Sci. Bull.
DOI 10.1007/s11434-015-0844-6

www.scibull.com
www.springer.com/scp

Review

Life & Medical Sciences

Cell therapy in diabetes: current progress and future prospects

Ying Wang · Tang Hai · Lei Liu · Zhonghua Liu · Qi Zhou

Received: 1 March 2015 / Accepted: 29 May 2015

Abstract Diabetes mellitus, characterized by the impaired metabolism of insulin secretion in β cells, is becoming one of the most prevalent diseases around the world. Recently, cell replacement based on differentiation of various pluripotent stem cells, including embryonic stem cells, induced pluripotent stem cells and multipotent stem cells, such as bone marrow mesenchymal stem cells, adipose-derived stem cells and gnotobiotic porcine skin-derived stem cells, is becoming a promising therapeutic strategy. Cells derived from pancreatic tissues or other tissues that are relevant to β cell differentiation have also been used as cell source. However, in spite of hopeful experimental results, cell therapy in diabetes still confronts certain obstacles, such as purity of cells, functional differentiation of stem cells and possible tumorigenesis, which, in turn, lead to the seeking of new-generation tools, such as xenogenetic materials. In this review, we will summarize the current knowledge and future prospects of cell therapy in diabetes mellitus.

SPECIAL TOPIC: Stem cell, Basis and Application

Electronic supplementary material The online version of this article (doi:10.1007/s11434-015-0844-6) contains supplementary material, which is available to authorized users.

Y. Wang · Z. Liu (✉)
College of Life Sciences, Northeast Agricultural University of China, Harbin 150030, China
e-mail: liu086@126.com

Y. Wang · T. Hai · L. Liu · Q. Zhou (✉)
State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
e-mail: zhouqi@ioz.ac.cn

Keywords Diabetes · Cell therapy · Signaling pathway · Xenotransplantation

1 Introduction

According to the data of International Diabetes Federation (IDF), in 2011 there were 366 million people with diabetes, and the number is expected to rise to 552 million by 2030 [1]. The report emphasized that diabetes will become a global epidemic disease as influenza. Diabetes is a blood sugar metabolic disorder owning to lack of insulin secretion in β cells and increases risk of several long-term chronic complications, including cardiovascular disease, stroke, and micro-vascular damage to retina, kidney and nerves. Two major types of diabetes were defined based on their pathogenic mechanisms. Type I diabetes is caused by an autoimmune system dysfunction, which results in destruction of pancreatic β cells and then insulin deficiency. Unlike type I, type II diabetes is more complicated by relating to genetic and environmental factors, which results in loss of glucose homeostasis due to impaired insulin secretion of β cells in response to elevated blood sugar. As both types are closely related to β cells, cell or tissue replacement therapy appears to be the most effective way of curing diabetes.

During the past 20 years, islet transplantation has been proved to be an efficient strategy to treat diabetes and relieve the risk of complications. However,insufficient supply of immune-compatible donors becomes the major obstacle suppressing its widespread usage. Thus, exploration of new therapeutic strategy, such as cell therapy was needed. Cell derivations used in the replacement study must possess the character of β cells, i.e., producing insulin. Pluripotent stem cells (PSCs), such as embryonic

Published online: 19 July 2015

stem (ES) cells and induced pluripotent stem (iPS) cells, have the potential to differentiate into all kinds of cells in the body, including β-like cells and their progenitors. Multipotent stem cells, such as bone marrow mesenchymal stem cells (BMSCs) [2, 3], adipose-derived stem cells (ADSCs) [4] and gnotobiotic skin-derived stem cells (gSDSCs) [5], can also be reassembled into insulin-producing cells. Moreover, several other pancreatic endocrine cells and non-pancreatic tissue were enhanced to differentiate into β cells by using genetic modification and small chemical compounds. However, certain obstacles lie in the way of bench-to-bedside translation in diabetes cell replacement. Lack of knowledge about β cell differentiation and unsuccessful differentiation of β cells was considered the most important obstacle to break through. As a new strategy, xenogenetic cell therapy is becoming a hot topic in clinical application also. Here, we review the current knowledge about differentiation of β cells from various types of cells, the signaling pathways explored in induction of cell differentiation and the obstacles lies ahead of cell therapy and xenotransplantation studies in diabetes.

2 Derivation of β-like cells from various origins

In the process of embryonic pancreas formation, ventral bud is fused with dorsal bud to form the early pancreas structure. Insulin-producing β cells, derived from progenitor cells arising along the exocrine and ductal tissues [6], form the scattered islets of Langerhans along with other endocrine cells, including glucagon-producing α cells, somatostatin-producing δ cells and pancreatic polypeptide-producing PP cells [7] (Fig. 1).

ES cells, which are derived from inner cell mass (ICM) of blastocyst stage embryos, possess the abilities of self-renewal and differentiating into all types of cells. iPS cells, which are similar to ES cells in terms of developmental pluripotency, can be acquired by ectopic expression of transcription factors. Both ES and iPS cells are powerful research tools that could provide significant evidence in preclinical research [8, 9]. Several studies have been reported to differentiate these pluripotent stem cells into β-like cells in mouse and human (Table S1). According to the studies, strategies were divided into two types. One was to generate pancreatic lineage cells by activating or inhibiting pathways in embryonic bodies (EBs) using a few compounds, and then, following the development of pancreas, the cells were sequentially differentiated into posterior foregut, pancreatic endoderm, pancreatic endocrine progenitors, and insulin-expressed cells [10–12]. Another was to overexpress markers of definitive endoderm (DE) [13–16], the origin of pancreatic, by transgenetic technology, such as Pdx1 [17, 18], Ngn3 [19], Sox17 [20], Pdx1 and Foxa2 [21], Pdx1 and Ngn3 [22], Pdx1 and MafA either with Ngn3 or NeuroD [23, 24], to enhance the efficiency of pancreatic differentiation. To mimic the in vivo structure of pancreatic islet, in recent years, β-like cells with normal function in modulating blood glucose have been produced from human pluripotent stem cells by inducing signaling pathways in 3D biomaterial environment system [25].

Parthenogenetic stem cells (pSCs) can be derived from parthenogenetically activated oocytes and share similar functional and differentiation abilities with ES cells and iPS cells. The HLA-homozygous human pSCs are histocompatible with significant portion of human population and may reduce the risk of immune rejection after transplantation. Trichostatin A (TSA) pretreatment in differentiation process of human pSCs was reported to increase the proportion of definitive endoderm cells [26].

Bone marrow-derived stem cells (BMSCs) [2, 3, 27, 28] and adipose-derived stem cells (ADSCs) [4] are multipotent stem cells that can be the alternative sources for obtaining pancreatic hormone-producing cells through in vitro or in vivo induction. Insulin-secreting ability of differentiated cells could be evaluated through genetic modifications, such as transfecting or infecting segments of Pdx1 [29], Pdx1 and β cellulin [30], IPF1, HLXB9 or FOXA2 [31]. However, some modifications got insulin (INS) gene silenced [32]. In addition, gnotobiotic porcine skin-derived stem cells (gSDSCs) treated with bone morphogenetic protein 4 (BMP-4) were reported to be reprogrammed and subsequently differentiated into insulin-producing cells [5]. It was proved that some cells derived from cord blood (CB) [33], hepatic oval [34, 35], splenocyte [36], labia minora dermis-derived fibroblasts [37] and skin fibroblasts [38] could also contribute to further therapies in diabetes.

Although β cells were generated from preexisting β cells rather than from pluripotent stem cells during postnatal and adult life in vivo [39], lots of evidence has shown that cells derived from pancreatic tissue can also be directly differentiated into β-like cells in vitro, such as pancreas-derived multipotent precursor (PMP) cells [40], conophylline in pancreatic endocrine cells [41], pancreatic-derived pathfinder (PDP) cells [42], islet-enriched fractions (IEFs) [43, 44], pancreatic duct cells [45, 46] and exocrine cells [47]. In addition, during the development of pancreas, Pax4, a common transcription factor between α and β cells, could convert α cells into β cells [48–51].

3 Mimic signaling pathways of pancreas development by soluble factors

Pancreas is induced along the anterior–posterior axis (A–P axis) of DE-derived primitive gut. Epithelial–mesenchymal interaction plays a key role in early pancreatic development.