FUTURE DEVELOPMENTS OF STEM CELL TECHNOLOGY FOR DEGENERATIVE MYELOPATHY

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PASS WITH DISTINCTION

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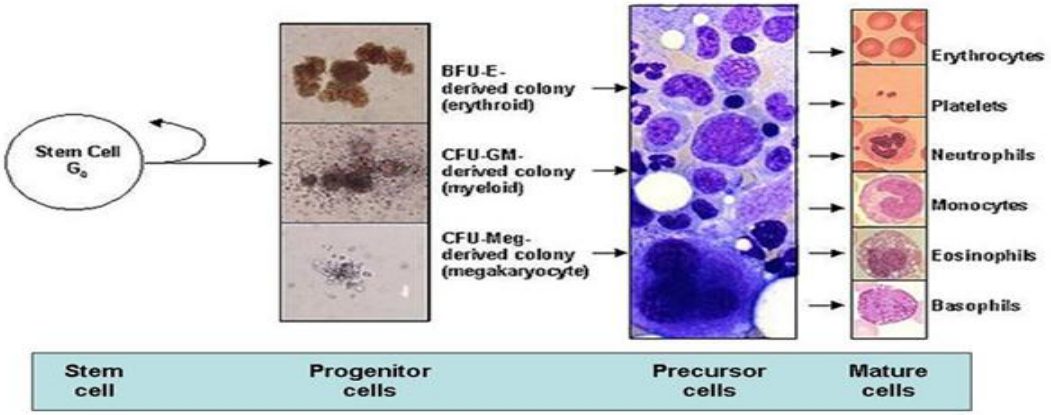
Abstract
Stem cell research is a comparatively recent and controversial technology. The potential of stem cell use in medicine has created great excitement throughout the profession, and it is believed that this new technology will unveil treatments and possibly even cures for many of the worlds worst diseases including Alzheimer's, Parkinson's, diabetes, heart disease and even types of cancer. If this is to be the case, we must not neglect the avenues this will open to the world of veterinary medicine. This paper will discuss the possible uses of stem cells in the treatment of Degenerative Myelopathy, an autoimmune disease whereby the patients own immune system attacks the Central Nervous System.

Introduction
Stem cell research first came in to play in the mid 1800's when scientists discovered that some cells could generate other cells. This was further developed in the early 1900's by the recognition of blood cells being made by cells contained in bone marrow. In 1969 the first bone marrow transplant was performed, this successfully treated two siblings with severe combined immunodeficiency. From this point stem cells research has become a major source of interest and debate.

Stem cells are unique due to there ability to renew themselves, and their ability to create other cells which are 'specialized'. Stem cells themselves are unspecialized cells, meaning they are not specifically adapted to carry out an intricate function in the body, unlike, for example, nerve cells. However, the task they carry out is integral to the body, and is found at all stages of development. Stem cells can be understood as a 'repair-kit' to the body. They continuously replicate themselves, as well as producing new cells which go on to replicate again and form specialized cells.
[from http://www.hematology.org]



Above is a simplified example of how stem cells can create specialized cells in the body.

Embryonic Stem Cells
There is specific interest in embryonic stem cells which are found in human embryos during the blastocyst stage, due to their potential to form all the other cells present in the human body. It is believed that if scientist can learn to control the replication of these cells in laboratory conditions, they could go on to grow body tissues and even whole organs, which would see an end to the long list of patient's seeking organs from a shortage of donors.

A great advantage of producing transplant organs using stem cells is the avoidance of transplant rejection, where the body's immune system attacks the transplanted organ due to the recognition of foreign proteins. Stem cell technology would mean that the transplant organ could be grown from the patient's own stem cells, resulting in an exact DNA match of the tissues, no chance of rejection, and no need for immunosuppressant drugs post transplant.

An example of how stem cells are already being used in medicine is in the treatment of leukemia. Donated bone marrow from relatives or from a donor registry is transplanted into the patient to replace their dysfunctional immune system for a healthy one. The bone marrow contains stem cells which replenish the cells lost in previous chemotherapy. Red blood cells used for oxygen transport; white blood cells which fight infection and platelets needed in blood clotting are all produced in the bone marrow. This has already improved the treatment of leukemia, giving patients a much better hope of recovery.

These new ideas and technologies, whilst still in their primary stages, could go on to create huge advancements in the treatment of patients in both ordinary medicine and veterinary medicine. Specifically in my interest, the treatment of Degenerative Myelopathy (DM) in dogs.

Discussion

Chronic degenerative radiculomyelopathy (Degenerative Myelopathy) is a condition found mainly in German Shepherd Dogs (GSD), although cases have been reported in other large breeds. It was first describes as a specific degenerative neurologic disease in 1973, and continues to be of speculation today. The fact that it is seen so commonly in the GSD suggests that the breed has a genetic predisposition to the disease, and researchers claim a mutated gene found in numerous breeds of dogs such as Boxers, Chesapeake Bay Retrievers, Rhodesian Ridgebacks and of course the German Shepherd Dog, is responsible for the condition. However, there is little evidence of the condition being as frequent or as severe in other breeds compared to the GSD.

It has been proposed that the condition is due to the immune system attacking the myelin sheath, an insulating sheath which surrounds the axon of the neurons in the spinal cord. There is much evidence to support this theory. Dogs afflicted with DM have been found to have antigen-binding cells specific to canine myelin basic protein. They also show increased circulating immune-complexes of whose antigens appear to be markers of inflammation, the same of which have been present in patients with other inflammatory diseases of the Central Nervous System. The swollen axons and patchy demyelination are very apparent when tissue samples taken from inflicted dogs are examined under the microscope. The destruction of the myelin begins in the lumbar spine of the animal; the loss of this insulating coating causes slower nerve impulses and a loss of communication between the brain and the lower body of the animal. This is not unlike the human disorder Multiple Sclerosis (MS) where demyelination is also the cause of deteriorating neurological function. Research material has led scientists to believe that DM may well

be the canine form of MS. If this is the case, might it then be possible to apply similar treatments to both of these conditions?

The symptoms of DM can be misleading, often being confused for arthritis. Initially the back end of the dog is affected; a combination of muscle weakness and lack of coordination severely affects balance; causes a noticeable limp and results in difficulty rising from lying or sitting positions. Because the condition is progressive, the dog will eventually experience incontinence problems, and the front end of the animal will begin to deteriorate also.

Degenerative Myelopathy is a non-recessive and progressive disease. Current treatment of the condition is basic and used mainly to improve the quality of the dog's life until DM progression necessitates euthanasia. The current treatment of DM involves four basic approaches;
[http://neuro.vetmed.ufl.edu/neuro/DM_Web/DMofGS.htm]

1) **Exercise:**
This has shown to be greatly beneficial to DM sufferers. Improved coordination, muscle performance, strength and stamina have all been the result of regular and structured exercise regimes. Walking and swimming prove to be the most beneficial as they cause the least stress on the animal's joints.

2) **Dietary Supplementation:**
As in most cases, better overall health is expected to result in a stronger resilience to the disease. Various supplements have been suggested due to their known benefits to the nervous tissue and muscle fibers. However, there is little evidence of significant improvement because of these supplements alone.

3) **Medication:**
At present two medications seem to reduce the rate of progression of DM. These are aminocaproic acid (EACA) and n-acetylcysteine (NAC). EACA can be injected or giving orally and has few side effects. Although this medication has been known to cause gastrointestinal irritation, these cases are rare. NAC is an anti-oxidant with neuroprotective effects and is also administered orally. It can cause vomiting and increased bleeding times, but again this is not common.

A drawback of these medications is the high cost of the product and also the complexity of the dosage requirements. An example of how they may be administered follows; 2 parts aminocaproic acid solution (250 mg/ml) with 1 part chicken broth and give 3 ml of this mixture orally every 8 hours. 75 mg/kg of NAC divided in 3 doses a day for 2 weeks; this must be diluted with chicken broth. Then dosage is then reduced to 3 doses every other day.
We can see here that this method of treatment is quite intricate and time consuming, difficult for busy people with other commitments.

4) **Other supportive measure:**
Other measures to be taken include using worming and flea treatments which do not increase the immune systems activity. Acupuncture can reduce pain and slows the progression of DM, although again this is an inconvenient and expensive treatment. Physiotherapy is another option as, like exercise, this can encourage muscle memory and tone, as well as easing pain and stiffness. This is often very beneficial to dogs who also suffer from arthritis, another common problem in the older GSD.

Although these treatments are certainly beneficial to inflicted dogs and helpful in minimizing discomfort, they are by no means cures, and gradual progression of the disease is always expected. Without treatment, dogs will succumb to total paralyses within in as little as 3 months of initial diagnosis. In best case scenarios untreated dogs may remain active for up to 2 years, nevertheless euthanasia is still unavoidable at this point. From this we can see that more research and new treatments need to be found if we want to control the disease and give our animals the best quality of life we can. This is why I feel new technologies such as stem cell development are integral to the future treatment of this condition.

What Stem Cell Technology will do for the future of DM.

I believe that with the development of stem cell technology, a revolutionary treatment for DM which will prevent progression and possibly even reverse the clinical signs of DM, will become available.

Much of the following is based on research which has already been tested (although on a very small scale) on human patients suffering from Multiple Sclerosis. As I have already mentioned, the similarities between these two conditions are great, and I feel that the scientific progress made in either condition will only be beneficial to the treatment of the other.

Stem cells have the ability to produce new specialized cells. This means that in certain conditions stem cells would be able to reconstruct the myelin material which surrounds the axons of the nerve. By producing myelin, the reconstruction of the myelin sheath could take place and would effectively reverse the problems caused by DM. Once the myelin sheath is fully functional the nerve would once again be able to send impulses to the body with the efficiency it did before the onset of DM.

To achieve this, stem cells would first be taken from the patient. This would mean an exact DNA match of the proteins in the stem cells with the patients, avoiding the chance of rejection by the body. The next step would to be to suppress the patient's immune system. This could be done by using chemotherapy which works by damaging dividing cells. The treatment attacks the cells involved in the immune system, these cells are produced in the bone marrow. Once this has taken place, the harvested stem cells are injected back into the body. The cells will multiply and begin to repair damage in the body. Recognizing the damaged tissue of the nervous system, the stem cells will divide to produce Oligodendrocytes (specialized cells which wrap around the axon forming

myelin) and will regenerate the myelin sheath, in turn restoring the central nervous system back to its healthy state.

This is taking a major leap in scientific work, and as yet would be impossible to trial as the consequences could be disastrous. Cells are living things and so can not be administered like a drug; their activity in the body is still ambiguous due to the difficulty of replicating those exact conditions in laboratory trials. However, because of the ever improving understanding of genetics, these techniques are becoming more and more realistic.

I predict that eventually, the stem cells taken from the patient for transplant would be ordinary skin cells; this would eliminate the need for any invasive surgery and reduces stress on the animal, an important factor to consider when treating a dog with DM as surgery and stress can aggravate the condition. These skin cells can be coaxed to revert back to pluripotent stem cells, this would be achieved by genetic modification and specific growth conditions. This method of obtaining stem cells avoids the ethical factors which complicate embryonic stem cell usage, and are a lot easier to obtain, especially in the case of veterinary work. The culture of stem cells can then be manipulated to produce neural cells, specifically Oligodendrocytes. By injecting the Oligodendrocytes into the lumbar spine (the source of damage caused by DM) the neurons could be restored and the effects of DM reversed.

At this point in time I can imagine two courses of treatment for DM sufferers. The first being the injection of Oligodendrocytes into the spine would be a constant treatment, in which the patient would be injected on a regular basis. The regularity and dosage of these treatments would depend on the severity of the particular patient's condition, and the outcome of previous treatments and progress. This course of treatment would prevent the progression of the disease and possibly even decrease the previous damage.

The second scenario would be a better alternative, but may take scientists longer to perfect. In this case the injected cells would be actual stem cells, these would go on to produce the neural cells whilst already inside the body. The newly injected stem cells would be cultivated so that they do not display the problems of over immunity which was evident whilst in the body. Simply put, they would no longer 'attack' the patients own cells, but instead only carry out the normal task of protecting the body from pathogens. The new cells injected into the patient would effectively 'reset' the patient's immune system, resulting ultimately in a cure for the disease.

To make the process safer, if scientists can create a way of destroying only the specific lymphocytes in the blood which are causing the damage, the course of treatment before the transplant would be much less severe and greatly reduce the risk of infection. The transplanted cells would therefore only replace the malfunctioning lymphocytes. This would improve the treatment in many ways. Firstly the patient would be at a much smaller risk of infection and other diseases during the course of the treatment as the dog would have some natural immunity throughout the process. This is a major advantage as it is incredibly difficult to keep a dog quarantined and protected from sources of

pathogens. It also would reduce the recovery time, as well as making the treatment less toxic to the patient as lower doses of chemotherapy would be used. It may also reduce the cost of extra medication such as antibiotics which are used during the periods of low immunity in the dog due to chemotherapy or drug treatment.

We can see that the future of stem cell use could be most beneficial to both pets and their owners, and my ideas are only a small sample of what we may be able to expect of new veterinary medicine.

Conclusion

The future of stem cell research is an overwhelming prospect with so many possibilities looking promising. However these techniques could take years to accomplish, and we cannot predict what challenges may lie ahead.

Already research has been significantly affected by the ethical debate surrounding embryonic stem cell use. Pro-life campaigners argue that embryonic stem cells research is ethically wrong and should be made illegal, whilst scientists argue that experiments need to be carried out on all stages of development in order to fully understand these cells and work out how we can manipulate them to act in specific ways. Alternative methods of creating embryonic stem cells are being trialed in order to avoid these ethical issues. One of these is the use of an ovum which has been genetically 'rigged' to start dividing without fertilization by a sperm. As the developing embryo needs some genes from a sperm cell to ensure development, these cells will die within a few days, meaning they are not capable of independent human life. This, scientists feel, will avoid the ethical debate and will enable them to practice research on these special embryos. Other methods which side step ethical regulations are constantly being tested.

Cost is also an important consideration. Although stem cell use could potentially save millions in the future, the cost of research and initial treatment is great, and one that most people are unwilling or unable to pay. As the technology progresses we can possibly expect prices to lower, however this seems quite a distant prospect at the moment. The expense of the research and application of this technology will undoubtedly slow down the progress being made, especially in veterinary medicine where funds are significantly lower than in human medicine, although it is encouraging to remember that the work in one area will always be useful to the other.

The difficulty with stem cell technology is that you are working with living cells; their nature is adaptable and unpredictable. Researchers cannot guarantee the way in which they will react, and may never understand fully the reasons they work in the way they do. This results in having to take risks and could potentially lead to dangerous situations. However, if we consider the possibilities this research might open up to medicine, these are risks many of us are willing to take.

I feel that the future of stem cell technology will greatly improve the treatment of DM and other immune related disorders. Using these fascinating units of life, we could potentially 'reprogram' our bodies and so reverse the effects of disease. This would be a

major leap in medicine, but one which I believe may be a possibility in the future of scientific research.

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