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Mini Review

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STEM CELL therapy and Diabetes

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Abstract

Diabetes is the most prevailing disease with progressive incidence worldwide. To the moment, there is no permanent treatment available for diabetes. Hopefully, stem cell-derived islets may likely be the future therapy. However, the field has limited capability to generate beta-like cells with both phenotypic maturation and functional glucose stimulated insulin secretion that is like primary human islets. Several promising approaches to cure diabetes are to use Mesenchymal stem cells (MSCs) from perinatal tissues or human pluripotent stem cells (hPSCs), including embryonic stem cells (hESCs) and human induced PCSs (hiPSCs). It is also crucial to establish a reliable method of delivering the cells to patients ensuring rapid in-vivo engraftment and function. Overcoming these barriers to beta cell differentiation and transplantation will be key to bring this dream to the clinic. Much research reported the generation of stem cell-derived beta-like cells expressing key maturation genes and capable of dynamic glucose-responsive insulin secretion. Other have investigated the potential of vascularized transplant scaffolds, as well as gas chamber to support beta cell survival and function following transplantation. Here, we summarize recent advances in the differentiation of MSCs and hPSCs into pancreatic beta cells. The generation of stem cell-derived islets with functional glucose stimulated insulin secretion has brought the field closer to clinical translation, but still the challenges for the need of improving their insulin content and secretory capacity.

Key Words: Mesenchymal Stem Cells, Diabetes, Hescs, Hipsc, Differentiation, Transcription Factors, Beta-Like Cells, Transplantation.

Introduction: Diabetes is a chronic disease which requires constant care throughout life, as uncontrolled diabetes can affect the function of other tissues leading to more severe conditions like diabetic foot, neuropathy, retinopathy, and nephropathy [1].

Diabetes is a widespread disease that has 2 major types, Type 1 diabetes (T1DM) (insulin-dependent) resulting from autoimmune destruction of pancreatic (beta) β cells. Diabetes type 2 (T2DM) resulting from failure of β cells as result of hyper secretion of insulin to overcome insulin resistance [2].

Although islet transplantation was proven to be successful, the availability of donors, the number of functional cells recovered, cell loss after transplantation and the necessity of immunosuppressive drugs are major limiting factors. To overcome these obstacles, stem cell-derived beta cell therapy had been proposed as a feasible solution [3].

Despite significant advances in the generation of beta-like cells from human pluripotent stem cells (hPSCs) or adult and perinatal mesenchymal stem cells (MSCs) over the past 10 years, only recent protocols had reported stem cells derived-islets with dynamic glucose responsive function and reversal of diabetes after transplantation.

In this review, we highlighted these recent accomplishments and discuss the next steps in this field, with a focus on the limitations, as well as future considerations of recent strategies for transplantation.

Generation of Pancreatic Progenitors and Beta Cells from Mesenchymal Stem Cells and Human Pluripotent Stem Cells

Mesenchymal stem cells (MSCs) from perinatal tissues had the great advantage regarding immunomodulation and plasticity for beta cell differentiation. Though allogenic, the immunosuppres-

sive nature of the cells in addition to the non-invasive method of isolation makes the birth related MSC an ideal choice for diabetic therapy. What makes them even more attractive is the readiness in terms of their availability with minimal ethical issues. The main sources of MSCs from perinatal tissues are the Wharton jelly, placenta, umbilical cord, chorionic membrane, chorionic villi, cord blood, limb bud, endometrium, amniotic membrane, and amniotic fluid [4].

MSCs derived from the placenta and umbilical cord express variable pluripotent markers like Oct 3/4, SSEA1, and NANOG, which undoubtedly contribute to their high proliferative capacity and wide range of differentiation [5]. A human clinical trial involving the transplantation of amniotic fluid derived MSCs transplanted in diabetic patients has shown protective effect on the damaged pancreatic cells, by interfering with insulin receptor/PI3K signaling pathway [6]. One-step differentiation of CD117+ cells of amniotic-derived MSC has shown the expression of PDX1 and other pancreatic-related genes [7]. Researcher also suggested that although umbilical cord and placenta derived MSCs have expressed pancreatic progenitors, this is mostly donor and protocol dependent [8]. Unlike the adult tissue-derived mesenchymal cells, most of the perinatal tissue-derived MSC have demonstrated robust trilineage differentiation exhibiting the plasticity like embryonic stem cells and pluripotent stem cells [9-11].

On the other hand, the progress in understanding the molecular mechanisms of pancreas development, together with the advent of techniques of hESCs differentiation and generation of mouse and human induced-pluripotent stem cells (hiPSCs) offered new fascinating possibilities of future treatment for patients with diabetes by the transplantation of in vitro insulin-secreting cells [12-14]. β cell generation from hPSCs including human embryonic pluripotent (hESCs) and human induced pluripotent (hiPSCs) is based on successful doctrinarian of culture conditions and the energizing of regulatory genes involved in pancreas development [15].

Generally, the strategies for the generation of functional beta-like cells are based on mimicking in vitro the developmental stages of in vivo pancreas and beta cell development by the exposition of the sequentially cultured differentiating hESCs or hiPSCs to cocktails of various key growth factors and small molecules that could activate transcription factor cascades and signaling pathways specific for the phases of definitive endoderm, pancreatic endoderm, pancreatic progenitors, endocrine progenitors, and finally of beta cell lineage differentiation (Fig. 1)

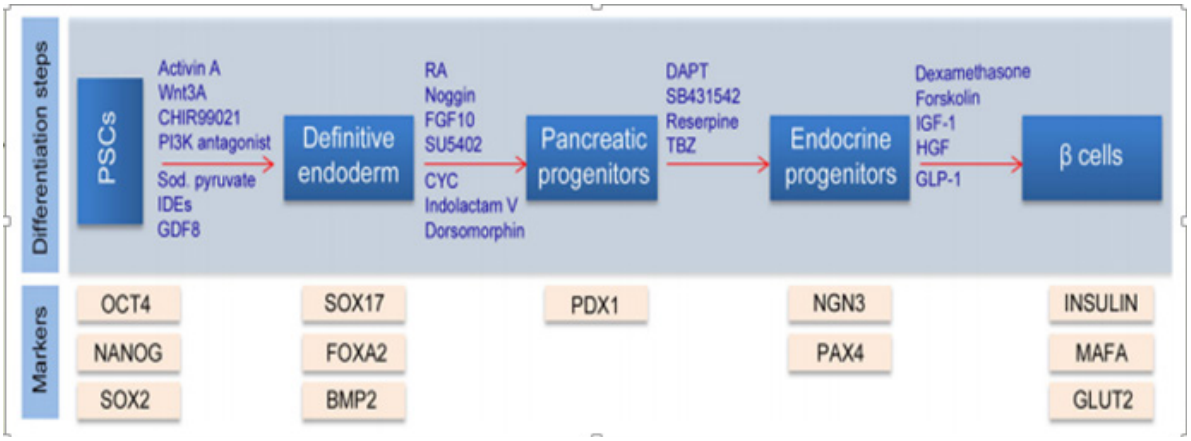

Figure 1: A schematic diagram of the differentiation protocol for insulin-secreting beta cells (β cells) derived from hESCs and hiPSCs. The major markers of the differentiation stages, the growth factors and other molecules controlling the signaling pathways are shown in above fig.

PSCs can be differentiated into pancreatic insulin secreting beta cells using a step wise protocol into definitive endoderm (DE) (SOX17-positive cells) then, pancreatic progenitors (PDX1-positive cells) then, pancreatic endocrine progenitors (NGN3-positive cells) and finally β cells.

The cells are treated with one or more of the reagents indicated for each differentiation stage as shown in the figure. For each step of differentiation, a stage-specific marker is used for confirmation. CHIR99021 (Wnt signaling activator), DAPT (the gamma secretase inhibitor), CYC (Cyclopamine), Dorsomorphin (a BMP type 1 receptor inhibitor), Dexamethasone (a synthetic adrenocortical steroid), FGF10 (fibroblast growth factor 10), Forskolin (an adenylate cyclase activator), GDF8, HGF (hepatocyte growth factor), GLP-1 (Glucagon-like peptide-1), IGF-1 (insulin like growth factor 1), IDEs (small molecules IDE1 and IDE2, Noggin (BMP antagonist), PI3K (Phosphatidylinositide 3-kinases), Reserpine (inhibitor of vesicular monoamine transporter 2), RA (retinoic acid), SB431542 (TGFβ inhibitor), SU5402 (FGF receptor antagonist), TBZ (tetrabenazine; inhibitor of vesicular monoamine transporter 2) [14&15]

It is worth saying that the efficiency of beta cell differentiation from MSCs is much lower, compared to the pluripotent stem cell-based differentiation (the average efficiency reported from the differentiation of hiPSCs and MSCs is 80 and 60% respectively) [16].

For more efficient differentiation, of patient-derived iPSC, the stage-specific expression of markers NKX6.1, PDX1, NEUROD1,

and MAFA has been considered critical for generating functional cells during the differentiation course [17]. MSCs-based protocols primarily focus on generating insulin-positive cells but do not focus on the stage-specific expression of genes.

Furthermore, positive insulin gene expression does not necessitate the release of the hormone from the cells. In addition to insulin gene expression, the co-expression of PDX1 and NKX6.1 is equally important to drive insulin secretion from mature beta cells [18]. Critical analysis suggested that despite of the PDX1 and NKX6.1 expression in some protocols, the cells are not functional. A possible explanation for this controversy, perhaps is the low expression of PDX1/NKX6.1.

PDX1 functions together with NKX6.1 to initiate insulin transcription (or insulin gene expression) during the differentiation course, which results in the release of the C-peptide molecule. The high level of PDX1 and NKX6.1 level, will in turn lead to augmentation of the transcription of insulin gene and thus elevated levels of C-peptide release [19]. conversely, reduced PDX1 and NKX6.1 gene level result in the decrease of the insulin gene transcription leading to the generation of nonfunctional markers.

Other studies also emphasized that PDX1 drives the co-expression of NEUROD1 and MAFA, which in turn is crucial during the maturation of β cells [20]. Furthermore, to maintain the PDX1 levels, the synergistic expression of FoxA2 is mandatory during the endodermal and pancreatic stages [21]. High efficiency of pluripotent stem cell differentiation is dependent on FoxA2 expression during the early stages of β cells differentiation. During the initial endoderm differentiation from pluripotent stem cells, Sox-17+ve/FoxA2+ve cells are generated which in turn are converted to pancreatic cells. However, FoxA2 was not expressed in most MSC-based differentiation protocols. Interestingly, one study revealed that incorporating lentiviral transfection of micoRNAs analyzed FoxA2 during the differentiation, hence increased the efficiency of conversion to 85% [22&23].

Furthermore, very few protocols have succeeded to generate glucose-stimulated insulin secreted cells from MSCs [24]. Many protocols have variable pancreatic marker expression (beta or alpha or delta and beta genes expressed together in the same cell) or have failed to demonstrate glucose-specific insulin secretory responses and [25, 26]. Results suggested that MSCs are ideal protectants that can aid in the survival of cell grafts after transplantation in vivo [27]. Islets, co-transplanted with MSCs as protectants, survived 2 months more than the animals transplanted with islets alone [28]. Moreover, data demonstrated that MSCs transplanted alone have reversed the hyperglycemia in animal models by driving the repair of the damaged cells through the paracrine activity of MSCs [29]. Infusion of MSCs in T2DM patients proved promising improvements in their blood glucose levels, hence reducing the diabetic complications [30].

Encapsulation of Stem Cells-Derived Pancreatic Progeny for Cell Therapy

The in vivo maturation of stem cells-derived pancreatic progenitors requires a suitable transplantation site, and an appropriate encapsulation. The pancreas can provide an appropriate microenvironment for the maturation of islets. However, a surgical way for delivery has limited its consideration as an ideal transplantation site [31]. It is worth saying that pancreatic progenitors transplanted subcutaneously or under kidney capsules had fortunately differentiated into functional beta cells [32], despite that it is not exposed to a 'pancreatic' microenvironment.

The crucial vascular system supplying nutrients and oxygen to the transplanted progenitors as well as the biocompatibility properties of the membrane also carries cues to facilitate the maturation into beta cells [33]. The assessment of islet function following their coating with alginate derivatives had been widely investigated. Purified alginate improved survival of encapsulated islets and prevented their necrosis compared to non-purified alginate capsules [34]. Additionally, modification of alginate capsules incorporated with the chemokine CXCL12 protected the islets and improved their function by serving as an immune-isolating material without the need for immune-suppression [35&36]. Recently, Cell Pouch by Sernova are being developed which facilitates formation of a pre-vascularized scaffold at the target site before cell delivery [37]. Another innovative Beta-O2 device consisting of a gas chamber next to the encapsulated cells to allow for the proper diffusion of oxygen to the cells. This chamber can be refilled to maintain a continuous supply of oxygen [38].

In conclusion, more research work must be done to obtain fully functional pancreatic β cells in vitro. For instance, for each stage during pancreatic β cell differentiation, a genome-wide transcriptional analysis should be performed to recognize the defects in the transcription factors involved. Furthermore, comparing in vivo pancreatic development with in vitro pancreatic differentiation is mandatory to identify the difference in gene expression, which may account for the functional differences. Also, various differentiation protocols should be applied to understand the signaling pathways controlling the differentiation process in vitro.

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