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Immuno-isolation of MSCs: Clinical application in diabetic therapy

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ABSTRACT

Basic research on cell therapy strategies for diabetes using stem cells has considerably advanced in the last decade. The generation of functional beta cells from human pluripotent stem cells is possible, and these can replace the traditional pancreatic islet transplantation to treat diabetics. In the present review we focused on various strategies to be followed for successful transplantation of MSCs in diabetic therapy.

1. Introduction

Diabetes involves the loss of function and/or absolute number of insulin-producing β-cells in pancreatic islets. Current accepted therapy for diabetes includes oral medication, insulin replacement and pancreatic islet transplantation [1]. Allogenic islet transplantation is currently being investigated as a potential cure. However transplanted islets experience hypoxia and inflammation-mediated immune response, leading to early damage and subsequent failure of the graft.

Graft-versus-host disease (GVHD) remains a significant potentially life-threatening complication of allogenic transplantation. Since the discovery of the human leukocyte antigen (HLA) system over 50 years ago, have clarified the nature of HLA variation between transplant recipients and donors as a chief etiology of GVHD. The discovery of HLA system increased the availability of suitable donors to the patients who are in need of an organ for transplant [2]. Because of scarcity of matched donors researchers are working on stem cells to use them as an alternative source in cell based therapies to lower the morbidity and mortality for those suffering from end stage or severe pancreatic dysfunction.

Stem cells are the potential unlimited source of cells for transplantation, encapsulation of stem cells provides a physical barrier between graft and host and can inhibit the formation of teratomas, providing a better platform for clinical application [3,4].The promising features of mesenchymal stem cells (MSCs), including their regenerative properties, Immunomodulatory and ability to differentiate into diverse cell lineages, have generated great interest among researchers on cell-based therapies for various diseases. MSCs, can be isolated from several tissues, exhibit a strong capacity for replication in vitro, and can differentiate into osteoblasts, chondrocytes, and adipocytes. MSCs show tremendous potential for the treatment of immunological and non immunological disorders [5, 6]. Though a uniform mechanism governing MSC-based therapy has not yet been discovered, available data has revealed several working models that promote the beneficial effects of MSCs [7].

The longevity of the transplanted cells and the functional performance depend on several strategies like-

- ***Cell mass required for transplantation:*** The total number of islets present in an adult human pancreas is approximately 1 million, thus, one intact pancreas is adequate to achieve glucose homeostasis in a diabetic recipient. Thus two to four donor pancreases are required to achieve sufficient cell number [8].

- ***Potential sites for transplantation:*** The transplantation site should have the ability to support and nourish the cells immediately after transplantation and it should be easily accessed with minimal risks to the patient. The site should also provide sufficient space to accumulate the cells volume equivalent to approximately 3 to 5 cc of fluid containing naked cells or 6 to 10 cc of encapsulated islets. Sites reported to allow successful islet transplantation were liver, spleen, pancreas, omentum to accumulate large grafts, immunoprivileged sites to prolong allograft survival such as the testes and kidney capsule [9, 10, 11, 12].

- ***Immuno-isolation of cellular grafts:*** The principal aim of immuno isolation is to isolate the graft from the host's macrophages, large molecules of the immune system, such as antibodies and complements, which can damage the graft using a selectively permeable physical barrier between the two [13].

- ***Microencapsulation:*** Microcapsules are characterized by dimensions of the order of hundreds of microns or less. Alginate, polycation poly-L-lysine (PLL) layered on alginate, poly-Lorinthine (PLO) coating, polyelectrolyte coatings, barium cross-linking of alginate, hydroxyethyl methacrylate-methyl methacrylatecoating has been successful in microencapsulated cell therapy for short and intermediate application. In spite of the aforementioned efforts to address the key challenges associated with alginate encapsulation, there are fundamental drawbacks in its use for long term cell encapsulation application such as cell therapy for chronic diseases [14-22].

- ***Macroencapsulation:*** Macrocapsules are characterized by dimensions of the order of 0.5–1.5 mm in diameter and up to few cm in length. The large encapsulation volume of macrocapsules facilitates high cell loading densities. Few studies reported that polyacrylonitrile-polyvinylchloride (PAN-PVC) macrocapsule led to the development of islet implants which were shown to reverse hyperglycemia in dogs and rodents over several months [23-26].

- ***Bio printing:*** Cells were seeded into a bio absorbable alginate hydrogel matrix before 3D printing. Bio printing of a nanofiber matrix embedded with encapsulated cells could be used to create a smart "cell sheet" with desired pore sizes as a ready-to-use cell source. The advancements in tissue engineering and regenerative medicine have made it possible to regenerate damaged organs or tissues into functional organ or tissue with the help of 3D bio printing [27, 28].

- ***Encapsulated MSCs in Diabetes Therapy***: One of the first clinical trials using encapsulated allogenic islets by Calafiore et al. gave a hope that encapsulated islets can be viable post transplantation [29]. Preclinical studies reported co-transplantation of MSCs and islets which improved graft vascularisation thereby increasing the chances of graft survival for longer time in vivo [30,31,32].

2. Conclusion

Transplantation of encapsulated MSCs has the potential to restore glucose homeostasis in diabetes without the need for immunosuppression. But there is a need to focus on several major obstacles like immune responses. With proper cell type and biomaterial will hopefully provide a clinically useful means of β-cell replacement to reduced morbidity and mortality and the potential for a more normal lifestyle for the countless people diagnosed with diabetes every year.

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