Regenerative medicine – a potential cure for type 1 diabetes?

Health & Medicine, Diabetes

Diabetes is a chronic disorder characterised by a patient’s blood glucose concentration being above normal levels. The increased concentration of blood glucose can lead to more serious secondary health conditions such as, blindness, cardiovascular disease, stroke and lower body amputations. There are 2 types of diabetes type 1 and 2. Type 1 is an autoimmune disorder where β-cells are destroyed. Regenerative medicine is the process of regenerating destroyed tissue usually with stem cells. With the growing number of diabetes cases this essay aims to explore the possible options to reverse the destruction of β-cells with the use of stem cells.

Diabetes

In 2015 the international diabetes federation (IDF) estimated that 415 million people suffer from T1DM or T2DM. The is estimated to increase up to 642 million people by 2040. The IDF also estimated that in 2015, 5 million deaths per year worldwide were due to DM. This ranks DM as one of the top 3 non-communicable diseases (NCD) that lead to death after neoplastic diseases (comprising of 8 million deaths per year) and Ischaemic heart disease (comprising of 5. 7 million deaths per year) (IDF Diabetes Atlas 7th edn, 2016).

The mortality rate for DM has only recently increased to 5 million deaths per year as it was only 2 million deaths per year in 2000 (Roglic et al., 2005). The increase in both the incidence and mortality of DM has mainly been seen in developing countries all across the world. More developed countries such as Sweden (Tancredi et al., 2015) and the USA (Gregg et al., 2014) have

seen a decrease in mortality due to improved treatment and management for the disorder (IDF Diabetes Atlas 7th edn, 2016).

The two most prominent types of diabetes mellitus (DM) are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM occurs due to an inability to regulate blood glucose as the β-cells of the pancreas have become destroyed. T2DM is caused by an insufficient or a lack of response to insulin brought on an unhealthy lifestyle (Hall and Guyton, 2011). T1DM is a result of an autoimmune response against the β-cells of the pancreas. Currently treatment for DM is to counteract hyperglycaemia by injecting insulin into the blood stream in order to lower the blood glucose concentration (Peng et al., 2018).

The main reasons that DM leads to mortality is not due to the increase in the blood glucose concentration but the complications that arise from it. Even with treatment DM can lead to both macrovascular and microvascular complications. The macrovascular problems arise from log term damage to arteries leading to cardiovascular decisisae, coronary artery disease, stroke and lower extremity amputations. The microvascular complications from DM occur due to the impairment of capillaries and other smaller blood vessels leading to diabetic nephropathy, neuropathy and retinopathy (Gregg, Sattar and Ali, 2016). Even with treatment these complications can arise due to the chronic exposure of hyperglycaemia. with this in mind he best way to counteract T1DM is not to treat the disorder with insulin but to replace the destroyed β-cells of the pancreas and restore it to its normal metabolic function. Currently the method that shows the most promise results in

regenerating destroyed tissue is the use of stem cells by grafting new β-cells onto the pancreases.

Stem cells

Stem cells are cells capable of differentiating into several different cells types and have been considered to have a therapeutic potential against DM. Cells such hematopoietic stem cells found in the bone marrow have the ability to differentiate into several types of blood and immune cells but no other kinds (Hall and Guyton, 2011). This ability to differentiate into a multiple specific cell types is referred to as a multipotent stem cell. Pluripotent stem cells unlike multipotent stem cells have the ability to differentiate into any type of cell (Hall and Guyton, 2011). Embryonic stem cells (ESC) are a type of pluripotent stem cell that is found within the inner cell mass of a blastocyst which can differentiate into any cell type for the species (Nelson et al., 2009). As seen in table 1 there ae several types of stem cells currently begin researched to be potentially grafted onto the pancreas to replace the destroyed β-cells. Even though ESC presents the best option for grafts they have an enormous ethical concern due to them having to be harvested from human blastocyst. Due to the enormous ethical concerns linked with ESCs many researchers are turning to other forms of stem cells such as induced pluripotent stem cells (iPSC) for its pluripotent nature and mesenchymal stem cells (MSC) for their immunomodulatory properties (Abdi et al., 2008).

iPSC are stem cells that are created by inducing somatic cell to enter a more primitive stem cell like state where it expresses a pluripotent nature. iPSC cells can be produced by the use of four different transcription factors (Klf-4, Sox-2, Oct-3/4 and c-Myc) (Takahashi and Yamanaka, 2006). Currently there have been no in vivo trials for humans suffering from T1DM and most in vivo trials have been made with non-obese diabetic (NOD) mice models. When the iPSC are differentiated into β-cells the main method of determining if a successful differentiations has occurred is to check for the expression of PDX1 and NKX6-1 from the β-cell (Hrvatin et al., 2014). Early in vitro differentiation attempts with human iPSC where not able to co-express PDX1 and NKX6-1 and resulted in β-cells that expressed both insulin and glucagon in unison while also having a poor recognition of glucose (Hrvatin et al., 2014). However, Pagliuca et al. (2014) where able to generate monohormonal β-cell from iPSC that secreted a similar concentrations of insulin as adult β-cell. The Cells created by Pagliuca et al. where grafted onto NOD mice models and saw a temporary reversal in hyperglycaemia and mimicked mice models that had transplanted human cadaver islet cells. The iPSC cells showed continued to produce insulin at 18 weeks after the transplant and had a lower mortality and morbidity than control mice.

Unfortunately, one of the major problems with iPSC is that they will still be targeted by the anti-human immunoglobulins that destroyed the β-cells originally (Chen et al., 2015). The main way to combat this autoimmune destruction is with immunosuppressive drugs witch will lead to a higher risk of neoplasia and infections (Chen et al., 2015). This adds to the already

existing danger of iPSC becoming cancerous and being aneuploidy (Schlaeger et al., 2014). Even though iPSC struggle with combating autoimmune destruction other stem cells appear to be able to handle this issue better.

MSC have shown to have beneficial immunomodulatory effects when used to treat T1DM. Both Bassi et al. (2012) and Li et al. (2010) showed that when adipose derived mesenchymal stem cells (AD-MSC) where tested in vivo in NOD mice. Inflammation around the pancreas decreased and suppressed T-helper cells which are the immune cells responsible for initiating the autoimmune response also reversing hyperglycaemia in 78% of the mice. Bassi et al. (2012) claimed this was due to an increase in TGF-β1 (a cytokine that dampens an autoimmune response in T1DM) and regulatory T-cell tregs (a compound found to inhibit self-reactive effector T-cells).

Additionally, when observed with GFP under microscopy AD-MSC did not divide into more β-cells, but it allowed already exciting β-cells began dividing showing the beneficial microenvironment provided by the AD-MSC (Kono et al., 2014). These beneficial immune responses were also replicated by taking the surrounding culture media of MSC and injected it into NOD mice without any of the MSC's (Gao et al., 2014).

Both iPSC and MSC have been showed to possess some form of therapeutic effects but unfortunately both these types of stem cell are still destroyed by autoimmunity. MSC's benefits when transplanted only appear to work up to 9 weeks and by 12 weeks the benefits are gone (Bassi et al). iPSC's do survive

longer than MSC but lack the Immune protective microenvironment, some suggestions to combat the autoimmune response would be to encapsulate the transplanted iPSC's in a semi permeable protective shell (Gao et al., 2014). Capsules containing iPSC's have even been coated with chemokines like CXCL12 which supress and repel T-cells. Unfortunately, these capsules do not fully protect the transplanted cells and lowers the surface area for nutrient exchange (Gao et al., 2014). Both of these stem cells showing promise in the treatment of T1DM but overcoming the autoimmune destruction by the immune system is still the biggest challenge facing these techniques.

Conclusion

With the ever-growing number of DM cases each year the economic and social stress of the disorder grows with it. T2DM can be avoided with a healthy lifestyle but there is unfortunately no current preventative method for the development of T1DM. The use of regenerative medicine to restore lost and destroyed tissue consistently been a promising form of treatment for T1DM but as there have been no human transplants of stem cells it is still hard to tell if it will work. NOD mice models have shown promising results for individual treatment options but they have never been able to fully counteract hyperglycaemia for extended periods of time. The use of perhaps several different regenerative treatments could be a beneficial option to explore. Combining the beneficial immune environment that MSC's provide with the strong differentiation of iPSC's which are encapsulated with chemokines to become immunologically invisible. The flexibility of stem cells

allows for many options for treatment but until human in vivo experiments begin there will still be many hurdles to overcome with reversing T1DM.