

## Mesenchymal Stem Cells for Type 1 Diabetes Treatment - A Review Article

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### ABSTRACT

Islet cell transplantation has therapeutic potential to treat type 1 diabetes, which is characterized by autoimmune destruction of insulin-producing pancreatic islet  $\beta$  cells. It represents a minimal invasive approach for  $\beta$  cell replacement, but long-term blood control is still largely unachievable. This phenomenon can be attributed to the lack of islet vasculature and hypoxic environment in the immediate post-transplantation period that contributes to the acute loss of islets by ischemia. Moreover, graft failures continue to occur because of immunological rejection, despite the use of potent immunosuppressive agents. Mesenchymal stem cells (MSCs) have the potential to enhance islet transplantation by suppressing inflammatory damage and immune mediated rejection. In this review we discuss the impact of MSCs on islet transplantation and focus on the potential role of MSCs in protecting islet grafts from early graft failure and from autoimmune attack.

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### Introduction

Type 1 diabetes mellitus (T1DM) is characterized by beta cells destruction therefore, the disability of producing insulin. It is well known how difficult it is for T1DM patients to take their daily insulin injections to maintain the glucose levels stable, or to adapt with the modern techniques such as insulin pumps that can't guarantee total recovery and an easy way of life, as well as the long term complications of these treatments [1].

Despite all of this, one method has the highest potential capability of succeeding which is the transplantation of pancreatic islets of Langerhans. This kind of therapy stays limited by numerous factors, such as the lack of donor pancreases [2].

Either the whole pancreas or pancreatic islets have been transplanted in clinical experimental trials. The first whole pancreas transplantation was performed in the 1960s and became more common in the 1980s. On the other hand, islet transplantation in the 1970s depended on islets derived from animal models and were effectively transplanted without the need of major surgery. Islet transplantation was first clinically used to treat human type I diabetes patients in 1989 [3].

### Islet transplantation: difficulties and challenges

At the times of introducing the first pancreatic islet transplantation in the 1980s, less than 10% of the treated patients remained insulin

independent only for 1 year. But this percentage increased in the 2000s when Edmonton tested new steroid-free immunosuppressive drugs on seven patients in a medical trial and all of them achieved insulin independence at 1 year.

There are two known sources for pancreatic islets, one from the patient's own pancreas (autotransplantation), and the other from a diseased donor's islets (allotransplantation). Islet autotransplantation is performed on chronic pancreatitis patients using islets extracted from their own pancreas as a means of preventing from later occurrence of diabetes [4].

Islet allotransplantation begins with selecting the appropriate pancreas from deceased donors, followed by the extraction, isolation, and purification of islets. The transplantation outcomes are affected by donor related factors such as: age, body mass index and the cause of death (cardiac or brain death) in addition to the duration of the ischemic cold storage [5].

### Difficulties of islet transplantation

While the duration of the ischemic cold storage presents itself as a crucial factor of the transplantation outcomes, its ability of improving the quality of islets used for transplantation is still unexplained.

In the early days of islet transplantation, the reasons of graft failure were unclear and confounded by the toxic  $\beta$ -cell immunosuppressive agents. Many studies proved that ischemic cold procedures with duration of more than 8 hours might result

in a decrease in islet yield. One way of avoiding such damage, is by keeping the procured pancreas in a solution containing high percentage of oxygen [6].

On the other hand, there are other difficulties related to the pancreas transplantations, such as the differences between the rates of diseased donors and recipients. Donors over 50 years are unsuitable to donate for transplantation according to some centers.

There are other pancreas related, like organ damage during the organ removal procedure, arterial damage, fatty appearance of pancreas (pancreatitis), lack of islets and all of these factors can lead to organ discard, which decreases the chance of successful transplantation. For example, in the UK less than 50% of patients proceed to transplantation [7].

### **MSCs: introduction and characteristics**

Newly introduced methods lead to an obvious decrease in the concerns related to embryonic or induced pluripotent stem cells for T1DM therapy. One of these methods is using mesenchymal stem cells (MSCs).

Many researches have been conducted on different types of stem cells, but scientists preferred utilizing MSCs because they can be isolated from many different sources like placenta, navel cord blood, cartilage and bone marrow. MSCs have many advantages over other types of stem cells; they are multipotent and have regenerative, low immunogenicity and high immunomodulatory properties. Unlike embryonic stem cells, MSCs do not face any ethical problems [8].

### **History**

Since the first discovery of bone marrow stromal cells by friedenstein et al. in 1968 they were identified as adherent, fibroblast like populations in adult bone marrow and capable of differentiating into other cells of mesenchymal lineage such as fat and cartilage [9]. In 1991 Caplan was the first to name them mesenchymal stem cells (MSCs) to refer to their multipotent properties [10].

### **Properties**

An early study valuating the function of MSC in vivo explained systemic infusion of allogeneic Bone Marrow derived from animals. After adding host MSCs, Nauta et al. demonstrated the occurrence of significant long-term engraftment enhancements associated with endurance to donor and host antigens [11].

MSCs are derived from different tissues such as bone marrow, adipose tissue, nervous tissue, umbilical cord, amniotic fluid, placenta and dental pulps. They have the ability to differentiate into lines of mesenchymal tissues including bone, fat, and cartilage. Unproved suggestions claim that these cells can differentiate into other types of tissues and including cardiomyocytes, lung epithelial cells, neurons, hepatocytes, and pancreatic islets [12, 13].

MSCs transplantation can theoretically increase beta cell mass via the following effects:

1. Beta cell replacement through in vitro or in vivo differentiation.
2. Local microenvironment modification by production of cytokines, chemokines and factors to stimulate endogenous regeneration.
3. Reduction or prevention of autoimmunity to beta cells [14].

Although several MSC transplantation studies have clearly shown the outcome of controlled glucose metabolism, there

have been observations of decreased insulin resistance as well as enhanced beta cell function effects. Moreover, the mechanisms of MSC treatment for T2DM still has not been well understood. Some studies have suggested that the immunomodulatory and inflammatory effects of MSCs are what contribute to the resulting reduction of insulin resistance [15, 16].

### **Laboratory isolation of MSCs**

The most commonly isolated MSCs are from bone marrow, where bone marrow aspirates are gradient centrifuged to isolate mononuclear cells, followed by in vitro culture. Although MSC preparations generated ex vivo appear homogenous under the light microscope, they probably compromise a heterogeneous group of progenitor cells and, on most occasions, do not fulfill strict criteria for a stem-cell entity at a single cell level (ie, self-renewal and multi-lineage differentiation capacity) [12].

Kerby et. Al assessed the role of alginate encapsulation and co-transplantation of mouse islets and kidney MSCs in vitro. Encapsulated islets alone or co-encapsulated with MSCs (islet+MSC) were transplanted intraperitoneally into diabetic mice, and blood glucose concentrations were monitored. They demonstrated that islets co-encapsulated with MSCs in vitro had increased glucose-stimulated insulin secretion.

After six weeks 71% of the co-encapsulated mice were cured compared with 16% of the islet-alone group [17].

### **MSCs and immune system**

Recent studies clearly showed that beside the MSCs ability to differentiate and engage in tissue repair, they have compelling immunomodulatory properties. While the MSCs produce their solvent factors, they can modify the excretion profile of the dendritic cells (DCs) creating an expanded production of IL-10, which is an anti-inflammatory cytokine, and a lower production of the factors that can inhibit T cell production [18, 19].

These exclusive immunomodulatory functions, made the MSCs approachable for both allogeneic and autologous transplant investigations. For the identical reason, they have been suggested as a treatment for autoimmune diseases, and also for the treatment of empirical models of some autoimmune diseases such as (RA); rheumatoid arthritis, (SLE) systemic lupus erythematosus [20] and (MS) multiple sclerosis [21-24].

MSCs have shown several immunomodulatory effects after being tested on a variety of animals connected to alloreactive immunity (which is the body's immune reaction to organ and stem cell transplantation), tumor immunity or auto immunity.

One early in vivo study showed that systemic infusion of allogeneic MSCs from baboons' bone marrow extended the allogeneic skin's survival up to 11 days in comparison with 7 days in animals not given MSCs [25]. Furthermore, we have currently showed that the infusion of syngeneic host-derived MSCs conducted the decrease rejection of allogeneic stem cell grafts in a murine allogeneic bone marrow transplantation model [26]. Nevertheless, the possible immunological mechanisms involved with these observations were not referred to.

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