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Research Progress and Prospects of Stem Cell Transgene Therapy for Diabetes

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ABSTRACT
Diabetes is a chronic disease that affect human's healthy a lot.Traditional treatment methods ,like the injection of insulin,can not cure this disease completely, and affect the life quanlity of patients. However, stem cells, which have the ability to renew themselves and turn into different types of cells, provide a new way for treating diabetes. Transgene technology's development increases the probability of stem cells turn into the right cells and make sure they have correct functions , increase the successful probability of cell therapy plans. This paper looks at the research background, common stem cell types, and transgene strategies of stem cell transgene therapy for diabetes in a systematic way, analyzes the key progress, technical problems, and difficults meeting to using this therapy in clinics, and talks about future development directions. It aims to give references for more needed students in this field.

KEYWORDS
Diabetes; Stem cell; Transgene

1 Introduction

Diabetes mellitus is mainly divided into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The former has the feature of not having enough insulin because immune systems damage pancreatic islet β-cells, while the latter has insulin resistance and β-cells that work worse over time [1]. According to numbers from the International Diabetes Federation, the number of people with diabetes around the world went over 537 million in 2024 and is expected to go up to 783 million by 2045. Its complications, like nephropathy, neuropathy, and cardiovascular diseases, badly harm patients' life quality [2].

In common situations ,traditional treatments always use insulin replacement, oral drugs in order to lower blood sugar, that decrease people's life quality. Although these ways can control blood glucose, they can't fix damaged pancreatic islet tissue or turn back the disease process. Stem cell therapy might cure diabetes by adding functional β-cells and adjusting the immune environment. But simple stem cell transplantation has issues like low efficiency in turning into target cells, short survival time, and unstable functions. By introducing specific functional genes, transgene technology can control which way stem cells turn into other cells, make cells better at avoiding death, and help them not be attacked by the immune system. So it has become a key way to make therapy work better [3]. This paper talks about how to choose stem cell types, how to make transgene targets and vectors better, progress in lab and animal studies, and problems in using this therapy in clinics. It aims to show clearly the current research status and development trends in this field.

2 Core Foundations of stem cell transgene therapy for diabetes mellitus

2.1 Common stem cell types and their characteristics

Stem cells from different places are different in how they can turn into other cells, how likely they are to cause immune reactions, and how easy they are to use infuture。 These are quite important ways to determine weather it can be used.

• Mesenchymal Stem Cells (MSCs): They have many sources (e.g., bone marrow, adipose tissue, umbilical cord), don't easily cause immune reactions, and can adjust immune systems. They also help fix the body's own pancreatic islets by releasing substances. At the same time, MSCs are easy to grow and make more of in labs, and can take in new genes. This makes them the most studied cell type now [4]. Studies show that after transgene modification, umbilical cord mesenchymal stem cells (UC-MSCs) can turn into islet-like cells 30%-50% more often [5].

• Embryonic Stem Cells (ESCs): ESCs can turn into almost any cell type, including functional β-cells, very well. But arguments about ethics and the risk of immune rejection limit their use in clinics [6].

• Induced Pluripotent Stem Cells (iPSCs): These cells come from changing regular body cells. They have both the ability of ESCs to turn into other cells and the advantage of being from the patient's own body, so they can avoid immune rejection. But low efficiency in changing regular cells, possible risk of causing tumors, and not being fully mature when turning into target cells are still major problems [7].

• Pancreatic Stem/Progenitor Cells: These cells naturally tend to turn into pancreatic islets and are very good at turning into the right cells. But they are hard to get, and it's not easy to make more of them in labs. So their use in clinics is limited [8].

2.2 Key transgene strategies and targets

Transgene technology makes treatment better by controlling how stem cells turn into other cells, how well they work, and the environment they live in. The main ways include three types:

• Directional Differentiation Regulation: Put in genes that control pancreatic islet development to help stem cells turn into β-cells. For example, making more PDX-1 (Pancreatic and Duodenal Homeobox 1) can start insulin gene expression, which makes MSCs turn into islet-like cells much better [9]; making Ngn3 (Neurogenin 3), Pdx1, and MafA (V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog A) at the same time can make β-cells from iPSCs release 2-3 times more insulin [10].

• Anti-Apoptosis and Survival Enhancement: High glucose and inflammatory substances in the body of diabetic patients easily make transplanted cells die. Putting in genes that stop cell death (e.g., Bcl-2, survivin) can decrease cell death rate. Studies show that UC-MSCs with Bcl-2 gene live 40% more in high-glucose environments, and can keep releasing insulin for more than 8 weeks [11].

• Immune Regulation and Tolerance Induction: To fix the immune-related β-cell damage in T1DM, put in genes that reduce inflammation (e.g., IL-10, TGF-β). These genes can stop immune cells from becoming active and lower the risk of transplant rejection. For example, MSCs that make IL-10 can lower the insulitis score of diabetic mice by 50%, and keep their blood glucose normal for up to 12 weeks [12].

2.3 Selection and optimization of transgene vectors

The safety, how well vectors can put genes into cells, and how stable the new genes work all affect therapy results directly. Common vectors are split into viral vectors and non-viral vectors:

• Viral Vectors: Retroviruses, lentiviruses, and adeno-associated viruses (AAV) are used a lot. Lentiviral vectors can put foreign genes into cells stably, and over 80% of cells can take the genes. But they might cause gene changes [13]; AAV vectors don't put genes into cell DNA, so they are safer. But they can only carry small gene pieces (<4.7 kb), so they are good for small functional genes [14].

• Non-Viral Vectors: Liposomes, nanoparticles, and other non-viral vectors don't easily cause immune reactions and won't change cell DNA. But they aren't good at putting genes into cells (usually less than 30% of cells take the genes). In recent years, cationic polymer nanoparticles with targeting peptides (e.g., islet-targeting peptide Exendin-4) can make 50%-60% of MSCs take new genes [15].

3 Research progress of stem cell transgene therapy for diabetes mellitus

3.1 In vitro experiments and animal model studies

Lab experiments and animal models are very important to check if the treatment works. In recent years, there have been many important findings:

• Differentiation Efficiency and Functional Verification: In 2022, Wang et al. put Pdx1 and MafA into human Adipose-Derived Mesenchymal Stem Cells (hAD-MSCs) using lentiviral vectors. 75% of the induced islet-like cells could make insulin, and their Glucose-Stimulated Insulin Secretion (GSIS) was 80% similar to normal islet cells [16].

• Efficacy in Animal Models: In mice with T1DM (made by streptozotocin, STZ), after transplanting UC-MSCs with IL-10 gene, the mice's blood glucose went back to normal in 1 week and stayed normal for up to 16 weeks. Pancreatic islet tissue slides showed that the number of β-cells was twice as many as in the control group [17]; in rats with T2DM, MSCs with Glucagon-Like Peptide-1 (GLP-1) gene could both improve insulin resistance and β-cell function, making insulin sensitivity 35% higher [18].

• Optimization of Combined Strategies: Mixing stem cell transgenes with biomaterials (e. g., alginate microencapsulation) can make a "cell-vector" system. This system reduces the loss of transplanted cells. Studies show that this system can make transplanted cells live up to 20 weeks in mice, and is 40% better at controlling blood glucose than just transplanting cells [19].

3.2 Current status of clinical research

Now, clinical research on stem cell transgene therapy for diabetes is still in the early stage. The tests were so far mainly focus on safety and initial effectiveness:

• Safety Verification: In 2021, a Phase I clinical trial (NCT04867332) in China included 12 T1DM patients. After giving them UC-MSCs with PDX1 gene, no serious bad reactions (e.g., infection, tumor formation) happened in 6 months. Only 2 patients had mild fever. This shows the plan is safe [20].

• Preliminary Efficacy: In 2023, a Phase II clinical trial in South Korea for T2DM patients showed that after transplanting bone marrow MSCs with GLP-1 gene, patients' glycated hemoglobin (HbA1c) went down by 0.8%-1.2% compared to before. They also used 20%-30% less insulin, and the effect lasted more than 6 months [21].

• Existing Limitations: Current clinical studies have small numbers of patients (most have less than 30 cases) and short

follow-up time (most less than 1 year). Also, there are no standard ways to prepare cells or check how well therapy works. More Phase III clinical trials with more patients and longer follow-up are needed.

4 Current technical bottlenecks and challenges

4.1 Limitations at the cellular level

• Insufficient Differentiation Maturity: Although stem cells induced in labs can make insulin, most of them are "immature β-cells" that can't respond to blood glucose well. Their GSIS is 30%-50% weaker than normal islet cells.

• Tumorigenic Risk and Safety: Gene changes caused by viral vectors and the ability of stem cells to grow non-stop may cause tumors. Some mice in animal tests had teratoma-like growths; also, pollution during cell preparation (e. g., mycoplasma, endotoxins) may bring risks to clinics.

• Cell Survival and Functional Maintenance: The high-glucose, oxidative stress, and inflammatory environment in diabetic patients can make a lot of transplanted cells die. Studies show that less than 20% of cells live 1 month after transplantation.

4.2 Optimization difficulties of transgene technology

• Balance Between Vector Safety and Efficiency: Viral vectors are good at putting genes into cells but may change cell DNA. Non-viral vectors are safer but not good at gene delivery. Finding a balance between the two is still veryimportant。

• Precision of Gene Expression Regulation: Too much of the foreign gene may make cells work badly (e.g., too much insulin causes low blood sugar). Too little of the gene makes therapy not work. There's no good way to control when and where the gene works.

• Immune Rejection and Immunogenicity: Even if using the patient's own stem cells, the vector proteins or foreign gene products from transgene modification may cause immune reactions, making the transplant fail.

4.3 Barriers to clinical translation

• Lack of Standardization and Normalization: The sources of stem cells, conditions for growing them, ways to do transgene, and how to transplant them are not the same everywhere. Results from different labs are hard to compare, which slows down clinical use.

• Ethical and Regulatory Issues: Using ESCs causes ethical arguments. The technology to make iPSCs also has problems like whether cell sources are legal and how to protect privacy. Also, different countries have different rules for gene therapy products, which makes cross-border clinical research harder.

• Long-Term Efficacy and Cost Issues: Current studies don't follow patients for long, so it's hard to check long-term effectiveness and safety. Besides, preparing stem cells and doing transgene modification costs a lot, which limits their wide use.

5 Future development directions and prospects

5.1 Technical optimization strategies

• Precision Differentiation Regulation: Use single-cell sequencing to understand how pancreatic islets develop. Find key factors that control this process (e.g., new transcription factors, non-coding RNAs). Make a "multi-factor system" to help stem cells turn into mature β-cells better .

• Innovation of Vectors and Gene Editing Technology: Develop new non-viral vectors (e.g., virus-like particles, smart nanocarriers that respond to environment) to make gene delivery better. At the same time, use CRISPR-Cas9 gene editing to turn on or off body's own genes precisely, so foreign genes don't need to be added [32].

• Microenvironment Regulation and Combination with Biomaterials: Make an environment like the one where pancreatic islets grow in the body (e.g., 3D biological scaffolds, systems with blood vessels). This helps transplanted cells live better and work well. Also, use biomaterials to carry anti-inflammatory factors or nutrients to make the transplant environment better.

5.2 Improvement of clinical translation pathways

• Establishment of Standardized Systems: Make 统一 standards for preparing stem cells, doing transgene modification, and checking quality. Build a network of multi-center clinical research. Do clinical trials with more patients and longer follow-up to check if therapy works and is safe.

• Personalized Treatment Strategies: Based on patients' genes, how long they have had diabetes, and their complications, make personalized plans for stem cell types and transgene. For example, T1DM patients may need more immune-regulating genes, while T2DM patients may need genes that improve insulin sensitivity.

• Regulatory and Ethical Collaboration: Work with other countries to make the same approval standards for gene

therapy products. Also, make ethical review better to balance technology innovation and ethical rules.

5.3 Interdisciplinary integration and development

In the future, we need to combine stem cell biology, genetics, materials science, and clinical medicine together to help human build a healthy future and a world with advanced treatment. For example, use artificial intelligence to predict how stem cells turn into other cells and how it works. This can speed up the search for diabetes. Also, use bioprinting to make "islet organoid-biological scaffold" complexes for precise transplantation. These ways will bring new chances to stem cell transgene treatment for diabetes.

6 Conclusion

By combining the ability of stem cells to turn into other cells and the precise control of transgene technology, stem cell transgene therapy is a very tremendous way to treat diabetes. Current research has made big progress in choosing better cell types, finding good transgene targets, and checking effectiveness in animals. But there are still problems like stem cells not being fully mature when turning into β-cells, needing safer vectors, and lacking standard ways for clinical use. In the future, we need to improve technology, make standard systems, and work across different fields. This will help turn basic research into clinical use, and finally reach the goal of curing diabetes.

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