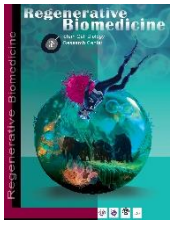

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Review Article

The Impact of Nanofibers on Stem Cell Differentiation to Insulin-producing Cells

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Abstract

Pancreatic islet transplantation has the potential to treat insulin-dependent diabetes, but challenges such as donor shortages, limited differentiation capacity, and transplantation effectiveness need to be addressed before it can be widely adopted as a usual therapy. Daily insulin injections may save lives, but they do not fully replace the body's natural β cell-regulated blood glucose levels. There is a lot of optimism regarding the potential for this disease to be treated, thanks to the breakthroughs in cell therapy and tissue engineering in the last several decades. The purpose of this review paper is to compile research that has been conducted on the use of nanofibers to differentiate stem cells into insulin-producing cells. Since 2016, research has been going on continuously. The literature review indicated that polylactic acid and polycaprolactone-based scaffolds were the most frequently utilized materials in the experiments, each accounting for 21%. To create insulin-producing cells, this research employed 46% mesenchymal stem cells, 42% induced pluripotent stem cells, 8% endometrial stem cells, and 4% embryonic stem cells. In addition, 46%, 36%, and 18% of mesenchymal stem cells are related to wharton's jelly mesenchymal stem cell, adipose-derived stem cells, and conjunctiva derived mesenchymal stem cells, respectively. While limited research has been done, findings indicate that incorporating stem cells into nanofiber scaffolds has the potential to increase the production of insulin-producing cells.

Keywords: Diabetes, β-cells, Nanofibrous scaffold, Cell differentiation, Pancreatic islet

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Introduction

Diabetes is an intricate condition resulting from a combination of genetic and environmental influences. Type 1 and type 2 diabetes (T1D and T2D) are metabolic disorders that result in high blood glucose amounts. T1D is caused by a lack of insulin production, while T2D is a result of reduced insulin sensitivity and activity. The prevalence of T1D in children is increasing, and it can lead to diabetic ketoacidosis, which can result in rapid death if it isn't detected and treated as soon as possible. T1D is an autoimmune disease caused by the immune-mediated destruction of pancreatic β cells within the islets of Langerhans. This causes the body to be unable to produce sufficient insulin to control the amount of glucose in your blood, which in turn causes symptoms such as being overly thirsty, urinary frequency, an unidentified reduction in weight, vision problems, and high starvation. For individuals with T1D, regularly administered insulin injections are necessary because of the lack of endogenous insulin. T1D is commonly known as insulin-dependent diabetes (1-3).

The gold standard for treating this form of diabetes is daily insulin injections, which are painful for patients and expensive for both individuals and society. Islet transplantation is an additional method for treating T1D. The primary obstacles in islet transplantation include limited availability of suitable islets for transplantation, degradation of extracellular matrix components leading to inadequate islet engraftment, and cell mortality causing functional decline over time (4, 5). As a promising new approach to treating T1D, stem cell differentiation has emerged in recent years. Stem cells can differentiate into different types of cells, which makes them a potential tool for tissue engineering for replacing damaged or lost organs or tissue (6).

The interactions among islet cells and the extracellular matrix are crucial for the cell viability, growth, and insulin production of islets. Hence, it appears necessary to utilize a substrate as a supporting structure for mimicking a three-dimensional *in-vivo* microenvironment. Multiple synthetic and natural materials in different configurations have been assessed for their suitability as a framework for islet culture and implantation due to their ability to facilitate easy transplantation, observation, and removal in the event of graft failure (4, 7).

Electrospinning is an appropriate option for creating nanofibrous scaffolds with a high surface area, suitable interconnected pores, controllable fabrication parameters, resemblance to the natural extracellular matrix, and growth factor preservation during cell culture (8). Various studies have shown that artificial nanofibers made from synthetic and natural materials can guide stem cells to develop into insulin-producing cells (Figure 1A, B). Because of the issues with the present treatment approach, scientists are looking for a new way to treat T1D. To facilitate future research, this review paper compiles studies of the potential of nanofibers as an appropriate microenvironment for the differentiation of stem cells into cells that produce insulin.

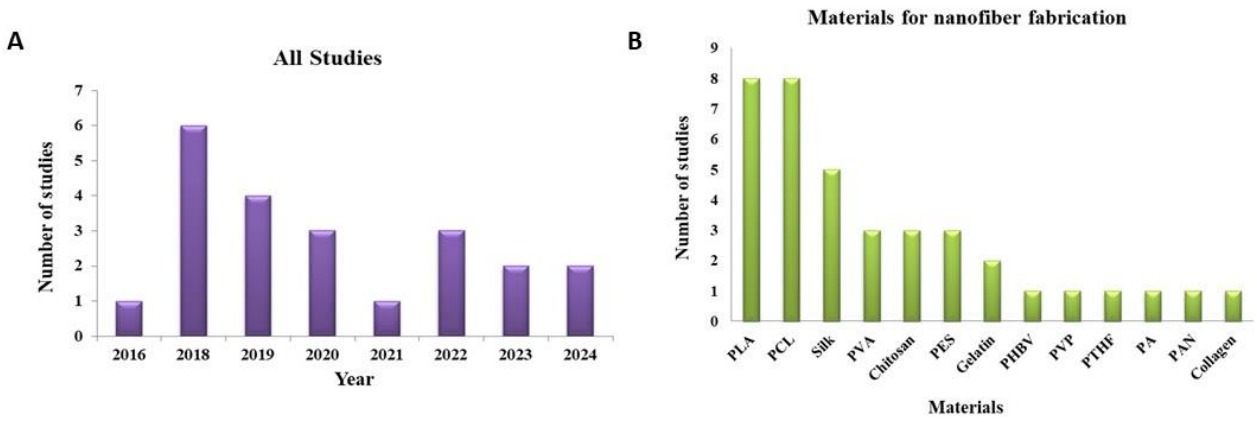

Figure 1 A. The quantity of research projects carried out on utilizing nanofibers to induce the differentiation of stem cells into insulin-producing cells. These studies have been ongoing since 2016. **B.** Various materials have been utilized in research for producing nanofibers.PLA and PCL-based scaffolds were the most frequently utilized materials in the experiments, each accounting for 21%.

Stem cell types for nanofiber-driven insulin-producing cells generation

Stem cells are undifferentiated cells capable of differentiating into other types of cells and reproducing themselves. They exhibit pathological targeting, tissue repair, anti-inflammatory, and immune system control functions, which have attracted attention in regenerative medicine. Stem cells are categorized into four types based on their differentiation potential: unipotent, multipotent, pluripotent, and totipotent stem cells (9). Mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) have been the majority of the cells investigated for differentiation into insulin-producing cells in a nanofiber matrix (Figure 2A). A brief overview of these cells is provided below.

MSCs -loaded nanofibers for generating the insulin-producing cell

Mesenchymal stem cells (MSCs) are multipotent adult stromal progenitor cells with the ability to self-renew and differentiate into various lineages and cell types. MSCs primarily originate from bone marrow. Furthermore, MSCs can be acquired and separated from various tissues, including bone marrow, adipose tissue, skin, umbilical cord blood, amniotic fluid, and the placenta. It is now possible to produce MSCs by differentiating ESCs and iPSCs, in addition to isolating them from tissues. MSCs are characterized by three properties: their capacity to differentiate into osteoblasts, adipocytes, and chondrocytes; their adhesive to plastic while keeping a standard culture environment in a tissue culture flask; and their detection of the expression of particular surface markers like CD105, CD73, and CD90 using flow cytometry (10). Nearly half of all trials aimed at developing insulin-producing cells have focused on these cells. Among MSCs, 46%

were associated with wharton's jelly mesenchymal stem cells (WJMSCs), 36% with adipose-derived stem cells (ADSCs), and 18% with conjunctiva derived mesenchymal stem cells (CJMSCs) (Figure 2B).

Differentiation of iPSCs to beta cells in a nanofibrous matrix

IPSCs were generated by reprogramming mouse fibroblast somatic cells through retroviral transduction of four transcription factors: Oct4, Sox2, Klf4, and c-Myc (OSKM). In the shape, gene transcription, differentiation capacity, and tumor creation, iPSCs are typically similar to ESCs. iPSCs can differentiate into primary germ layers in vitro, including ectoderm, mesoderm, and endoderm (10). Several studies (42% of the total) utilized iPSCs as a type of stem cell for creating insulin-producing cells on nanofibers (Figure2A).

Nanofibers application for cultivating insulin-producing cells from stem cells

Diabetes mellitus, a metabolic disorder defined as T1D or T2D, is common. T1D causes pancreatic β-cells to decrease in mass. Diabetics have high blood glucose due to insulin deficiency. Therefore, these individuals need insulin administration and lifetime blood glucose regulation. Insulin injections do not cure all disease problems. Diabetes causes continuous pancreatic β-cell death. Hence, replacing destroyed β-cells is the ideal diabetes treatment (11). Regenerative medicine relies on the ability to generate new β-cells from sources of expandable stem cells. ES cells derived from humans show potential as the origin of new β-cells. The finding that adult stem cells can be converted into iPSCs has opened up the potential for creating cell types specific to individual patients (12).

Differentiation of cells on cell culture plates is inefficient for stem cell therapy. Native tissue-like cell-cell and cell-matrix interactions can be induced by cell culture on biocompatible and biodegradable scaffolds. These interactions affect cell signaling, promoting survival and differentiation (13). In comparison to conventional scaffolds, nanofibrous electrospun scaffolds offer several advantages that enhance cell-scaffold interactions, including high porosity, interconnected pores, decreased friction, and an enhanced surface area-to-volume ratio (14). In several studies, the researchers fabricated nanofibers of different materials such as polycaprolactone, polylactic acid, polyvinyl alcohol, silk, polyethersulfone, and poly (3-hydroxybutyrate-co-3-hydroxyvalerate). Then to insulin-producing cells generation, iPSCs cultured on scaffolds and compared to a 2D environment in in-vitro and in-vivo conditions. The results indicated increasing cell viability, enhancing pancreatic endocrine genes transcription and translation, and promoting insulin and C-peptide secretion with increasing glucose concentration in the nanofibers group compared to 2D culture. Also, promoting insulin and PDX1 gene expression and identification of c-peptide in the plasma were observed after implantation of nanofibers containing insulin-producing cells in diabetic animal models (15-19).

Material	Stem cells type	Investigated markers	Main results	Ref.
PCL/PVA	iPSCs	Insulin, glucagon, pdx1, ngn3 and glut2	Increasing cell viability, enhancing pancreatic endocrine genes transcription and translation, and promoting insulin and C-peptide secretion with increasing glucose concentration in nanofibers group.	(15, 16)
PHBV		pdx-1, Glut-2, and Insulin		
Silk		Insulin, Pdx1, Glut2, Ngn3 and Glucagon	Promoting cell viability, pancreatic endocrine genes transcription, insulin translation, and insulin and C-peptide secretion were observed in the differentiated cells on the scaffolds than 2D culture group.	(22)
PLLA/PVA		Pdx1, insulin, glucagon and Ngn3	Enhancing cell viability, pancreas-specific transcription factors and insulin and C-peptide secretion were observed in the nanofiber groups than 2D culture.	(5)
Polyethersulfone		Insulin, glucagon, pdx1, ngn3 and glut2	Enhancing cell viability, pancreatic endocrine genes transcription and translation, and insulin and C-peptide secretion were observed in 3D culture than 2D culture.	(13)
Polyethersulfone coated by collagen		Insulin, glucagon, pdx1, ngn3 and glut2	Enhancing cell viability, pancreatic endocrine genes transcription and translation, and insulin and C-peptide secretion were observed in 3D culture than 2D culture.	(23)
PLLA/PCL		Pdx1, glucagon and Glut2	Increasing pancreatic endocrine gene and SOX-17 transcription and insulin and C-peptide secretion in 3D culture than 2D culture.	(19)
Silk/PES		Insulin and pdx1	Increasing pancreatic endocrine gene transcription and insulin and C-peptide secretion in 3D culture than 2D culture.	(17)
PCL		Insulin, Glucagon, and Somatostatin, Amylase, CK19, PDX1, ISL1, NKX2.2, and NGN3	Reducing CK19 and amylase expression, Promoting insulin and PDX1 gene expression in in-vitro and in-vivo studies and also identification of c-peptide in the plasma after implantation in diabetic animal models were observed in nanofibers containing insulin-producing cells.	(18)
Silk fibroin /PLLA	CJMSCs	Pdx-1, Glucagon, GLUT-2 and Insulin	Increasing pancreatic endocrine gene transcription and insulin release in the 3D culture than in the 2D culture. Insulin release and gene expression were higher in differentiated cells on the PLLA scaffolds than in the silk scaffolds.	(6)
PCL surface treated with plasma		Glucagon, GLUT2, insulin and Pdx-1	Promoting cell viability, pancreas-specific markers, and insulin release were higher in 3D culture than 2D culture. The expression of insulin-producing cells markers was higher in plasma-treated nanofibers than untreated nanofibers.	(21)
PLLA coated with Matricaria chammomila L.	ADSCs	Insulin and Pdx-1	Pancreas-specific transcription factors and Pdx1 and Ngn3 proteins expression were observed in nanofibers coated in rabbit animal models after 21 days.	(20)

silk/PES	Endometrial stem cells	Insulin, glucagon, pdx1, ngn3 and glut2	Promoting cell viability, transcription and translation of pancreas-specific markers, and insulin and C-peptide secretion were observed in 3D culture than 2D culture.	(7)
PCL-PTHF		-	Increasing cell penetration, proliferation, and differentiation in in-vitro conditions, reducing hyperglycemia, and prolonging the life span of the implanted rats than diabetic control were observed in large lattice scaffolds.	(4)
PLLA/PVA		Insulin, glucagon, pdx1, ngn3, and glut2	Increasing cell viability, expression of pancreas-specific markers at the protein and mRNA level, and insulin and C-peptide secretion were observed in 3D culture than 2D culture.	(24)
Chitosan/PLA		Foxa2 and Sox17, Sox1, Sox7, Nanog, Oct4, insulin, and glucagon, pdx1, ngn3	Increasing cell viability, promoting Foxa2 and Sox17 in presence activin A and ZnO, enhancing pancreas-specific markers in 3d culture than control group.	(14)
PCL/chitosan /berberine		-	Promoting pancreatic markers, increasing in weight and insulin, decreasing blood sugar were observed in 3D models in *in-vitro* and *in-vivo*.	(25)
PA or PAN	ESCs and iPSCs	Sox17, FoxA2, Pdx1, insulin	Differentiation of both stem cells on PA nanofibers with 300 nm in diameter to Insulin-Producing Cells was higher than PAN nanofibers.	(26)
Chitosan/PLA	WJMSCs	Sox17, FoxA2, Pdx1, HNF4α, Ngn3 and Nkx2.2, SRY	Increasing cell viability, DE and pancreas-specific markers, and disease's significant improvement in the diabetic animal models by ipGTT and hyperglycemia investigation in 3D scaffolds than control group.	(27)
silk/gelatin		-	Increasing pancreatic markers expression, and insulin and, C-peptide secretion were observed in 3D groups than 2D groups.	(28)
PLA/Wax		-	A notable upregulation of all target lncRNAs was noted throughout beta-cell differentiation. HI-LNC71 and HI-LNA12 showed the most pronounced expression in the resulting beta-cell progenitors.	(29)
PRP-PVP-PCL		Insulin, glucagon, pdx1, and glut2	Promoting degradation rate, hydrophilicity, cell viability, pancreatic marker expression and insulin and, C-peptide secretion were observed in 3D culture than 2D culture.	(30)
PCL/fish gelatin		Insulin, glucagon, pdx1, and glut2	Increasing pancreatic markers expression at both RNA and protein levels, and insulin and, C-peptide secretion were observed in 3D groups than 2D groups.	(31)

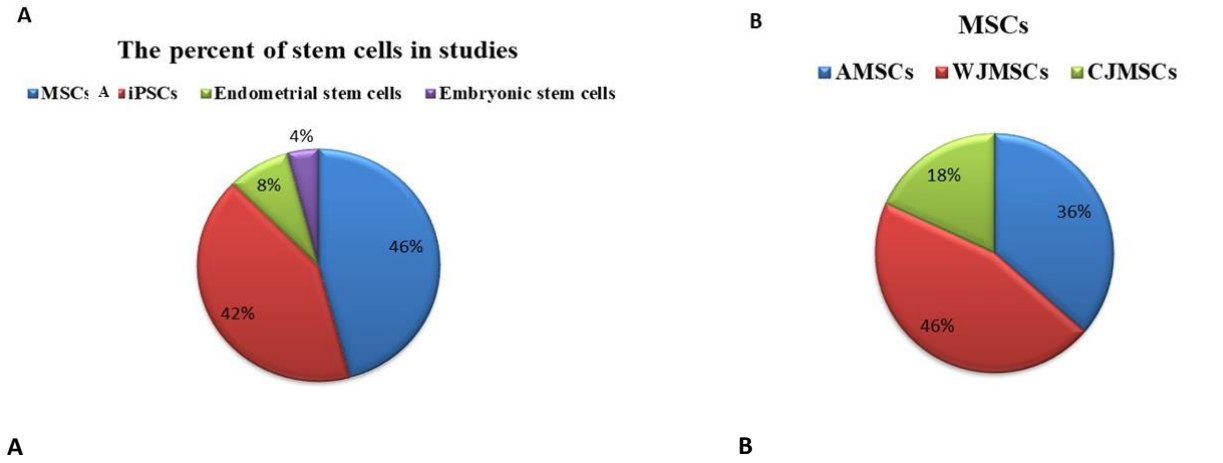

Figure 2. The presence of stem cells in studies. A. The type of stem cells used to generate insulin-producing cells in this study varied, with 46% MSCs, 42% iPSCs, 8% endometrial stem cells, and 4% embryonic stem cells. B. Among MSCs, WJMSCs account for 46%, ADSCs for 36%, and CJMSCs for 18%.

In other studies, MSCs were utilized for the fabrication of insulin-producing cells on a 3D matrix system. The expression of pancreatic markers indicated that MSCs could differentiate into these cells. Studies conducted on animals also confirmed these findings (20, 21). Separate studies were conducted in which nanofibrous matrices were utilized to facilitate the differentiation of embryonic and endometrial stem cells into β-cells. The results that were obtained were similar to those of earlier studies. Furthermore, they demonstrated that the diameter of the nanofibers can affect the differentiation rate. Table 1 provides a summary of nanofiber scaffolds used for generating insulin-producing cells. These findings suggest that stem cells can
efficiently interact with various materials in scaffolds and have the potential to significantly improve the healing process in diabetic patients.

Conclusion

Nanofibers have a significant potential to influence the differentiation of stem cells into insulin-producing cells, making them a promising area of study in regenerative medicine and diabetes research. Nanofibers, nano-sized fibers usually composed of biocompatible materials like polymers, have demonstrated the ability to create ideal conditions for stem cells to differentiate into particular cell types, such as insulin-producing cells. To facilitate stem cell differentiation, nanofibers imitate the ECM of target tissues. Cell migration, differentiation, and proliferation are all regulated by the ECM. Nanofibers, which have a structure very similar to the ECM and physical properties such as high surface area and suitable porosity,

can improve stem cell adhesion, proliferation, and differentiation into insulin-producing cells by delivering signals that direct the cells to this particular lineage.

Ultimately, utilizing nanofibers in the process of stem cell differentiation to create insulin-producing cells shows significant promise for progressing regenerative medicine and diabetes research. Nanofibers can assist in addressing challenges in current cell-based therapies for diabetes by creating a biomimetic environment that aids in guiding stem cell differentiation. Additional research is required to comprehensively the mechanisms that influence the effect of nanofibers on stem cell differentiation and to enhance their utilization in producing functional insulin-producing cells.

Abbreviations

Adipose-derived stem cells (ADSCs), Conjunctiva derived mesenchymal stem cells (CJMSCs), Cellular myelocytomatosis (c-Myc), Induced pluripotent stem cell (iPSCs), Krüppel-like factor 4 (KLF4), Oct-4 (octamer-binding transcription factor 4), PDX1 (Pancreatic And Duodenal Homeobox 1), Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), Polycaprolactone (PCL), Polylactic acid (PLA,), SRY-box transcription factor 17 (SOX2), Type 1 diabetes (T1D), Type 2 diabetes (T2D), Wharton's jelly-derived mesenchymal stem cells (WJMSCs).

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Availability of data and materials

The datasets generated or analyzed during the current study are available on request from the corresponding author.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

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