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How can Stem Cells be used to treat type 1 Diabetes?

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Abstract

This article will explore the use of stem cells to treat type 1 diabetes. I will outline information about the disease itself, before explaining what the different types of stem cells are. Then I will discuss how the different types of stem cells can be used to treat type 1 diabetes, and debate some of the ethical issues associated with the use of stem cells.

Introduction

Type 1 Diabetes Mellitus is a disease estimated to effect between 11-22 million people worldwide[1] , accounting for 5-10% of all cases of diabetes (the others being type 2 and gestational diabetes).[2] Every year, around 80,000 children worldwide develop the disease.[3] Furthermore, type 1 disease is estimated to cost the NHS £1 billion per year.[4] Various studies are being conducted into the use of different types of stem cells to treat type 1 diabetes.

What is Type 1 Diabetes?

Type 1 Diabetes Mellitus (T1DM) is a metabolic disorder leading to chronic hyperglycaemia (this is where the blood glucose level is abnormally high). It results from the autoimmune destruction of the beta cells of the islets of the Langerhans in the pancreas. Beta cells are the cells which produce insulin, which is the hormone which lowers the blood glucose level[5] – this means that people with T1DM are insulin-deficient, and thus can't lower their blood glucose level. T1DM usually develops in children, although the exact cause isn't known. The most common symptoms of diabetes are polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). There is no cure[6] – however, if left untreated, T1DM can lead to serious chronic complications.[7] The main 3 chronic complications arise from microangiopathy (damage to small blood vessels) due to the high blood glucose concentrations. The endothelium of the vessels become thicker in order to take in more glucose. More glycoproteins form on the surface of the endothelial cells and so the blood vessels become thicker but weaker. They then leak and bleed, so certain areas of the body do not get enough blood. Diabetic retinopathy occurs when there is a lack of blood going to the retina. It can cause macular edema (swelling of the macula) and, ultimately, blindness.[8] Diabetic nephropathy (damage to the capillaries in the kidney glomeruli) can lead to chronic renal failure, eventually requiring dialysis. Finally, diabetic neuropathy, the most common of the complications, is damage to nerves in the body, affecting movement, touch, and the autonomic nervous system (the nerves serving vital organs which control important functions e.g. heart rate, respiration rate and digestion). Furthermore, diabetes doubles the risk of cardiovascular disease.[9]

What are Stem Cells?

Stem cells are undifferentiated cells that have the ability to differentiate into specialised cells. Stem cells in mammals fall into 2 main categories: embryonic stem cells, which are found in embryos, and adult stem cells, which are found in different tissues in the body. There are 2 properties of stem cells which make them what they are: firstly 'self-renewal'. Stem cells have the capacity to divide multiple times whilst maintaining their undifferentiated state. There are 2 mechanisms by which this occurs. The first is obligatory asymmetric replication, where the stem cell divides into one mother cell, which is identical to the original stem cell, and a second cell, which is differentiated, called a daughter cell. The second mechanism is stochastic differentiation, where the stem cell divides into daughter cells that are differentiated, and then another stem cell divides by mitosis to produce two more identical stem cells. The second property is its potency. Different types of stem cells have different potencies, which is the stem cell's ability to differentiate into other types of cell. The two main types of stem cells that are being researched for their potential use in diabetes are: human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). Both of these types of cells are pluripotent – that is, they can differentiate into nearly any type of body cell.[10] hESCs are derived from a blastocyst (a structure formed during the early development of mammals which later develops into the embryo), whereas iPSCs are directly derived from somatic (adult) cells.[11] This is one advantage to the use of iPSCs – they bypass many ethical issues and controversies surrounding the use of hESCs as their production does not include the destruction of human embryos. iPSCs can also be made from a patient's own somatic cells and so there is little or no risk of immune rejection. Other types of stem cells have different potencies – there are multipotent stem cells, such as the ones found in adipose tissue. These are stem cells

which can differentiate into more than one type of cell but still a limited number.

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Fig. 1: How are different stem cells formed?

A diagram showing the different stages of stem cell differentiation.

How can hESCs be used to treat type 1 diabetes?

Researchers at Harvard University have been successful in developing a technique to generate large quantities of glucose-responsive beta cells from hESCs in vitro. The hESCs are induced into definitive endoderm cells (one of three types of cells in the very early human embryo) and then into early pancreatic progenitor cells (which are cells that are similar to stem cells, but are closer to their final target cell) expressing PDX1+ and NKX6-1+ (these are proteins required for the development of beta cells). The cells were then transplanted into mice, where after 3-4 months, they developed into functional beta cells. These are very similar to bona fide beta cells (normal beta cells found in people without diabetes) – they have the flux Ca^{2+} response (the mechanism used to secrete insulin), and they can package insulin into granules for secretion, just as they do in humans. When exposed to glucose in vitro, they secreted insulin in quantities comparable to adult beta cells. Additionally, when tested in mice, human insulin was secreted into the serum, ameliorating the hyperglycaemia in the mice.[12] Currently, 40 patients are undergoing a clinical trial to test this potential treatment.[13] A pancreatic endoderm cell that has been derived from the hESCs is implanted under the skin of the patient, and then differentiates further into mature pancreatic beta cells, which can synthesise and secrete insulin, thus consequently regulating the blood glucose levels.[14]

What are the ethical issues associated with using hESCs?

As ever with [embryonic] stem cells, there are certain ethical issues which must be considered. Previously, unused embryos from IVF (in vitro fertilization) were donated for research.[15] However, embryos are now being produced for research purposes – these can't be implanted into the womb anyway. Some organisations, such as the Catholic Church, and other religious organisations, maintain that the use of embryos is tantamount to murder according to their belief that life starts at conception.[16] However, such ethical issues need to be balanced against the benefits of the research and the treatment – in this case, the millions of people around the world who suffer from type 1 diabetes will have something to gain from this research.

How can iPSCs be used to treat type 1 diabetes?

Firstly, the somatic cell must be reprogrammed into an iPSC. In the past, somatic cells were reprogrammed by transferring their nuclei into oocytes (immature female egg cells). This would change the gene expression and therefore the cell fate. In 2006, research showed that mouse fibroblasts could be converted to iPSCs by the introduction of 4 transcription factors (proteins involved in the production of messenger RNA from DNA) – Oct3/4, Sox2 (which are both involved in the self-renewal of undifferentiated hESCs), c-Myc, and Klf4 (which regulates proliferation (cell growth), differentiation, apoptosis (programmed cell death) and somatic cell reprogramming). These cells had the same morphology (shape) and growth properties of embryonic stem cells and when they were injected into blastocyst, the iPSCs contributed to the development of the mice's embryos. Furthermore, when the iPSCs were transplanted beneath the skin, tumours were formed containing tissues from all three germ layers.[17] This discovery had 2 main issues. Firstly, the method was very inefficient. Secondly, there were some variations in gene expression profiling between iPS cells and ES cells.[18] Additionally, 2 of the factors used (c-Myc and Klf4) are oncogenic and consequently 20% of the mice developed tumours. However a later study showed that the process could be repeated without c-Myc. This process is longer and less efficient but the mice didn't develop cancer.[19]

After their success using mouse cells, Yamanaka and his team developed iPSCs from human dermal fibroblasts by using the same 4 transcription factors. The human iPSCs had similar properties to hESCs: morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes, and telomerase activity. Furthermore, these cells could differentiate into cell types of the three germ layers in vitro and in tumours.[20]

A study in mice showed that insulin-producing cells derived from mice iPSCs improved hyperglycaemia. Streptozotocin is a drug which is toxic to beta cells [21] – this was injected into the mice to induce diabetes. When the non-fasting blood glucose levels were high enough (greater than 13.9 mM on 2 consecutive days), 5×106 of the insulin-producing cells were transplanted into the left subscapular renal space. Within 2-4 days, the blood glucose levels were normalized, whereas in the control group, the

mice remained hyperglycaemic with blood glucose levels of over 18.3 mM. Normoglycaemia was defined as 7.91±0.26?mM for this study – this was maintained for up to 35 days after the cells were transplanted.[22] Although this study shows that the use of iPSCs to treat diabetes may be effective, it was not long enough for any long-term effects to be witnessed. As shown by Yamanaka's study, tumour formation is an issue associated with using stem cells. Long-term data would be required to prove whether that is the case with this study.

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Conclusion

There are many studies being led into the potential use of stem cells, particularly induced pluripotent stem cells and human embryonic stem cells, for the treatment of type 1 diabetes mellitus. Such studies have both advantages and disadvantages but each new discovery is bringing the researchers closer to a long term treatment or cure for type 1 diabetes. There are also studies being lead into treatments and cures for type 2 diabetes – the reason that the aforementioned cures will not work for patients with type 2 diabetes is because they already produce insulin, however their cells have become resistant to the hormone. Stem cells are also being researched for their use in potential for many other conditions, such as heart disease. Stem cells provide an interesting future for medicine and soon they are likely to become a significant part of mainstream medical treatment.

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