases occur when the nervous system loses functioning of nerve cells. Most of the advances in stem cell research have been directed at treating degenerative diseases. While many treatments aim to limit the damage of these diseases, in some cases scientists believe that damage can be reversed by replacing lost cells with new ones derived from cells that can mature into nerve cells, called neural stem cells. Research that uses stem cells to treat nervous system disorders remains an area of great promise and challenge to demonstrate that cell-replacement therapy can restore lost function. Strategies to Repair the Nervous System The nervous system is a complex organ made up of nerve cells also called neurons and glial cells, which surround and support neurons see Figure 3. Neurons send signals that affect numerous functions including thought processes and movement. One type of glial cell, the oligodendrocyte , acts to speed up the signals of neurons that extend over long distances, such as in the spinal cord. The loss of any of these cell types may have catastrophic results on brain function. Although reports dating back as early as the s pointed towards the possibility that new nerve cells are formed in adult mammalian brains, this knowledge was not applied in the context of curing devastating brain diseases until the s. While earlier medical research focused on limiting damage once it had occurred, in recent years researchers have been working hard to find out if the cells that can give rise to new neurons can be coaxed to restore brain function. New neurons in the adult brain arise from slowly-dividing cells that appear to be the remnants of stem cells that existed during fetal brain development. Since some of these adult cells still retain the ability to generate both neurons and glia, they are referred to as adult neural stem cells. These findings are exciting because they suggest that the brain may contain a built-in mechanism to repair itself. Unfortunately, these new neurons are only generated in a few sites in the brain and turn into only a few specialized types of nerve cells. Although there are many different neuronal cell types in the brain, we now know that these new neurons can quot;plug inquot; correctly to assist brain function. Scientists are applying these new stem cell discoveries in two ways in their experiments. First, they are using current knowledge of normal brain development to modulate stem cells that are harvested and grown in culture. Alternatively, the stem cells can be induced to differentiate into neurons and glia while in the culture dish, before being transplanted into the brain. Much progress has been made the last several years with human embryonic stem ES cells that can differentiate into all cell types in the body. While ES cells can be maintained in culture for relatively long periods of time without differentiating, they usually must be coaxed through many more steps of differentiation to produce the desired cell types. Recent studies, however, suggest that ES cells may differentiate into neurons in a more straightforward manner than may other cell types. The Neuron When sufficient neurotransmitters cross synapses and bind receptors on the neuronal cell body and dendrites, the neuron sends an electrical signal down its axon to synaptic terminals, which in turn release neurotransmitters into the synapse that affects the following neuron. Oligodendrocytes supply the axon with an insulating myelin sheath. Each of these strategies is being aggressively pursued to identify the most effective treatments for degenerative diseases. Most of these studies have been carried out initially with animal stem cells and recipients to determine their likelihood of success. Still, much more research is necessary to develop stem cell therapies that will be useful for treating brain and spinal cord disease in the same way that hematopoietic stem cell therapies are routinely used for immune system replacement see Chapter 2. The majority of stem cell studies of neurological disease have used rats and mice, since these models are convenient to use and are well-characterized biologically. If preliminary studies with rodent stem cells are successful, scientists will attempt to transplant human stem cells into rodents. Studies may then be carried out in primates e. Human studies are rarely undertaken until these other experiments have shown promising results. These neurons

connect via long axons to another region called the striatum, composed of subregions called the caudate nucleus and the putamen. These neurons that reach from the substantia nigra to the striatum release the chemical transmitter dopamine onto their target neurons in the striatum. Currently, the causes of death of these neurons are not well understood. Although the drug works well initially, levodopa eventually loses its effectiveness, and side-effects increase. Ultimately, many doctors and patients find themselves fighting a losing battle. For this reason, a huge effort is underway to develop new treatments, including growth factors that help the remaining dopamine neurons survive and transplantation procedures to replace those that have died. As a result, these human studies were not pursued further. Another strategy was attempted in the s, in which cells derived from fetal tissue from the mouse substantia nigra was transplanted into the adult rat eye and found to develop into mature dopamine neurons. The success of the animal studies led to several human trials beginning in the mids. Also, researchers could measure an increase in dopamine neuron function in the striatum of these patients by using a brain-imaging method called positron emission tomography PET see Figure 3. Unfortunately, both studies showed that the transplants offered little benefit to the patients as a group. While some patients showed improvement, others began to suffer from dyskinesias, jerky involuntary movements that are often side effects of long-term L-dopa treatment. However, promising findings emerged from these studies as well. Additionally, autopsies on three patients who died of unrelated causes, years after the surgeries, indicated the presence of dopamine neurons from the graft. These cells appeared to have matured in the same way as normal dopamine neurons, which suggested that they were acting normally in the brain. Dopamine-Neuron Transplantation Figure 3. The image taken before surgery left shows uptake of a radioactive form of dopamine red only in the caudate nucleus, indicating that dopamine neurons have degenerated. Twelve months after surgery, an image from the same patient right reveals increased dopamine function, especially in the putamen. Reprinted with permission from N Eng J Med ; 10 p. Researchers in Sweden followed the severity of dyskinesia in patients for eleven years after neural transplantation and found that the severity was typically mild or moderate. These results suggested that dyskinesias were due to effects that were distinct from the beneficial effects of the grafts. Another study that involved the grafting of cells both into the striatum the target of dopamine neurons and the substantia nigra where dopamine neurons normally reside of three patients showed no adverse effects and some modest improvement in patient movement. The limited success of these studies may reflect variations in the fetal tissue used for transplantation, which is of limited quantity and can not be standardized or well-characterized. The full complement of cells in these fetal tissue samples is not known at present. As a result, the tissue remains the greatest source of uncertainty in patient outcome following transplantation. Scientists have investigated the behavior of stem cells in culture and the mechanisms that govern dopamine neuron production during development in their attempts to identify optimal culture conditions that allow stem cells to turn into dopamine-producing neurons. Preliminary studies have been carried out using immature stem cell-like precursors from the rodent ventral midbrain, the region that normally gives rise to these dopamine neurons. There is controversy about whether other organ stem cell populations, such as hematopoietic stem cells, either contain or give rise to neural stem cells Many researchers believe that the more primitive ES cells may be an excellent source of dopamine neurons because ES-cells can be grown indefinitely in a laboratory dish and can differentiate into any cell type, even after long periods in culture. Further investigation showed that these ES cells had differentiated into both dopamine and serotonin neurons. Since ES cells can generate all cell types in the body, unwanted cell types such as muscle or bone could theoretically also be introduced into the brain. Researchers strive to learn more about normal brain development to help emulate the natural progression of ES cells toward dopamine neurons in the culture dish. The recent availability of human ES cells has led to further studies to examine their potential for differentiation into dopamine neurons. Recently, dopamine neurons from human embryonic stem cells have been generated. These neurons showed many of the characteristic properties of normal dopamine neurons. One method with great therapeutic potential is nuclear transfer. This method fuses the genetic material from one individual donor with a recipient egg cell that has had its nucleus removed. The early embryo that develops from this fusion is a genetic match for the donor. This process is sometimes called quot;therapeutic cloningquot; and is regarded by some to be ethically

questionable. However, mouse ES cells have been differentiated successfully in this way into dopamine neurons that corrected Parkinsonian symptoms when transplanted into 6-OHDA-treated rats. The concept is based on research showing that new nerve cells are born in the adult brains of humans. The phenomenon occurs in a brain region called the dentate gyrus of the hippocampus. While it is not yet clear how these new neurons contribute to normal brain function, their presence suggests that stem cells in the adult brain may have the potential to re-wire dysfunctional neuronal circuitry. In 6-OHDAtreated Parkinsonian rats, however, the cells proliferated and migrated to the damaged areas. These diverse disorders must be investigated within the contexts of their unique disease processes and treated accordingly with highly adapted cell-based approaches. Spinal cord trauma destroys numerous cell types, including the neurons that carry messages between the brain and the rest of the body. In many spinal injuries, the cord is not actually severed, and at least some of the signal-carrying neuronal axons remain intact. Researchers have recently made progress to replenish these lost myelin-producing cells. In one study, scientists cultured human ES cells through several steps to make mixed cultures that contained oligodendrocytes. When they injected these cells into the spinal cords of chemically-demyelinated rats, the treated rats regained limited use of their hind limbs compared with un-grafted rats. Getting neurons to grow new axons through the injury site to reconnect with their targets is even more challenging. While myelin promotes normal neuronal function, it also inhibits the growth of new axons following spinal injury. In a recent study to attempt post-trauma axonal growth, Harper and colleagues treated ES cells with a combination of factors that are known to promote motor neuron differentiation. While many of these cells survived and differentiated into neurons, they did not send out axons unless the researchers also added drugs that interfered with the inhibitory effects of myelin. The growth effect was modest, and the researchers have not yet seen evidence of functional neuron connections. However, their results raise the possibility that signals can be turned on and off in the correct order to allow neurons to reconnect and function properly. Spinal injury researchers emphasize that additional basic and preclinical research must be completed before attempting human trials using stem cell therapies to repair the trauma-damaged nervous system. Since myelin loss is at the heart of many other degenerative diseases, oligodendrocytes made from ES cells may be useful to treat these conditions as well. For example, scientists recently cultured human ES cells with a combination of growth factors to generate a highly enriched population of myelinating oligodendrocyte precursors. When the growth factor-cultured ES cells were transplanted into affected mice, the cells migrated and differentiated into mature oligodendrocytes that made myelin sheaths around neighboring axons. These researchers subsequently showed that these cells matured and improved movement when grafted in rats with spinal cord injury. However, these results are sufficiently encouraging to plan clinical trials to test whether replacement of myelinating glia can treat spinal cord injury. Patients with ALS develop increasing muscle weakness over time, which ultimately leads to paralysis and death. The cause of ALS is largely unknown, and there are no effective treatments. Researchers recently have used different sources of stem cells to test in rat models of ALS to test for possible nerve cell-restoring properties. In one study, researchers injected cell clusters made from embryonic germ EG cells into the spinal cord fluid of the partially-paralyzed rats. Moreover, the transplanted cells had migrated throughout the spinal fluid and developed into cells that displayed molecular characteristics of mature motor neurons. However, too few cells matured in this way to account for the recovery, and there was no evidence that the transplanted cells formed functional connections with muscles.

5: Transplantation of Embryonic Cortical Tissue into Lesioned

In mice with brain lesions, a German team showed that within two months of transplantation, foreign embryonic neurons matured and fully incorporated into an existing network within the hosts' visual brain region.

The scientists were able to determine not only whether the stem cells transplanted into living animals survived but whether they matured into nerve cells, integrated into targeted brain circuits and, most important, were firing on cue and igniting activity in downstream nerve circuits. The new monitoring technique could in principle be used to determine the success of other kinds of stem cell transplantations. But the experiments in which such procedures have been attempted have met with mixed results, and those conducting the experiments are hard put to explain them. So optimizing the regimens becomes a matter of guesswork and luck. In the case of brain-oriented therapies, you have to look for behavioral changes, she said. Transplanted stem cells did what they were supposed to Lee is the senior author of a paper, appearing online April 30 in NeuroImage, detailing a series of experiments in which she and her colleagues combined functional magnetic resonance imaging, or fMRI, with a relatively new but increasingly widespread technology known as optogenetics, which employs laser light to stimulate specific cells that have been rendered sensitive to particular frequencies of light. The combination let the scientists selectively stimulate only nerve cells derived from newly transplanted neural stem cells, while simultaneously assessing resulting nerve-cell activity at the site of the transplant and elsewhere in the brain. Like embryonic stem cells, iPS cells have the capacity to differentiate into every cell type in the human body. Next, they inserted a gene coding for a photosensitive protein into these iPS cells. Then, in a dish, the researchers differentiated the genetically altered iPS cells into neural stem cells. Unlike iPS cells, which can differentiate into every cell type in the body, neural stem cells can mature only into nerve cells or a few other cell types that populate the brain. The scientists transplanted these genetically altered human cells into the brains of rats that were normal except for the fact that their immune systems were compromised, reducing the chances of an immune attack on the foreign cells. The particular region of the brain into which the cells were injected is called the striatum. Blue-light stimulation triggered activity not only within the striatum but at several other areas in the brain. Yellow light had no effect â€” proof that electrical activity in these cells had been triggered by stimulating the genetically inserted protein, not merely by shining light on them. Recording electrical activity To explore activity in those areas, the researchers turned to a different observation method: While fMRI has the advantage of imaging large portions of the brain simultaneously, it actually measures not electrical activity but blood flow in the small vessels permeating the entire brain. Active nerve cells require more nutrients, and increased blood flow in a specific location in the brain is considered an excellent proxy of electrical activity at that location. But, having now identified specific brain areas where fMRI scans indicated increased nerve-cell activity, Lee and her associates proceeded to directly record electrical activity in these areas by inserting electrodes there and watching what happened when they pulsed blue light into the striatum, where the neural stem cells had been transplanted. They saw, first, that the transplanted nerve cells had clearly integrated into striatal circuitry and were firing there when stimulated with blue light; and, second, that this triggered electrical follow-on activity in remote regions of the brain. Email him at goldmanb stanford. May 16, Bruce Goldman Tel goldmanb stanford.

CELL AND TISSUE TRANSPLANTATION INTO THE ADULT BRAIN pdf

6: Stem-cell therapy - Wikipedia

Exogenous stem cell therapies rely upon extraction, in vitro cultivation, and subsequent transplantation of stem cells into the regions of the brain affected by stroke. Studies have shown that adult NSCs can be obtained from the dentate gyrus, hippocampus, cerebral cortex, and subcortical white matter (layer underneath the cerebral cortex).

By Honor Whiteman The results of a small clinical trial offer hope for people left with motor impairment following a stroke, after finding that an injection of adult stem cells into the brain restored motor function for such individuals, to the extent that some patients regained the ability to walk. Researchers found that injecting SB stem cells into stroke-damaged brain areas restored motor function for patients. Lead study author Dr. While the trial only included a small number of stroke participants, the results have been met with much positivity, with some health experts claiming the findings could lead to "life-changing treatments" for stroke patients. In the United States each year, more than , people have a new or recurrent stroke. Ischemic stroke is the most common form, accounting for around 87 percent of all strokes. It occurs when the flow of oxygen-rich blood to the brain becomes blocked, primarily due to blood clots. Hemorrhagic stroke accounts for around 13 percent of all strokes, arising from leaking or ruptured blood vessels in the brain. Exactly how stroke affects a person is dependent on what side of the brain it occurs and the amount of damage it causes. Some individuals may experience temporary arm or leg weakness, for example, while others may lose the ability to speak or walk. According to the National Stroke Association, around 2 in every 3 stroke survivors will have some form of disability, and stroke is the leading cause of disability among American adults. There are treatments available for stroke, such as tissue plasminogen activator tPA - considered the "gold standard" treatment for ischemic stroke. It works by dissolving the blood clot that is blocking blood flow to the brain. However, tPA needs to be administered within hours of stroke occurrence, in order to maximize the likelihood of recovery - a time period that Dr. Steinberg and colleagues note is often exceeded by the time it takes for a patient to arrive at the hospital. If the treatment is not received in time, the chance of a full recovery from stroke is small. All participants had motor function disability as a result of their stroke; some patients were unable to move their arm, while others were unable to walk. Each patient underwent stem cell transplantation, which involved drilling a hole into the skull and injecting stroke-damaged areas of the brain with SB cells. After the procedure, each patient was monitored through brain imaging, blood tests, and clinical evaluations. Within a month of the procedure, the researchers noticed that the patients started to show signs of recovery, and such improvements continued over several months. On the motor function component of the Fugl-Meyer assessment - a stroke-specific impairment test - patients experienced an overall Steinberg notes that these improvements have been sustained for at least 1 year and more than 2 years for some patients. Gary Steinberg One participant who saw a significant improvement in motor function following the stem cell procedure is year-old Sonia Olea Coontz, of Long Beach, CA. After experiencing a stroke in May , she lost the use of her right arm, and while she had some use of her right leg, she often required the use of a wheelchair. Following the surgery, however, Coontz says her limbs "woke up," and Dr. Steinberg and colleagues hope the procedure could offer the same outcome for millions of other stroke survivors. Steinberg speculates that, soon after implantation, the SB cells secrete deposits near areas of the brain damaged by stroke, and these boost reactivation or regeneration of nerve tissue, which improves motor function. The researchers believe that such a treatment may not be limited to stroke patients - it has the potential to treat a number of brain injury-related conditions. But if we can figure out how to jump-start these damaged brain circuits, we can change the whole effect. We thought those brain circuits were dead. Gary Steinberg The researchers note that 78 percent of the participants experienced temporary headaches , which they say was related to the transplant procedure. Some of the patients also experienced transient nausea and vomiting, though no significant blood abnormalities were identified. One key benefit to using mesenchymal stem cells, according to the authors, is that they are not rejected by the immune system, despite them being derived from the bone marrow of donors. In this study, none of the participants received immunosuppressant drugs. The researchers are now in the process of recruiting for a randomized, double-blind, multicenter phase IIb trial, which will further assess the safety and

efficacy of the stem cell procedure in stroke patients with motor disability.

7: Stroke patients able to walk again after stem cell transplant

adult brain and the transplantation procedure The cells in tissue and suspension transplants actively prolif- erate, which is typical of cells at the stage of early.

Both sexes male and female can be used as recipients in this protocol. Experimental procedure of this protocol. Diagram showing the surgery procedure for transplantation, including preparation of host mice stage 1 , embryonic brain tissue preparation stage 2 and transplant the embryonic cortical tissue to host brain stage 3. At stage 1, an open-skull window was made on the host mouse and a lesion cavity was drilled in the cortex of host brain. At stage 2 embryonic brain was extracted from fetus mice. At stage 3, a piece of embryonic brain tissue was cut from the fetus brain, and grafted into the lesion cavity in adult mouse cortex. The host mouse was fixed to the custom-made steel plate. The cross-section view of the host brain after transplantation surgery. The open-skull window was covered with the bone flap and glued to the skull using Superglue. The anesthetized mice are monitored until the pedal withdrawal response is lost. Moisten the hair on mouse head with water and shave the hair over the head with a razor blade. Disinfect the shaved scalp with iodine tincture and make an arc-shaped incision on the scalp Figure 1A stage 1. Separate the scalp and expose the skull. Remove all fascia on the skull with a microsurgical blade. Mark the interested region on skull A standard stereotactic frame can be also used for this surgery. Make sure the skull has been glued tightly with the metal frame and then fix the frame to a custom-made steel plate tightly Figure 1B. The metal frame should not be glued to the skull until the skull was completely dried, otherwise the metal frame will not be able to adhere to the skull tightly. Use a high-speed dental drill to thin the edge of a circular cranial area approximately 2 mm in diameter and clean the skull fragment with compressed air. Drill slowly and prevent the drill bur from puncturing the thinned skull. Prevent the thinned area from being overheated by adding PBS at room temperature frequently. Remove the bone flap the separated skull piece gently with curved forceps after the skull has been thinned enough. Stop any bleeding from the exposed dura with a piece of gelfoam soaked in PBS. Choose a cortical region avoid large vessels and create a traumatic lesion cavity about 1 mm in diameter and 1 mm in depth using the high-speed dental drill with a new disinfected drill bur. Clean the tissue debris in the traumatic lesion cavity and blood leaked from the lesion cavity with PBS soaked gelfoam. Detach the metal frame from the mouse skull and stop any further bleeding from the traumatic lesion cavity with gelfoam if necessary. Cover the exposed cortex with a piece of gelfoam soaked in PBS to stop bleeding of the lesion cavity. Place the mouse on a heating pad and monitor the state of anesthesia keep the animal at the surgical level of anesthesia and inject more KX if necessary. Protect the cortex from desiccation by adding PBS dropwise to the gelfoam frequently. Embryonic brain tissue preparation Figure 1A stage 2; Video 2 Note: To maintain the viability of embryonic cortical tissue, try to finish the surgical process extracting and transplanting within 20 min. Cortical tissue extracted from the fetus at the Embryonic day 14 E14 or E15 is suitable for embryonic cortical tissue transplantation. Perform an abdomen incision, and then remove the entire uterine horn and transfer it into the prepared culture dish with cold HBSS. Cut open the uterine horn and remove the amniotic sac of each embryo. Transfer the embryo into another culture dish. Remove the meninges gently with a pair of forceps to fully expose the embryonic brain. Dissociate the cortical tissue and keep it in another culture dish with cold HBSS. Transplant the embryonic cortical tissue to host brain Figure 1A stage 3; Video 3 Video 3. Transplant the embryonic cortical tissue to host brain Take off the gelfoam on the brain of the host mouse and clear any remaining liquid or blood in the lesion cavity using gelfoam if necessary. Bleeding from the exposed brain and lesion cavity should be stopped before next step. Gently pick up the embryonic cortical tissue in the HBSS and carefully cut a piece of embryonic cortical tissue about 1 mm3 in HBSS with a pair of thin-tipped forceps. Place the tissue into the lesion cavity of the host brain and align the tissue to keep the same orientation as the host brain. If there is any debris of cortical tissue remains outside of the lesion cavity, clear the debris carefully. Take out the separated bone flap from well culture plate, and dry it with a piece of autoclaved filter paper and clean any debris on it if necessary. Ensure to use the same piece of bone flap removed before. Hold the edge of the bone flap with forceps and cover it lightly to the exposed host

brain. Keep it at original orientation and adjust the edge to make it fit well with the cranial window. Stop any bleeding with the gelfoam. Wait until the surgical region of the skull is dry. And then apply a small drop of Superglue with a toothpick to seal the seam surrounds the bone flap Figure 1C. Care should be taken to prevent the Superglue from infiltrating into the host brain. Suture the scalp and disinfect it with iodine tincture. The endogenous microglia undergo apoptotic death, and are lost within 36 h after transplantation. The survival and differentiation of transplanted tissue can be assessed at different time points from hours to weeks using intravital imaging or fixed tissue techniques. We observed that endogenous microglia of the grafted tissue were lost rapidly after transplantation starting from 1 h to 36 h after transplantation , and then microglia from host brain infiltrated into the donor tissue at early stage after transplantation from hours to 1 week. The proliferation of host-derived microglia lasted for at least one month and eventually restored the microglial population in grafted tissue. These data were reported in our recently published article Scientific Reports , 6: On the other hand, the endogenous neurons of the grafted tissue survived and projected axons and dendrites to the host brain. In Figure 2, we show an example of transplanting a graft from a YFP H-line transgenic fetus to the brain of an adult wild type mouse. In this example, neurons of grafted tissue survived and differentiated in the host brain 2 months after transplantation and projected nerve fibers to the host brain Figures 2A-2C. Fetal cortical tissue successful survived and differentiated in host brain. Neurons green in grafted tissue can survived and differentiated in host brain 2 months after transplantation and projected a multitude of axons and dendrites in the grafted tissue and the host brain. Iba-1 staining showed microglia red were uniformly distributed in the grafted tissue and the host brain. The white dash line shows the boundary between donor and recipient tissue. Magnified view of the yellow and white box regions in A, respectively, showing that neurons projected axons arrow and dendrites arrowhead and coexisted well with the microglia. The grafted cortical tissues were from a YFP H-line fetus, and the host was a wild-type adult mouse. Data analysis The development of the grafted tissue was examined by intravital two photon imaging or confocal imaging of fixed brain slices. The differentiation of the grafted tissue was analyzed by evaluating the projection of axons and dendrites of the fluorescently labeled neurons originated from the embryonic tissue. For confocal imaging, the stacks of images were acquired by using an Olympus confocal microscope FV , and the z-projection of each stack of images was performed by using the Z Project function of ImageJ software http: The images of different channels were merged by using the Merge Channels function of ImageJ. Notes To increase the success rate of the transplantation surgery, the fetuses should be extracted from the euthanatized pregnant mouse as soon as possible. After the transplantation surgery, each host mouse should be fed in a separate cage to promote the recovery of the host animal. A circular cover glass instead of the bone flap can be glued to the skull window for intravital two photon imaging.

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8: Repairing the Nervous System with Stem Cells | www.enganchecubano.com

Transplantation of embryonic cortical tissue for repairing the damaged brain has provided a potential therapy for brain injury and diseases. The grafted tissue can successfully survive and participate in reestablishing the functional neural circuit of the host brain.

Research has shown that there are also stem cells in the brain. In mammals very few new neurons are formed after birth, but some neurons in the olfactory bulbs and in the hippocampus are continually being formed. These neurons arise from neuralâ€¦ For years it was thought that the brain was a closed, fixed system. There were only a handful of discoveries, primarily in rats, birds, and primates, in the latter half of the 20th century that hinted at the regenerative capability of brain cells. During this time, scientists assumed that once the brain was damaged or began to deteriorate it could not regenerate new cells in the way that other types of cells, such as liver and skin cells, are able to regenerate. The generation of new brain cells in the adult brain was thought to be impossible since a new cell could never fully integrate itself into the existing complex system of the brain. It was not until that NSCs were discovered in humans, found first in a region of the brain called the hippocampus , which was known to be instrumental in the formation of memories. NSCs were later also found to be active in the olfactory bulbs an area that processes smell and dormant and inactive in the septum an area that processes emotion , the striatum an area that processes movement , and the spinal cord. Today scientists are investigating pharmaceuticals that could activate dormant NSCs in case the areas where neurons are located become damaged. Other avenues of research seek to figure out ways to transplant NSCs into damaged areas and to coax them to migrate throughout damaged areas. Still other stem cell researchers seek to take stem cells from other sources i. The most controversial of these stem cells are the ones procured from human embryos, which must be destroyed in order to obtain the cells. Scientists have been able to create induced pluripotent stem cells by reprogramming adult somatic cells cells of the body, excluding sperm and egg cells through the introduction of certain regulatory genes. However, the generation of reprogrammed cells requires the use of a retrovirus , and therefore these cells have the potential to introduce harmful cancer -causing viruses into patients. Embryonic stem cells ESCs possess amazing potential, since they are capable of being turned into any type of cell found in the human body , but further research is needed to develop better methods of isolating and generating ESCs. Stroke recovery is one area of research where much has been discovered about the promise and the complexities of stem cell therapy. Two main approaches can be taken to stem cell therapy: These stem cells are found in two zones of the dentate gyrus part of the hippocampus in the brain, as well as in the striatum part of the basal ganglia located deep within the cerebral hemispheres , the neocortex the outer thickness of the highly convoluted cerebral cortex , and the spinal cord. In rat models, growth factors cell growth-mediating substances , such as fibroblast growth factor-2, vascular endothelial growth factor , brain-derived neurotrophic factor, and erythropoietin , have been administered after strokes in an effort to induce or enhance neurogenesis, thereby staving off brain damage and spurring functional recovery. The most promising growth factor in the rat models was erythropoietin, which promotes neural progenitor cell proliferation and has been shown to induce neurogenesis and functional improvement following embolic stroke in rats. This was followed by clinical trials in which erythropoietin was administered to a small sample of stroke patients, who eventually showed dramatic improvements over individuals in the placebo group. Erythropoietin has also shown promise in patients with schizophrenia and in patients with multiple sclerosis. However, further studies need to be performed in larger groups of patients in order to confirm the efficacy of erythropoietin. Exogenous stem cell therapies rely upon extraction, in vitro cultivation, and subsequent transplantation of stem cells into the regions of the brain affected by stroke. Studies have shown that adult NSCs can be obtained from the dentate gyrus, hippocampus, cerebral cortex, and subcortical white matter layer underneath the cerebral cortex. Actual transplantation studies have been carried out in rats with spinal cord injury using stem cells that had been biopsied from the subventricular zone area underlying the walls of the fluid-filled brain cavities, or ventricles of the adult brain. Fortunately, there were no functional deficits as a result of the biopsy. There have also been studies in rats in which ESCs or fetal-derived neural stem cells and

progenitor cells undifferentiated cells; similar to stem cells but with narrower differentiation capabilities have been transplanted into regions of the brain damaged by stroke. In these studies, the grafted NSCs successfully differentiated into neurons and glial cells, and there was some functional recovery. The major caveat , however, with exogenous therapies is that scientists have yet to fully understand the underlying mechanisms of differentiation of the progenitor cells and their integration into existing neuronal networks. In addition, scientists and clinicians do not yet know how to control the proliferation, migration, differentiation, and survival of NSCs and their progeny. This is due to the fact that NSCs are partially regulated by the specialized microenvironment, or niche , in which they reside. There has also been research into hematopoietic stem cells HSCs , which usually differentiate into blood cells but can also be transdifferentiated into neural lineages. These HSCs can be found in bone marrow , umbilical cord blood, and peripheral blood cells. Interestingly, these cells have been found to be spontaneously mobilized by certain types of strokes and can also be further mobilized by granulocyte colony stimulating factor G-CSF. Studies of G-CSF in rats have shown that it can lead to functional improvement following stroke, and clinical trials in humans appear promising. Exogenous studies have also been carried out in rats with HSCs. The HSCs were administered locally at the site of damage in some studies or administered systemically through intravenous transplantation in other studies. The latter procedure is simply more feasible , and the most effective HSCs seem to be those derived from the peripheral blood. The research that has been done on stem cell therapies for epilepsy and Parkinson disease also demonstrates the promise and difficulty of properly cultivating stem cells and introducing them into a living system. With regard to ESCs, studies have shown that they are capable of being differentiated into dopaminergic neurons neurons that transmit or are activated by dopamine , spinal motor neurons, and oligodendrocytes non-neuronal cells associated with the formation of myelin. In studies aimed at treating epilepsy, mouse embryonic stem cell-derived neural precursors ESNs were transplanted into the hippocampi of chronically epileptic rats and control rats. After transplantation, no differences were found in the functional properties of the ESNs, as they all displayed the synaptic properties characteristic of neurons. However, it still remains to be seen whether ESNs have the ability to survive for prolonged periods in the epileptic hippocampus, to differentiate into neurons with the proper hippocampal functions, and to suppress learning and memory deficits in chronic epilepsy. NSCs, on the other hand, have already been observed to survive and to differentiate into different functional forms of neurons in rats. However, it is unclear whether NSCs can differentiate into the different functional forms in appropriate amounts and whether they can synapse properly with hyperexcitable neurons in order to inhibit them, thereby curbing seizures. Treatments for Parkinson disease also show promise and face similar obstacles. Clinical research has been carried out on the transplantation of human fetal mesencephalic tissue tissue derived from the midbrain , which forms part of the brainstem into the striata of Parkinson patients. However, this tissue is of limited availability, which is what makes ESC transplantation more appealing. Indeed, research has already shown that transplantable dopaminergic neuronsâ€”the kind of neurons affected in Parkinson diseaseâ€”can be generated from mouse, primate, and human ESCs. The one major difference between mouse and human ESCs, however, is that human ESCs take much longer to differentiate up to 50 days. Also, differentiation programs for human ESCs require the introduction of animal serum in order to propagate , which might violate certain medical regulations, depending on the country. Researchers will also need to figure out a way to get ESC-derived dopaminergic progenitor cells to survive for a longer period of time after transplantation. Finally, there is the issue of the purity of ESC-derived cell populations; all the cells must be certified as dopaminergic precursor cells before they can be safely transplanted. Nevertheless, differentiation and purification techniques are improving with each study. Indeed, the generation of large banks of pure and specific cell populations for human transplantation remains an attainable goal.

CELL AND TISSUE TRANSPLANTATION INTO THE ADULT BRAIN pdf

9: Cell and tissue transplantation into the adult brain (Book,) [www.enganchecubano.com]

Neural stem cells (NSCs) are self-renewing, multipotent cells that generate the neurons and glia of the nervous system of all animals during embryonic www.enganchecubano.com neural stem cells persist in the adult vertebrate brain and continue to produce neurons throughout life.

Development[edit] In vivo origin[edit] There are two basic types of stem cell: ESCs are not limited to a particular cell fate; rather they have the capability to differentiate into any cell type. They are capable of forming multipotent neurospheres when cultured in vitro. Neurospheres can produce self-renewing and proliferating specialized cells. These neurospheres can differentiate to form the specified neurons, glial cells, and oligodendrocytes. Some neural cells are migrated from the SVZ along the rostral migratory stream which contains a marrow-like structure with ependymal cells and astrocytes when stimulated. The ependymal cells and astrocytes form glial tubes used by migrating neuroblasts. The astrocytes in the tubes provide support for the migrating cells as well as insulation from electrical and chemical signals released from surrounding cells. The astrocytes are the primary precursors for rapid cell amplification. The neuroblasts form tight chains and migrate towards the specified site of cell damage to repair or replace neural cells. One example is a neuroblast migrating towards the olfactory bulb to differentiate into periglomercular or granule neurons which have a radial migration pattern rather than a tangential one. The origin and identity of NSCs in the adult brain remain to be defined. Quiescent stem cells are Type B that are able to remain in the quiescent state due to the renewable tissue provided by the specific niches composed of blood vessels, astrocytes, microglia , ependymal cells, and extracellular matrix present within the brain. These niches provide nourishment, structural support, and protection for the stem cells until they are activated by external stimuli. Once activated, the Type B cells develop into Type C cells, active proliferating intermediate cells, which then divide into neuroblasts consisting of Type A cells. The undifferentiated neuroblasts form chains that migrate and develop into mature neurons. In the olfactory bulb, they mature into GABAergic granule neurons, while in the hippocampus they mature into dentate granule cells. They also have important role in adult animals, for instance in learning and hippocampal plasticity in the adult mice in addition to supplying neurons to the olfactory bulb in mice. The results of this ongoing investigation may have future applications to treat human neurological diseases. Furthermore, in Evan Y. Jaime Imitola , M. D and colleagues from Harvard demonstrated for the first time, a molecular mechanism for the responses of NSCs to injury. They showed that chemokines released during injury such as SDF-1a were responsible for the directed migration of human and mouse NSCs to areas of injury in mice. All these results have been widely reproduced and expanded by other investigators joining the classical work of Richard L. Sidman in autoradiography to visualize neurogenesis during development, and neurogenesis in the adult by Joseph Altman in the s, as evidence of the responses of adult NSCs activities and neurogenesis during homeostasis and injury. The search for additional mechanisms that operate in the injury environment and how they influence the responses of NSCs during acute and chronic disease is matter of intense research. The loss of cells is amplified by the lack of regenerative abilities for cell replacement and repair in the CNS. One way to circumvent this is to use cell replacement therapy via regenerative NSCs. NSCs can be cultured in vitro as neurospheres. The withdrawal of these growth factors activate differentiation into neurons, astrocytes, or oligodendrocytes which can be transplanted within the brain at the site of injury. NSPCs induce neural repair via intrinsic properties of neuroprotection and immunomodulation. Some possible routes of transplantation include intracerebral transplantation and xenotransplantation. There are two ways to culture the hmNPCs, the adherent monolayer and the neurosphere culture systems. The neurosphere culture system has previously been used to isolate and expand CNS stem cells by its ability to aggregate and proliferate hmNPCs under serum-free media conditions as well as with the presence of epidermal growth factor EGF and fibroblast growth factor-2 FGF2. Initially, the hmNPCs were isolated and expanded before performing a 2D differentiation which was used to produce a single-cell suspension. This single-cell suspension helped achieve a homogenous 3D structure of uniform aggregate size. Damage can escalate and eventually lead to apoptosis or cell death. Current treatments focus on preventing further damage by

stabilizing bleeding, decreasing intracranial pressure and inflammation, and inhibiting pro-apoptoic cascades. In order to repair TBI damage, an upcoming therapeutic option involves the use of NSCs derived from the embryonic peri- ventricular region. Stem cells can be cultured in a favorable 3-dimensional, low cytotoxic environment, a hydrogel , that will increase NSC survival when injected into TBI patients. The intracerebrally injected, primed NSCs were seen to migrate to damaged tissue and differentiate into oligodendrocytes or neuronal cells that secreted neuroprotective factors. There are two approaches to using NSCs as a therapeutic treatment: The hGalhNSCs induced better and faster brain recovery of the injured tissue as well as a reduction in motor and sensory deficits as compared to only hNSC transplantation. Importantly, this assay allows discrimination between neural stem and progenitor cells. Snyder were the first to isolate multipotent cells from the mouse cerebellum and stably transfected them with the oncogene v-myc. Since then, neural progenitor and stem cells have been isolated from various areas of the adult central nervous system, including non-neurogenic areas, such as the spinal cord , and from various species including humans.

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