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Abstract

Much of the current research using stem cells focuses on their possible roles in regenerating tissues, more specifically organ formation. By studying their regenerative properties, it has been discovered that stem cells may play an important role in regenerating other parts of the body such as cartilage and bone as well. Since cartilage does not easily regenerate or repair itself and bone takes a long period of time to fully heal, using stem cells on the infected areas could greatly improve a person's recovery from these conditions as well as their daily functioning, especially because these conditions are some of the leading causes of disability and many disorders involving cartilage damage are only treatable using very invasive methods such as surgery. These stem cells, specifically adult stem cells, taken from the bone marrow have been evaluated for their reparative properties in animal models with positive results. Although research has not yet had a fully restored functional joint using stem cells in a human model, these studies show the potential for the use of these cells in certain degenerative diseases such as arthritis or even bone fractures.

Introduction

Stem cells, though newer in their clinical implications have changed the medical practice because of their potential implications in their regenerative abilities. These cells are not only able to differentiate themselves into different cell types, but are then able to also renew themselves during cell division, leading to limitless possibilities. Because these cells can differentiate into almost any type of cell, there has been a large amount of research done on the different potential parts of the body that could be helped by using stem cells. Many of these areas of research have centered on regenerating different tissues

in the body including brain tissue, muscle, blood, and bone. The different types of stem cells also allow for scientists to discover new possibilities available with each. The different cells include embryonic stem cells and adult stem cells, although both are harvested from the body, they can each have different differentiation potential and therefore different potential in regenerative medicine. While embryonic stem cells coming from small embryos are more well known because of their ethical implications, adult stem cells, or cells that have been harvested from individuals and reprogrammed, have also been studied extensively with good results pointing towards their successful differentiation and regeneration into the desired cell type.

As the body goes through changes as it gets older or injuries occur, certain conditions may arise involving the degradation of bone and cartilage, especially in the joints. One of the main conditions that is most common is arthritis which is the breakdown of the cartilage in the joints of the body, usually caused by age. This disorder affects a majority of people not only in the United States, but also in the world. In cases of disorders such as these, stem cells have been thought to be a possible treatment option because of their regenerative properties. As the parts of the body affected are mainly in or around the joints, many of the areas do not get sufficient blood flow for self-repair which ultimately leads to a worsening of the condition. Current methods of repair also include much more invasive approaches including surgery or waiting for the bone to regrow naturally. Instead of these current methods, stem cells offer a new treatment option, which could possibly bring quicker relief and healing to the areas in need because they are made of cells and are able to replicate quickly. The use of stem cells in regeneration of bone and cartilage has been studied in certain conditions like those of arthritis and bone density problems as well

as bone fractures, but much more research needs to be done on the topic in order to get solid evidence of the results of this method of treatment of cartilage degradation and bone density issues or fractures.

Based on the previous research done on the effectiveness of a stem cell to regenerate tissue, especially connective tissues like bone and cartilage, including stem cells in the treatment of disorders that affect these areas seems to be the next step of regenerative medicine. Though there have been a number of studies done in mice and other animals, there is still a need to have human studies done and documented properly in order to understand the true healing power of these cells. While the type of stem cell used can have an impact on the end results, most of the studies have found the results to be generally positive. Based on the way research currently points, stem cells seem to be a useful and viable tool in the treatment of certain conditions such as cartilage regeneration and bone repair and also in regenerative medicine as a whole.

How Stem Cells Work

In order to understand how exactly stem cells may help in the regeneration of bone and cartilage, it is important to understand how exactly they work and how they may help in these conditions. The first important thing to note is that stem cells have different types. The most well known types of stem cells are embryonic stem cells (ESCs) and adult stem cells (ASCs). Embryonic stem cells are those that come from places such as the umbilical cords of babies or from developing embryo blastocytes. These cells are undifferentiated, pluripotent cells that are able to be formed into any cell desired. Though their differentiation potential is endless, they are often not very easy to acquire which makes them a bit more difficult to use. It is these types of cells that are most commonly the topic of

ethical concerns because of their being harvested in developing embryos. While these cells are successful in differentiation, the other type of stem cell, the adult stem cell, is what is more commonly used in the studies used to treat cartilage and bone disorders.

Adult stem cells are much more common than embryonic stem cells as they can be found on all parts of the human body. Compared to embryonic stem cells though, while these cells may be more readily available, they often require more work to become usable stem cells (Chen et al. 2006). Many common sources of these types of cells include skin, muscle, bone, etc. Many researchers believe that these types of cells lay undividing for long periods of time until needed, like in the case of an injury, when they will begin to divide for their respective location. Even though these cells differentiate most often into the certain types of cells of the niches they occupy based on their original location, recent research has been able to reprogram these adult stem cells to become like embryonic stem cells, called induced pluripotent stem cells (iPSCs) with the help of the introduction of certain embryonic genes. Though division does occur in these adult stem cells, the time period they divide in culture is relatively unknown, so in order to get the number of cells required for stem cell replacement therapies, there will have to be methods created in which to expand their numbers in cell cultures. Despite these flaws, adult stem cells are still more commonly used in certain procedures and for the sake of this paper, we will be discussing the use of adult stem cells rather than embryonic stem cells in regenerative procedures.

As mentioned previously, the location of the adult stem cell can be a deciding factor in the outcome of the results. The success of this type of method is very dependent upon the type of cell being used. From each location within the body, cells will have different needs for their regeneration. Since adult stem cells are used, the most common way to use

them is to create the induced pluripotent stem cells as they can then become many different types of cells rather than the certain niche they occupied. Based on these original locations though, the cell will have different genes and conditions such as molecules, growth factors, and other markers which will also help in the future differentiation of the cell as adult stem cells seem to have somewhat of a memory of their history (Tamer & Reis 2009).

Regardless of the cell type, the overall process of transforming the cell is relatively similar. The adult stem cell will first be harvested from the original site (such as skin epithelial cells, bone marrow, etc.) and will have copies of four genes (embryonic genes) inserted into the cells in order to make them like embryonic stem cells. After the insertion of these genes, the cells then become induced pluripotent stem cells. Since they are embryonic-like in their potential uses, the cells then require a specific environment in order to differentiate into the desired cell type (Chen et al. 2006) and (Caplan 2007). Each of the different environments required will need a different type and amount of certain growth factors in order to replicate conditions within the body (Guan 2015). After the cells have differentiated and are in large enough amounts, they can then be grafted into the body of the patients with these bone and cartilage disorders.

What Kinds of Bone/Cartilage Disorders Stem Cells Can Be Used On

The majority of the articles and research looked at involved the knee joint, therefore the scope of this paper will be limited to those disorders of the cartilage and bone in the knee. While the majority of the articles look at the knee, there is also some research out there on the possible uses of these cells in other joints such as the elbow. The knee itself is a “bony” joint which connects the upper and lower leg, acting as a sort of hinge connected

by ligaments and tendons. This just means that the joint itself does not fit together like in ball-and-socket joints such as the shoulder, therefore the bones are resting upon each other with only thin layers of cartilage between them. There are three bones within the joint, the tibia, femur, and patella, and while the patella floats on top of the joint itself, the tibia and femur connect at their respective condyles with little pads of tough cartilage to act as shock absorbers and keep the bones from rubbing together, called menisci (singular: meniscus). These menisci provide a gliding surface for the joint to move as well as a cushion for the bones.

Within the knee joint, other than injuries to the ligaments, the major cause of pain and dysfunction is arthritis. There are different types of arthritis but one of the major types is osteoarthritis which is the degradation of bone and cartilage in the body. This type of arthritis can be caused naturally by aging or by some type of previous chronic injury such as meniscal tear. While this type of condition is most commonly found in older individuals (over 65) it can also be prevalent in younger people as well. This type of condition is degenerative and will often not heal on its own, since the cartilage is non-vascular, there is little to no blood flow to those areas of the body leading to a lack of self-repair and requires either lifestyle changes or assistive devices in order to manage the symptoms without actually healing the condition. The only ways to fully restore function includes invasive surgeries such as joint replacement, which can be hard to recover from as well, especially in older individuals whom the condition affects most.

When the cartilage gets worn down, there can also be damage done to the bone as well caused by the friction of the hard surfaces rubbing against each other. While bone degeneration is common in patients suffering from arthritis, there are also other

disorders/conditions which may benefit from stem cells such as bone fractures or bone density issues (Granero-Molto 2009). While current medicine can make sure a bone heals how it is supposed to, oftentimes the process is lengthy as it is dependent on the bone mending itself, often in a cast. Bone healing can also depend upon the person's own body such as their age and other factors that influence the rate at which their bone heals. While there is nothing wrong with the method currently to heal broken bones and often the bones are "good as new", stem cells may offer a little boost to the healing process, speeding it up. Stem cells however, may be able to help those with certain bone disorders including weakening of the bones or lack of bone density. Oftentimes the only options for patients with these disorders involve taking medications and special living plans in order to manage their conditions (Kassem & Abdallah 2007). Though not ideal, these plans do manage to help the patients control their conditions and continue with their lives.

It is important to understand how stem cells can help with these disorders as they can be later used in the treatment of other bone and cartilage conditions in other parts of the body as well. With an understanding of how stem cells can work in joints to repair cartilage and bone, medical procedures can be changed forever. An example of this would be in certain conditions such as the repair of the meniscus in the knee. As they are non-vascular, oftentimes the cartilage is repaired with sutures but a high chance of re-tear or just shaved out. With an understanding of how stem cells may signal regeneration of this tissue, there could possibly be a change in how this procedure is performed and the increase of positive prognoses because of it.

Previous Findings on Stem Cell Viability in These Procedures

As with any type of medical procedure, evidence must first be supportive of the benefits in animal models before there can be any tests started in humans, though there has been some positive results on human bone regeneration using stem cells (Pagnotto et al. 2007). Studies on the benefits of stem cells have so far been mostly positive in the research models. Animals such as rabbits and rats have shown positive results of bone and cartilage regeneration (Koga et al. 2008) and (Nakagawa et al. 2016). Many of the studies done on bone marrow cells also use things like the adeno-associated virus (AAV) as a vector in transduction of the bone marrow cells for their use in bone repair (Pagnotto et al. 2007). These findings show that when stem cells were transplanted into the affected sites, the cartilage and bone grew back with as much strength as before and in a quicker time span than it would have without the cells.

As mentioned previously, the cells original location can play a role in their respective potential healing sites. Since these types of cells often have some type of memory even when becoming iPSCs, the site where they are harvested from can have an impact on the healing process and relative success of this procedure. In the studies done on the different sources of stem cells and their general healing success it was found that synovium mesenchymal cells (cells from the synovial membrane) were often more efficient at regenerating cartilage tissues (Koga et al. 2008) and (Ogata et al. 2015) while bone marrow cells typically work better when trying to regenerate bone (Granero-Molto 2009). While they will still have some successful healing when not the ideal cell type, the differences in their regenerative properties have to do with the cell "memory and their ability to become induced to their respective future cell types (Tamer & Reis 2009).

They have also found in some studies that though there are certain cells that work better for the different healing sites, cells can be taken from many different parts of the body and be able to have some success in tissue regeneration. Though most of the research on these procedures involve sites such as bone, muscle, skin, etc., there have been a few studies done on strange sources of cells such as urine and menstrual blood which have shown relative success when grafted into the knee joint (Guan 2015).

In all the cases of cartilage regeneration looked at, there was relative success in regeneration by stem cells. As mentioned before, the synovium cells were especially successful in their treatment of cartilage damage and were the most often used type of cell in the experiments (Koga et al. 2008) and (Ogata et al. 2015). One unexpected benefit from the stem cells other than their regenerative properties was their ability to also affect the bone surrounding the cartilage repair. In one of the studies, the researchers found that the bone surrounding the sites the cartilage was repaired also benefitted from the cells and had some healing as well (Ogata et al. 2015). In the studies observing stem cell use in fracture repair, researchers found that while implanting cells may be successful in some cases, there are also limitations to the treatment (Kassem & Abdallah 2007), (Granero-Molto et al. 2009), (Guan et al. 2015).

With any potential treatment, there are certain factors that can make a procedure less likely to be effective. Some of these limitations include the age of the patient and the extent of the damage. With a patient's age, not only is it a factor that will affect their healing time but it is also something that is affecting the cells as they become less effective over time in their ability to heal and regenerate and because the cells are taken from the respective individual, their age can affect the success of a treatment such as this one. How

badly the damage extends can also be important to the success of the procedure because while stem cells are able to help regenerate tissue, if the damage is too great or extensive, the cells may not be able to regenerate enough to fully heal the damage done and result in less than expected success (Caplan 2007). There are also certain growth factors that can determine the relative success of the procedure. In the knee with cartilage especially there is a growth factor called Lubricin. This growth factor was seen in increased amounts in those models who underwent a very successful stem cell transplant than those who had lower levels who underwent the same procedure (Nakagawa et al. 2016). This means that a person's own chemical balance can also affect the success of this procedure or that the success of the stem cells stimulated the production of the growth factor but in either case it is not as simple as just implanting the stem cells and hoping for them to do their job and regenerate.

Other Treatment Options

Though stem cells seem like a viable option based off of the current research, this type of procedure still requires research in human models in order to get an idea of its effectiveness. As of now, treatments for these types of disorders included surgery or lifestyle changes in the case of cartilage repair. These types of changes could be anything from the lessening of high impact activities to an inclusion of an assistive device. Surgeries can include minor arthroscopic procedures to invasive replacement procedures. With bones, oftentimes with a fracture a person just needs to wait out the healing process, often while being casted or in a supportive device. Other conditions require a person to take medications or also change their lifestyles such as their daily activities as well. Either way, stem cells seem to be a possible treatment option for those who are living with these

conditions as the treatment itself would be very minimally invasive and have few risks. Combined with the use of stem cells in certain conditions, treatments like gene therapy may have an increased effectiveness. Since stem cells regenerate quickly, transplanting these normal genes into the stem cells and allowing them to differentiate will allow the correction of certain genetic disorders in a much more rapid way than before, treating the defective cells more quickly. Gene therapy on its own may not be effective but when combined with something like stem cells, the prognosis is much greater for success (Pagnotto et al. 2007).

Arguments Against Stem Cells

Though seen by the research most of the evidence for stem cell treatment of these disorders is positive, there is still some criticism of the methods (Chen et al. 2006) and (Tamer & Reis 2009). It was also discussed that the methods are not ideal for everyone as they do have their limitations such as a person's age and the injury itself. Problems can be furthered by the cells themselves and their "memories" in the induction of these cells into their desired cell types (Koga et al. 2008).

Since much of the research thus far has been only on animal models, there comes safety concerns whether the procedure is safe for humans and whether or not it will even be beneficial to them. Although the research indicates that the method is safe to use on the models, there are still many obstacles that must be overcome in order to get human trials and tests done. These different obstacles include research grants, review boards, and all types of rules and regulations on the trials themselves. Since there has been some research done on humans in areas like bone regeneration, it seems like a relatively safe practice, so

it will just take time to get the appropriate approvals on more trials which can then lead to further results.

Another big issue with injuries, especially knee injuries, is that there may be some type of placebo effect. Since many of these conditions (besides bone fractures) cannot heal themselves on their own, they will require some kind of medical intervention. The placebo effect is feeling an improvement on one's condition when there lacks any actual healing or repair. With knee treatments, many studies have found that patients that are suffering from chronic knee injuries report feeling better after a minor arthroscopy procedure, even if there was nothing done except inserting a camera. These fake procedures have people reporting feeling better, even when nothing was actually done. While not all those who underwent the fake procedure reported improvement in their condition, skeptics still remain that the procedures may not signal actual healing, but rather a psychological fix.

Finally, the last major argument against stem cells is the use of embryonic stem cells. ESCs have many ethical issues tied to it, but are often hard to find and therefore not used in these types of studies or conditions. Adult stem cells however can be found in all humans and are relatively easy to harvest and reprogram, therefore leading to no major ethical conflicts. Though people may only think of embryonic stem cells when they hear of stem cells, they should be informed that there are many more sources of stem cells that do not involve the killing of embryos.

Conclusions

Research has documented the success of stem cells for treatment of bone and cartilage disorders in animal models. Though these results are promising, it is going to take more research in order to get these tests done on humans. Though there are a couple tests

that have been done on humans, safety precautions must be taken into account before any real trials may begin. The use of stem cells is a relatively easy method to regenerate tissues and can have potential positive effects on many different people. These cells are readily and easily available because they are in each person and are very quick dividing, therefore they can bring quick results to patients who have not had improvements to their conditions in months or years. Like any procedure, while these methods do have their limitations to the types of disorder and damages they can heal, if the option is available it would offer a much less invasive treatment than many of the current methods. Though this paper mainly looked at research done in the knee, with further testing and results, this type of procedure could potentially be used broadly in many different body parts. Since regenerative medicine is one of the fastest expanding areas of the medical field, it is not surprising if these tests would begin in humans in the near future. Though the animal models demonstrate improved healing, it is only when these tests are done in humans that we can gather conclusive data. With continued research into these procedures and this field and the mechanisms stem cells play, the range of disorders and conditions could possibly expand greatly leading to the treatment of other cartilage and bone disorders not just arthritis or bone fractures. These advancements could further change the way medicine treats people, changing our ideas of the limits of treatment that we currently have.

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