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INDUCED PLURIPOTENT STEM CELLS A NEW HOPE FOR DIABETIC PATIENTS: A REVIEW

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ABSTRACT

A search for a permanent cure for diabetes mellitus is in progress with numerous outstanding discoveries over the precedent few decades. Out of numerous outstanding discoveries the potential of pancreatic stem cells to renew functional β cells is a current important subject of research. Induced pluripotent stem cell tools can turn out to be an optional approach to produce insulin-producing cells in a secure and proficient way with keeping composition, similar to that of the resident β cells. Induced pluripotent stem cell technology is a technique used to yield embryonic-like stem cells. Induced pluripotent stem cell technology can generate completely functional β-like pancreatic cells. This new stem cell technology fetches innovative potential to use stem cell therapy for diabetes mellitus. This review gives an overview on recent advances in use of Induced pluripotent stem cell technology in diabetes mellitus.

INTRODUCTION:

Budding biotechnologies and advancements in stem cell biology have made the vision of tissue regeneration a potential tool. This technology can be used for the creation tissue. Stem cell biology is at present one of the stimulating field of biomedical research. Embryonic stem cells are totipotent cells that can be derived from the inner cell mass of a blastocyst during gastrulation. These cells can form embryoid bodies. Embryonic stem cells represent a potential source of cells can be used to somatic and germ line cells of the fully developed organism. These exceptional cell have significant utility in a variety of clinical applications. having capacity for self-renewal, proliferation, differentiation, and wide distribution. [1]

Pluripotent stem cells can be used to learn embryonic growth and cell differentiation and present a large amount expectation for regeneration of tissues. Induced pluripotent stem cells are considered important by scientist because they avoid the usage of embryonic material and can be patient modified. [2]

In recent years, stem cell therapy has become a very promising and advanced scientific topic.The development of treatment methods has evoked great expectation.This paper is a review focused on the expectation and reality of stem cell.Stem cell (SC) therapies hold remarkable promise for many disease, but there is a significant gulf between public expectations and the reality of progress toward clinical application

Stem cell biology

A blastocyst is formed after the fusion of sperm and ovum fertilization. Its inner wall is lined with short-lived stem cell, namely,embryonic stem cells. Blastocysts are composed of two distinct cell types; the inner cell mass (ICM), which develops into epiblasts and induces the developments of a foetus, and the trophectodem (TE).Blastocysts are responsible for the regulation of the ICM microenvironment. The TE continues to develop and forms the extraembryonic support structures needed for the successful origin of the embryo, such as the placenta.Astge TE begins to form a specialized support structure, the ICM cells remain undifferentiated,fully pluripotent and proliferative.pluripotency of stem cells allows them to form any cell of the organism.Human embryonic stem cells (hESCs) are derived from the ICM. During the process of embryogenesis, cells form aggregations called germ layers: endoderm, mesoderm and ectoderm(Fig.1), each

eventually giving rise to differentiated cells and tissues of the foetus and, later on, the adult organism.AfterhESCs differentiate into one of the germ layers, they become multipotent stem cells, whose potency is limited to only the cells of the germs layer. This process is short in human development. After that, pluripotent stem cells, and their key abilities are proliferation by the formation of the next generation of stem cell and differentiation into specialized cells under certain physiological conditions.signals that influence the stem cell specialization process can be divided into external, such as physical contact between cells or chemical secretion by surrounding tissue, and internal, which are signals controlled by genes in DNA.Stem cell also act as internal repair systems of the body. The replenishment and formation of new cells are unlimited as long as an organism is alive. Stem cell activity depends on the organ in which they are in; for example, in bone marrow, their division is constant, although in organs such as the pancreas, division only occurs under special physiological conditions.

Stem cell functional division

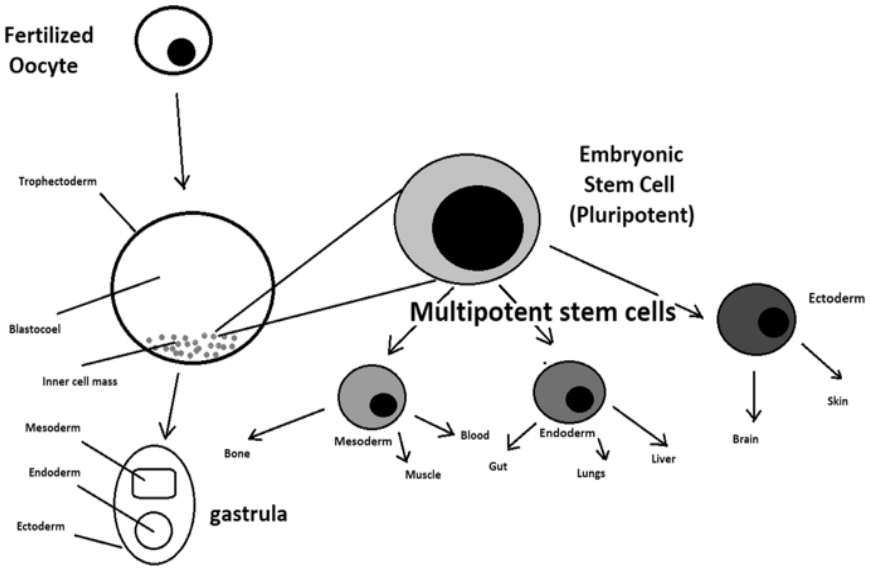

Fig. 1: stem cell functional division

Whole-body development

During division, the presence of different stem cells depends on organism development. Somatic stem cell ESCs can be distinguished. Although the derivation of ESCs without separation from the TE is possible, such a combination has growth limits. Because proliferating action are limited, co-culture of these is usually avoided.

ESCs are derived from the inner cell mass of the blastocyst, which is a stage of pre-implantation embryo ca. 4 days after fertilization. After that, these cells are placed in a culture dish filled with culture medium. Passage is an inefficient but popular process of subcul-turing cells to other dishes. These cells can be described as pluripotent because they are able to eventually differ-entiate into every cell type in the organism. Since the be ginning of their studies, there have been ethical restrictions connected to the medical use of ESCs in therapies. Most embryonic stem cells are developed from eggs that have been fertilized in an in vitro clinic, not from eggs fertilized in vivo.

Somatic or adult stem cells are undifferentiated and found among differentiated cells in the whole body after development. The function of these cells is to en- able the healing, growth, and replacement of cells that are lost each day. These cells have a restricted range of differentiation options. Among many types, there are the following:

Mesenchymal stem cells are present in many tissues. In bone marrow, these cells differentiate mainly into the bone, cartilage, and fat cells. As stem cells, they are an exception because they act pluripotently and can specialize in the cells of any germ layer. Neural cells give rise to nerve cells and their supporting cells—oligodendrocytes and astrocytes. Haematopoietic stem cells from all kinds of blood cells: red, white, and platelets. Skin stem cells form, for example, keratinocytes, which form a protective layer of skin.The proliferation time of somatic stem cells is longer than that of ESCs. It is possible to reprogram adult stem cells back to their pluripotent state. This can be per-formed by transferring the adult nucleus into the cyto- plasm of an oocyte or by fusion with the pluripotent cell. The same technique was used during cloning of the famous Dolly sheep.[3-6]

Diabetes mellitus overview

Diabetes mellitus (DM) is a global emerging disease with progressive incidence worldwide. There were 171 million people in the world suffering with DM in 2000 and is projected to increase to 366 million people by 2030. Two distinct types of DM are well characterized, i.e. type 1 (T1DM) and type 2 (T2DM), in which T1DM results from progressive β cell destruction mostly due to autoimmunity and T2DM that is mainly caused by a combination of insulin resistance and inadequate insulin secretion. As a consequence, β cell mass is reduced to about 50% in the later stages causing 20–30% of T2DM patients to initiate insulin therapy. T1DM and T2DM are associated with long-term major microvascular and macrovascular complications despite intensive

insulin treatment. Matching subcutaneous insulin dose to control blood glucose level is challenging for both diabetic therefore it is difficult to maintain a long-term control. Considering these problems have lead to the initiative of β cell replacement by islets allograft transplantation. [7-8]

Need of regeneration of functional β cell

Regeneration of functional β cell mass from human stem cells represent the most promising approach for cure in T1DM nowadays. Patients with T2DM who require exogenous insulin may also benefit from β cell replacement therapy, considering the occurrence of progressively worsening β cell failure. The efforts to regenerate functional β cells from adult pancreatic stem cells have been widely explored. However, the progress is slow due to the lack of a phenotype definition for pancreatic stem/progenitor cells. The use of human embryonic stem cells (ESCs) is limited by ethical issues and a great risk of tumorigenicity. At present, cellular reprogramming through induced pluripotent stem (iPS) cell technology represents a remarkable breakthrough in the generation of insulin-producing pancreatic β cells. [9-12]

Through a remarkable technology of so-called *cellular reprogramming*, it is now possible to generate pluripotent stem cells from terminally differentiated cells (e.g. skin fibroblasts) simply by modifying their epigenetic profiles. This can be achieved by deliberately inducing the expression of pluripotency-associated genes (i.e. turning on) while repressing the expression of differentiation-associated genes (i.e. turning off) with the end result is the reacquisition of embryonic traits . Subsequently, the resulting pluripotent stem cells can be directed to re-differentiate into cells of all three germ layers, thus crossing the cell lineage boundaries (fibroblasts to insulin-producing β cells). [13]

Current research on use of induced pluripotent stem cell in Diabetes mellitus

Park, I. H et al., summarized disease-specific stem cells in which they explained Tissue culture from diseased patients is an invaluable resource for medical research but is largely limited to tumor cell lines or transformed derivatives of native tissues. Here we describe the generation of induced pluripotent stem cells from patients with a variety of genetic diseases

with complex heritage and disease-specific stem cells offer an unparalleled prospect to review both ordinary and pathologic human tissue development in vitro, by this means facilitates disease study and drug development.[14]

Godfrey, K. J et al., provided insight on Stem cell-based treatments for Type 1 diabetes mellitus in which they explained research involving stem cells is at once promising and inconsistent, bone marrow-derived mesenchymal stem cell transplantation seems to offer the most compelling evidence of efficacy. These cells have been demonstrated to increase endogenous insulin production, while partially mitigating the autoimmune destruction of newly formed β-cells. [15]

Maehr, R., et al., reported generation of pluripotent stem cells from patients with type 1 diabetes They explained pluripotent cells generated from patients with T1D would be useful for disease modeling. They also explained that induced pluripotent stem cells can be generated from patients with T1D by reprogramming their adult fibroblasts. [16]

Rezania, A. demonstrated Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells in which they performed transplantation of insulin-secreting cells derived from human embryonic stem cells has been proposed as a therapy for diabetes. S7 cells were generated but found not fully equivalent to mature beta cells, their capacity for glucose-responsive insulin secretion and rapid reversal of diabetes *in vivo* makes them a promising alternative to pancreatic progenitor cells or cadaveric islets for the treatment of diabetes.[17]

Hansson, M., & Madsen, O. D provided opinion on Pluripotent stem cells, a potential source of beta-cells for diabetes therapy they elaborated the reconstitution of a functional beta-cell mass by transplantation of isolated islets can restore euglycemia in the absence of insulin treatment, a shortage of donor material is one of the factors preventing the general use of cell replacement therapy for the treatment of type 1 diabetes mellitus (T1DM). [18]

Bouwens, L., Houbracken, I., & Mfopou, J. K explained use of stem cells for pancreatic regeneration in diabetes mellitus as per them the endocrine pancreas represents an interesting arena for regenerative medicine and cell therapeutics. One of the major pancreatic diseases, diabetes mellitus is a metabolic disorder caused by having an insufficient number of insulin-

producing β cells. Replenishment of β cells by cell transplantation can restore normal metabolic control. [19]

Kawser Hossain reviewed recent advances in disease modeling and drug discovery for diabetes mellitus using induced pluripotent stem cells in which they explained Diabetes mellitus (DM) is a widespread metabolic disease with a progressive incidence of morbidity and mortality worldwide. Despite extensive research, treatment options for diabetic patients remains limited. Although significant challenges remain, induced pluripotent stem cells (iPSCs) have the capacity to differentiate into any cell type, including insulin-secreting pancreatic β cells, highlighting its potential as a treatment option for DM. Several iPSC lines have recently been derived from both diabetic and healthy donors. Using different reprogramming techniques, iPSCs were differentiated into insulin-secreting pancreatic βcells. Furthermore, diabetes patient-derived iPSCs (DiPSCs) are increasingly being used as a platform to perform cell-based drug screening in order to develop DiPSC-based cell therapies against DM. [20]

Madsen, O. D. Stem cells and diabetes treatment explained diabetes mellitus types 1 and 2 are characterized by absolute versus relative lack of insulin-producing beta cells, respectively. Reconstitution of a functional beta-cell mass by cell therapy--using organ donor islets of Langerhans--has been demonstrated to restore euglycaemia in the absence of insulin treatment. [21]

Soria, B. et al., reviewd opportunity for stem cells therapy for diabetes mellitus according to them Diabetes is a chronic disease characterized by a deficit in beta cell mass and a failure of glucose homeostasis. Both circumstances result in a variety of severe complications and an overall shortened life expectancy. Thus, diabetes represents an attractive candidate for cell therapy. Reversal of diabetes can be achieved through pancreas and islet transplantation, but shortage of donor organs has prompted an intensive search for alternative sources of beta cells. This achievement has stimulated the search for appropriate stem cell sources. Both embryonic and adult stem cells have been used to generate surrogate beta cells or otherwise restore beta cell functioning. In this regard, several studies have reported the generation of insulin-secreting cells from embryonic and adult stem cells that normalized blood glucose values when transplanted into diabetic animal models. [22]

Conclusion:

This new stem cell technology fetches innovative potential to use stem cell therapy for diabetes mellitus. This review gives an overview on recent advances in use of Induced pluripotent stem cell technology in diabetes mellitus.

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