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Review

The Potential and Challenges of Human Pluripotent Stem Cells in the Treatment of Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is a prevalent complication of diabetes, with current treatment options offering limited effectiveness, particularly in advanced stages. Human pluripotent stem cells (hPSCs), particularly induced PSCs (iPSCs), show promising potential in the treatment of DN due to their pluripotency, capacity for differentiation into kidney-specific cells, and suitability for personalized therapies. iPSC-based personalized approaches can effectively mitigate immune rejection, a common challenge with allogeneic transplants, thus enhancing therapeutic outcomes. Clustered regularly interspaced short palindromic repeats (CRISPR) gene editing further enhances the potential of hPSCs by enabling the precise correction of disease-associated genetic defects, increasing both the safety and efficacy of therapeutic cells. In addition to direct treatment, hPSCs have proven valuable in disease modeling and drug screening, particularly for identifying and validating disease-specific targets. Kidney organoids derived from hPSCs replicate key features of DN pathology, making them useful platforms for validating therapeutic targets and assessing drug efficacy. Comparatively, both hPSCs and mesenchymal SCs (MSCs) have shown promise in improving renal function in preclinical models, with hPSCs offering broader differentiation capacity. Integration with tissue engineering technologies, such as three-dimensional bioprinting and bioengineered scaffolds, expands the regenerative potential of hPSCs by supporting the formation of functional renal structures and enhancing *in vivo* integration and regenerative capacity. Despite current challenges, such as tumorigenicity, genomic instability, and limited direct research, advances in gene editing, differentiation protocols, and tissue engineering promise to address these barriers. Continued optimization of these approaches will likely lead to successful clinical applications of hPSCs, potentially revolutionizing treatment options for DN.

Keywords: diabetic nephropathy; human pluripotent stem cells; induced pluripotent stem cells; CRISPR gene editing; kidney organoids

1. Introduction

Diabetic nephropathy (DN) is a prevalent microvascular complication in diabetes and a primary cause of end-stage renal disease (ESRD). As diabetes rates rise, the incidence of DN has escalated globally alongside the rising rates of diabetes, severely impacting quality of life and straining healthcare systems [1]. DN progression is marked by proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis, often necessitating dialysis or kidney transplantation [2]. Current treatments, including renin-angiotensin-aldosterone system (RAAS) blockers and glycemic control, offer limited efficacy, especially in advanced stages, highlighting the urgent need for new therapeutic strategies [3].

Emerging therapies have shown promise. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, for example, have demonstrated the potential to slow DN progression, particularly in combination with RAAS blockers [4]. Additionally, kidney-targeted agents based on natural antioxidants, such as astragaloside IV, exhibit significant nephroprotective effects by reducing oxidative stress and fibrosis *in vitro* and *in vivo* [5]. Despite these advances, the complex pathophysiology, especially fibrosis and chronic inflammation, presents ongoing challenges. Further research is needed to understand DN mechanisms and develop effective therapies [6]. While new drug developments offer hope, DN remains challenging due to its multifaceted pathology involving chronic inflammation, oxidative stress, and fibrosis [7]. Current drugs provide some renal protection in the early stages but often fail as DN progresses, underscoring the importance of exploring alternative therapeutic options.

Human pluripotent stem cells (hPSCs), encompassing embryonic SCs (ESCs) and induced PSCs (iPSCs), hold great potential in regenerative medicine. hPSCs possess robust self-renewal capabilities and can differentiate into nearly all cell types under specific conditions. While ESCs,

derived from embryos, exhibit unlimited differentiation potential [8], their use involves ethical concerns [9]. By contrast, iPSCs are generated by reprogramming adult somatic cells to a pluripotent state, bypassing ethical issues and demonstrating similar multi-lineage differentiation potential to ESCs [10]. Due to their ability to differentiate into various cell types, such as renal and pancreatic β-cells, hPSCs are widely used in disease modeling, drug screening, and cell replacement therapies [11,12]. In renal regeneration, hPSCs have been successfully differentiated into functional kidney organoids, which simulate kidney development and serve as models for kidney disease [13]. For diabetes treatment, hPSC-derived pancreatic β-cells, capable of insulin secretion, offer promising prospects for cell-based therapies [14]. Furthermore, research indicates that optimizing culture conditions enhances hPSCs differentiation efficiency into functional cells, advancing applications in disease studies and regenerative medicine [15,16].

With advances in regenerative medicine, hPSCs show promising potential for repairing damaged renal tissues. Differentiated renal cells derived from hPSCs not only simulate kidney development *in vitro* but also hold potential for cell-based replacement therapy for damaged kidney cells [2]. The study indicate that hPSC-derived renal progenitor cells can form mature kidney structures, such as glomeruli and tubules, both *in vitro* and *in vivo*, and have demonstrated significant renal function improvement in animal models [17]. Patient-specific iPSCs offer the advantage of reducing immune rejection risks associated with allogeneic transplants, enabling personalized therapy. This approach could be transformative for DN, allowing tailored treatments through reprogramming patient-derived cells into renal or pancreatic β-cells, thus enhancing efficacy and reducing immune response [18,19]. Moreover, kidney organoids derived from hPSCs are valuable for drug screening and disease modeling, providing new avenues for DN research [13]. Despite the potential of hPSCs in DN, clinical applications face challenges, such as achieving efficient and consistent differentiation into target cell types, and ensuring the long-term survival and function of transplanted cells [10]. Safety concerns, including the risk of tumorigenesis, also remain and require further investigation.

2. Fundamentals and Characteristics of hPSCs

2.1 Definition and Types of hPSCs

ESCs are derived from the inner cell mass of early embryos and exhibit high pluripotency, enabling differentiation into various cell types from all three germ layers, namely, neurons, muscle cells, and endothelial cells [9]. Their strong self-renewal and differentiation capabilities make them crucial in regenerative medicine and developmental biology. However, obtaining ESCs raises ethical concerns due to embryo destruction [20]. These concerns are tied to the moral status of embryos, leading many countries to impose strict regulations on ESCs research [21]. As a result, researchers have turned to iPSCs to avoid ethical issues. iPSCs are generated by reprogramming somatic cells (e.g., skin or blood cells) into a pluripotent state using specific transcription factors such as octamer-binding transcription factor 4, SRY-Box Transcription Factor 2, Krüppel-like factor 4 [22]. This process eliminates the need for embryo destruction, addressing ethical dilemmas associated with ESCs [23]. iPSCs allow for the personalized reprogramming of patient-derived cells, facilitating tailored therapies [12]. Their development not only resolves ethical concerns but also enhances precision medicine.

The iPSC reprogramming technique represents a significant advancement, enabling somatic cells to revert to an embryonic-like state through specific transcription factors that activate pluripotency genes [24]. Recent advancements, such as non-integrating viral vectors and mRNA reprogramming, improve the safety of iPSCs by reducing genetic mutation risks [25]. iPSCs provide several advantages; for example, they bypass ethical controversies linked to ESCs and can be derived from the patient's own cells, minimizing the risk of immune rejection post-transplantation. This personalized source enhances the feasibility of tailored treatments in regenerative medicine [26]. Furthermore, iPSCs can be utilized for disease modeling, drug screening, and gene editing, offering extensive application potential in disease research [27].

2.2 Differentiation Potential of hPSCs and Their Application in DN Models

hPSCs possess the ability to differentiate into all three germ layers—ectoderm, mesoderm, and endoderm—each of which further develops into diverse tissues and organs, including the nervous system, muscles, blood, and liver tissue [28]. Under carefully controlled culture conditions and with specific signaling molecules, hPSCs can be directed *in vitro* to become desired cell types, a capability that makes hPSCs invaluable for developmental biology research, disease modeling, and regenerative medicine [29].

To direct the differentiation of hPSCs *in vitro*, researchers commonly replicate developmental cues using specific media and signaling factors. For instance, the addition of growth factors and pathway modulators such as bone morphogenetic protein 4 (BMP4), Wingless-related integration site (Wnt), and fibroblast growth factor (FGF) guides hPSCs to differentiate into cardiomyocytes, neurons, or hepatocytes (Fig. 1) [30]. Enhanced differentiation efficiency can be achieved with three-dimensional (3D) culture systems or co-culture methods, resulting in organoids or cellular clusters that closely resemble the functions of native tissues [31]. For example, the development of 3D microfluidic co-culture systems, for example, has enabled the generation of functional liver cells from hPSCs [32].

In DN research, hPSCs have shown promise in multiple applications. They are widely used to model the dys-

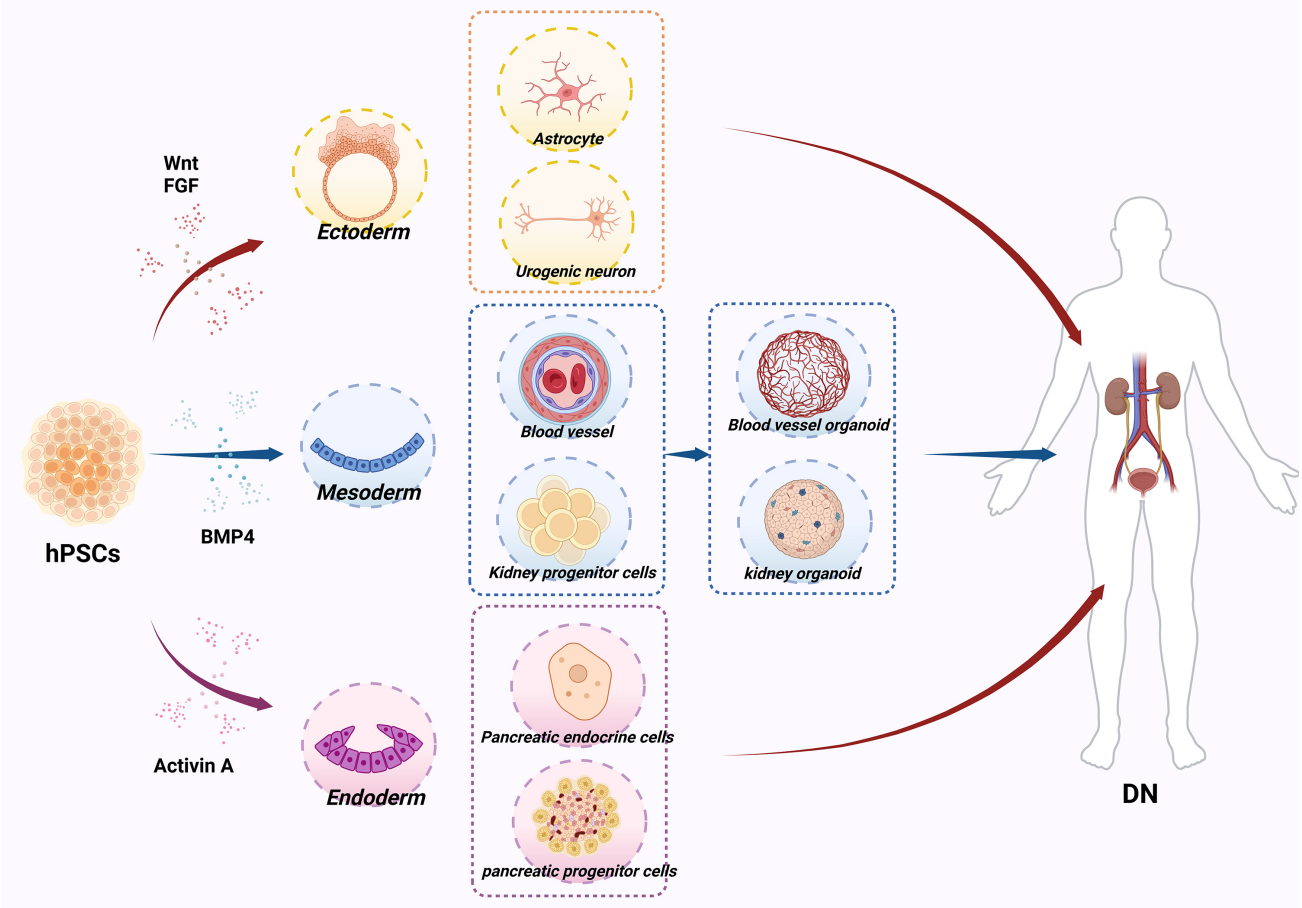

Fig. 1. Differentiation potential of human pluripotent stem cells (hPSCs) and their application in diabetic nephropathy (DN) models. Adding growth factors and pathway modulators, such as bone morphogenetic protein 4 (BMP4), Wingless-related integration site (Wnt), and fibroblast growth factor (FGF) can guide hPSCs to differentiate into cardiomyocytes, neurons, or hepatocytes. (Created with BioRender.com).

function of pancreatic β-cells, a key factor in understanding DN pathogenesis. For instance, Leite *et al.* [33] generated pancreatic endocrine cells from iPSCs to mimic the immune response in patients with type 1 diabetes, revealing that autoimmune cells selectively attack β-cells with minimal impact on α-cells. Balboa *et al.* [34] have highlighted the role of gene-editing techniques in studying complex β-cell dysfunction, emphasizing the role of hPSCs in advancing our understanding of diabetes. Gheibi *et al.* [35] further used insulin/glucose-responsive cells derived from iPSCs to model diabetes, providing a new platform for disease pathology research and therapeutic exploration.

Significant advances have also been made in using hPSCs to generate kidney progenitor cells and kidney organoids, offering new approaches to DN treatment. Bantounas *et al.* [17] developed a method for deriving kidney progenitor cells from hPSCs and successfully transplanted these cells into immunodeficient mice, where they matured into functional kidney units. Bajaj *et al.* [36] expanded on this by creating a 3D kidney organoid platform from hPSCs, enabling the assessment of nephrotoxicity in drug development and opening new paths for kidney disease research. Vascular organoids derived from hPSCs have also been used to model diabetes-related vascular damage, providing valuable insight into potential therapeutic targets for diabetic complications [37].

In diabetes cell therapy and transplantation studies, hPSCs show remarkable potential. For example, Ghila *et al.* [38] successfully used pancreatic progenitor cells derived from hiPSCs to perform transplantation treatments in diabetic mouse models, demonstrating an approach that could lead to future therapeutic applications. Such strategies, particularly when enhanced by cell encapsulation techniques, offer improved cell survival post-transplant, representing a significant step forward in cell-based diabetes treatments.

Furthermore, hPSCs are crucial for studying complications of diabetes in vascular and neural systems. Morizane [37] used vascular organoids derived from hPSCs to model diabetes-induced vascular damage, identifying new therapeutic targets for vascular complications. In another study, Gorashi *et al.* [39] created a model of

endothelial dysfunction in diabetes using patient-specific iPSCs, highlighting the role of hPSCs in vascular disease research. hPSC-derived urogenic neurons and astrocytes have also been applied to central nervous system models of diabetes-related complications, providing a novel platform for studying the neurological effects of diabetes [40].

As regenerative medicine and precision medicine continue to evolve, the applications of hPSCs have expanded considerably. Memon and Abdelalim [19] highlighted the crucial role of hPSCs in precision medicine in diabetes, noting that hPSC-derived cells can replicate disease states *in vitro*, offering an effective model for drug development and personalized treatment. Moreover, combining hPSCs with gene-editing technology allows researchers to introduce known pathogenic mutations into disease models, offering deeper insights into the specific contributions of these mutations and advancing research into diabetes mechanisms [41].

3. hPSCs for DN Regeneration

3.1 Differentiation of hPSCs into Kidney-Related Cells

hPSCs have the remarkable ability to differentiate into a wide variety of cell types, a feature that plays a significant role in the study and treatment of DN [9]. By adding specific growth factors, such as Wnt and BMP4, hPSCs can be directed to differentiate into kidney progenitor cells, which can further mature into key kidney cells such as tubular epithelial cells and podocytes—cells essential for kidney function [17]. The successful generation of these progenitor cells *in vitro* lays a crucial foundation for exploring cell replacement therapies for DN [11].

Combining hPSCs with biomaterial scaffolds effectively mimics the natural kidney developmental process and significantly enhances the production efficiency of kidney progenitor cells [17]. This approach allows for better control of cell culture conditions, ultimately generating different kidney cell types more efficiently [9]. Furthermore, using modular differentiation systems enables the creation of both tubular and collecting duct cells, providing a robust basis for the reconstruction of complex kidney organ structures *in vitro* [11].

To generate specific kidney cell types, factors such as activin A and FGF9 can be added to the culture medium to successfully induce hPSCs into functional podocytes and tubular epithelial cells [17]. These differentiated cells exhibit similar functional characteristics to native kidney cells and can be used in DN models to facilitate tissue repair [13]. Additionally, combining two-dimensional (2D) and 3D culture systems have significantly increased the efficiency and maturity of differentiated hPSCs, resulting in kidney cells that more closely resemble their natural counterparts [9].

Kidney cells derived from hPSCs show immense potential in cell replacement therapies, particularly podocytes and tubular epithelial cells, which can be transplanted to replace damaged kidney tissues and restore kidney function partially [10]. In animal studies, transplanted podocytes demonstrated a significant protective effects on the kidneys, reducing proteinuria and inflammation, which are key symptoms of DN [42]. Furthermore, when these differentiated cells were transplanted into immunodeficient mice, they formed mature kidney structures, including glomeruli and tubules, effectively mitigating kidney damage [42].

As differentiation techniques continue to advance, hPSC-derived kidney cells hold promise for future clinical applications in DN, potentially offering a way to replace damaged kidney tissue and restore kidney function [6]. Researchers have also developed a new method using synthetic mRNA encoding transcription factors, which allows for the rapid and efficient differentiation of hPSCs into critical kidney cells such as tubular epithelial cells and podocytes, providing new avenues for kidney regenerative therapies [11].

3.2 Paracrine Effects and Immunomodulation

The potential therapeutic application of hPSCs in DN extends beyond cell replacement therapy and includes significant paracrine effects, particularly through the secretion of exosomes that help protect kidney function. Exosomes derived from hPSCs are rich in microRNAs (miRNAs), such as miR-16-5p, which can inhibit vascular endothelial growth factor A (VEGFA), effectively protecting podocytes from damage induced by high glucose conditions [2]. Moreover, hPSCs secrete specific factors that inhibit transforming growth factor beta 1 (TGF-β1)-induced fibroblast transdifferentiation and cell proliferation, thereby reducing kidney fibrosis and significantly improving kidney function [42,43].

In DN models, exosomes and paracrine factors secreted by hPSCs have shown notable protective effects. These include mitigating kidney damage by regulating inflammatory responses and significantly reducing fibrosis and inflammation through modulation of the TGF-β/Smad signaling pathway [42]. This ability makes hPSCs highly promising in reducing fibrosis associated with DN. Furthermore, the miRNAs secreted by hPSCs effectively lower VEGFA expression, thereby further contributing to improved kidney function [2,44].

Beyond their paracrine effects, hPSCs also exhibit strong immunomodulatory capabilities. By secreting exosomes and anti-inflammatory factors, hPSCs can reduce the infiltration of pro-inflammatory macrophages and regulate T-cell activity. The study has shown that hPSC-derived exosomes can decrease the levels of pro-inflammatory cytokines while enhancing the population of anti-inflammatory macrophages, significantly alleviating the chronic inflammation commonly seen in DN [45]. In addition, the paracrine actions of hPSCs can alter the immune microenvironment in the kidney, reducing the infiltration of inflammatory cells into kidney tissues and offering further protection to renal structures [18].

3.3 Inhibition of Kidney Fibrosis

The antifibrotic effects of hPSCs in DN are primarily achieved through the regulation of multiple signaling pathways, reducing excessive deposition of the extracellular matrix (ECM) and thereby mitigating the progression of kidney fibrosis. The study has shown that exosomes secreted by hPSCs contain miRNAs, such as miR-16-5p, which can suppress the expression of VEGFA, thus helping to reduce fibrosis in the kidney [2]. Additionally, hPSCs have been shown to regulate the TGF-β/Smad signaling pathway, effectively inhibiting TGF-β1-induced fibrotic processes and significantly reducing fibrosis in DN [42].

hPSCs can also interfere with multiple fibrosis-related signaling pathways, including TGF-β/Smad, Wnt/β-catenin, and Notch pathways, to alleviate fibrosis in DN [46,47]. Moreover, by upregulating the nuclear factor erythroid 2-related factor 2 signaling pathway, hPSCs can mitigate ferroptosis, which further helps reduce oxidative stress and fibrosis in the kidney [48]. These interventions provide a multifaceted approach to controlling fibrosis associated with DN.

Another important mechanism of action for hPSCs is their ability to reduce extracellular matrix deposition. By decreasing the accumulation of key matrix components such as collagen and fibronectin, hPSCs are able to inhibit epithelial-mesenchymal transition in tubular epithelial cells as well as fibroblast transdifferentiation. These effects are largely mediated by exosomal miRNAs, such as miR-24-3p, and circular RNAs, such as circ_0080425, which collectively contribute to reducing the progression of kidney fibrosis [49,50].

Kidney fibrosis is a critical step in the development of DN and a major contributor to ESRD. The antifibrotic properties of hPSCs offer promising opportunities to delay or even reverse the pathological progression of DN, positioning them as a potential therapeutic tool [51]. These attributes make hPSCs a highly promising candidate for DN treatment, offering a novel approach to addressing kidney fibrosis and providing hope for patients with advanced kidney disease (Fig. 2).

4. hPSCs in DN: Advances and Applications

4.1 hPSCs for DN Treatment

hPSCs have demonstrated significant potential in DN research, particularly in modeling the disease mechanisms and exploring novel treatment strategies. In one study, Leite *et al*. [33] successfully used iPSCs to differentiate into pancreatic endocrine cells, effectively modeling the immune response of patients with type 1 diabetes. This model highlighted the specific attack of autoimmune cells on β-cells, while α-cells were largely unaffected, providing a valuable *in vitro* tool for further understanding the immune mechanisms involved in diabetes. Meanwhile, Bantounas *et al*. [17] developed a method for generating kidney progenitor cells from hPSCs, which were then transplanted into immunodeficient mice to form mature kidney structures. This advancement highlights the potential of hPSCs in DN treatment, particularly as an alternative to kidney transplantation or dialysis. Additionally, Morizane [37] used hPSCs to generate vascular organoids that successfully modeled diabetes-induced vascular disease, revealing new therapeutic targets and providing an effective platform for researching diabetic complications.

In terms of cell replacement therapy, Ghila *et al*. [38]. utilized pancreatic progenitor cells derived from iPSCs for transplantation in a diabetic mouse model, demonstrating improved insulin secretion and increased survival rates of the transplanted cells, offering promising avenues for future cell-based therapies. Similarly, Balboa *et al*. [34] reviewed the role of hPSCs in modeling β-cell dysfunction, emphasizing the importance of gene-editing technology in recreating complex β-cell pathologies, thereby providing valuable insights into diabetes mechanisms and therapeutic development. Petersen *et al*. [52] also successfully differentiated hPSCs into pancreatic progenitor cells, recapitulating the development of the human pancreas, which aids in understanding diabetes pathogenesis and lays the foundation for novel cell replacement therapies.

In the development of disease models and personalized therapies, Gheibi *et al*. [35] generated insulin and glucose-responsive cells for disease modeling and diabetes treatment, demonstrating the ability to recreate disease states *in vitro* and providing an effective platform for drug development and individualized treatment. Liu *et al*. [40] utilized urine-derived iPSCs from diabetic patients to generate neurons, astrocytes, and microvascular endothelial cells, offering new tools for investigating diabetes-related central nervous system disorders and expanding possibilities for personalized treatment. Concurrently, Gorashi *et al*. [39] developed a model for diabetic endothelial dysfunction using patient-specific iPSCs, which is valuable for studying vascular complications of diabetes and screening potential therapeutic drugs.

Furthermore, Bajaj *et al*. [36] developed an hPSC-based kidney model to evaluate drug nephrotoxicity, providing a novel research avenue for assessing the safety of DN-related drugs. Qi *et al*. [41] applied gene-editing techniques to introduce specific point mutations into hPSCs, creating disease model cells that are instrumental in understanding DN pathology and developing personalized treatment strategies. Memon and Abdelalim [19] discussed the potential of using hPSCs to achieve precision medicine in diabetes research, emphasizing their role in creating personalized disease models and developing therapeutic approaches, thus paving the way for individualized diabetes treatment.

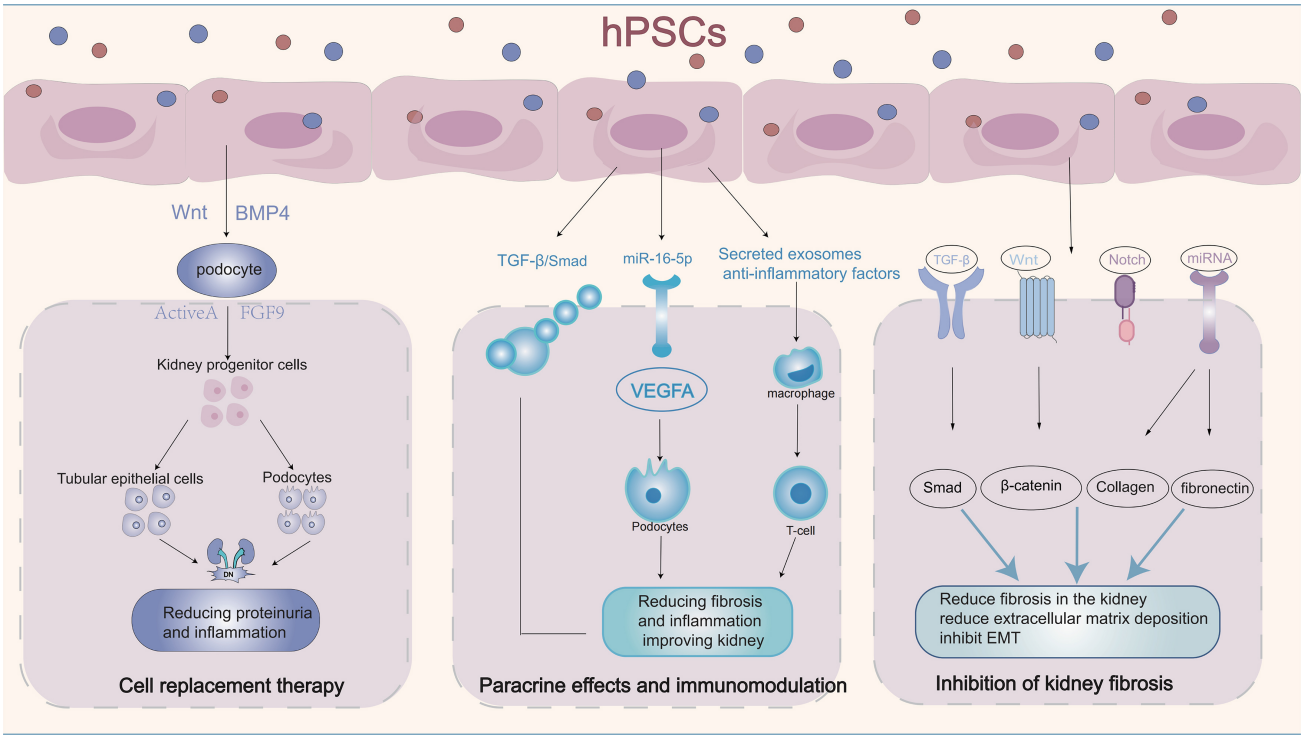

Fig. 2. Application of hPSCs in DN regeneration. hPSCs can differentiate into other cells by adding growth factors and pathway modulators, secreting exosomes for paracrine and immunomodulatory effects, and interfering with multiple fibrosis-related signaling pathways, achieving therapeutic effects for DN. TGF-β, transforming growth factor beta 1; VEGFA, vascular endothelial growth factor A. (Created with BioRender.com).

4.2 Current Use of hPSCs in DN Research

Currently, hPSCs in DN research are mainly in the experimental and preclinical stages, and have not yet been widely applied in clinical practice [2,53]. By contrast, mesenchymal SCs (MSCs) have already made their way into clinical use. For instance, a randomized, placebo-controlled, multicenter study evaluated the efficacy of allogeneic bone marrow (BM)-derived mesenchymal precursor cells in patients with DN, demonstrating good safety and tolerability along with positive effects on renal function in some patients [54]. These findings suggest that MSCs have shown initial clinical utility in DN treatment, laying the groundwork for further large-scale clinical trials.

MSCs, with their multipotent differentiation capability and immunomodulatory properties, have been extensively studied for DN treatment. They can be derived from a variety of tissues, including bone marrow, adipose tissue, umbilical cord, placenta, dental pulp, and amniotic fluid, with each source offering unique advantages in terms of efficacy, mechanism, and therapeutic potential (Table 1, Ref. [42,55–81]). BM-derived MSCs (BM-MSCs) were the first to be discovered and widely applied, and are known for their strong differentiation potential and immunomodulatory effects. Zhou *et al.* [55] found that intraventricular administration of BM-MSCs in DN rat models resulted in the cells colonizing the kidney, significantly reducing the proteinuria and renal mass index. Lang and Dai [56] demonstrated that BM-MSCs could inhibit renal fibrosis through suppression of the TGF-β1/Smad3 signaling pathway, showing their value in mitigating DN progression. Additionally, Luznik *et al.* [57] showed that systemic BM-MSC transplantation effectively restored islet function and prevented the onset of DN in type 1 diabetic mice.

Adipose-derived MSCs (AD-MSCs) have gained attention due to their relatively easy acquisition and minimally invasive nature. Takemura *et al.* [58] found that directly transplanting AD-MSC sheets into the kidneys of DN rats effectively slowed renal damage progression. In a Phase 1 clinical trial, Purwati *et al.* [82] evaluated the effects of autologous AD-MSC transplantation in patients with type 2 diabetes and observed significant reductions in blood glucose levels. However, Alicka *et al.* [59] noted that diabetic patients had reduced proliferation capacity in their AD-MSCs, potentially impacting their therapeutic efficacy. Umbilical cord-derived MSCs (UC-MSCs) have strong proliferative capabilities and low immunogenicity. Park *et al.* [60] found that UC-MSCs exert nephroprotective effects in DN through paracrine signaling. Montanucci *et al.* [61] demonstrated that UC-MSCs could improve immune dysfunction in patients with type 1 diabetes by restoring the regulatory T cell/T helper 17 (Th17) cell balance. Chen *et al.* [62] found that UC-MSCs significantly improved renal function in DN models by inhibiting the apop-

tosis signal-regulating kinase 1 and p38 mitogen-activated protein kinase pathways.

Placenta-derived MSCs (PL-MSCs), known for their non-invasive acquisition and immunomodulatory and tissue repair capabilities, have also been studied for diabetes treatment. In a clinical trial, Jiang *et al.* [63] infused PL-MSCs into patients with type 2 diabetes, observing reduced insulin requirements and improved renal function. Furthermore, Han *et al.* [64] showed that PL-MSCs reduced podocyte injury in DN by activating the sirtuin 1 (SIRT1)/peroxisome proliferator-activated receptor gamma coactivator-1 alpha/mitochondrial transcription factor A signaling pathway. Dental pulp-derived MSCs (DP-MSCs) have also garnered attention due to their powerful regenerative potential. Rao *et al.* [65] demonstrated that SCs from human exfoliated deciduous teeth (SHED) significantly improved kidney damage in DN models. Kanafi and Bhonde [66] highlighted the potential of DP-MSCs to differentiate into insulin-secreting cells, suggesting promising therapeutic potential for pancreatic regeneration.

Amniotic fluid-derived MSCs (AF-MSCs) possess multi-lineage differentiation potential and low immunogenicity, offering promising clinical applications. Feng *et al.* [67] investigated the role of SIRT3 in AFSCs, showing that it regulated mitochondrial autophagy and enhanced AFSCs' therapeutic efficacy in DN. Kim *et al.* [68] found that AF-MSCs promoted angiogenesis and re-epithelialization in diabetic mice, accelerating wound healing and further demonstrating their potential in treating diabetic complications.

5. Advantages and Challenges of Induced Pluripotent Stem Cells in the Treatment of DN

iPSCs exhibit more significant advantages than MSCs in the treatment of DN, primarily due to their pluripotency, enhanced differentiation potential, immunomodulatory capacity, and suitability for personalized therapy.

5.1 Enhanced Pluripotency and Differentiation Potential

iPSCs possess high pluripotency, enabling them to differentiate into various specialized cell types, which is particularly crucial for cell replacement therapy in DN. Osafune [53] emphasized that the pluripotency of iPSCs allows them to generate renal lineage cells, providing new possibilities for DN treatment. By contrast, MSCs have relatively limited differentiation potential and cannot generate specific renal cells. Thanaskody *et al.* [83] pointed out that iPSCs can be generated from adult somatic cells through genetic reprogramming without involving embryonic destruction, thus avoiding ethical controversies. Their ability for self-renewal and differentiation into multiple specialized cell types makes iPSCs a significant cell source in regenerative medicine, offering broader regenerative potential in DN treatment compared to MSCs.

5.2 Immunomodulation and Enhanced Therapeutic Effects

iPSC-derived MSCs (iPSC-MSCs) exhibit significant advantages in immunomodulation and therapeutic efficacy. Cheng *et al.* [84] demonstrated that iPSC-MSCs combined with low-dose rapamycin can significantly prolong the survival time of transplanted islets, enhancing immunosuppressive effects. iPSC-MSCs display remarkable immunomodulatory functions by inhibiting the release of *Th1* pro-inflammatory cytokines, thereby enhancing the ability to counteract diabetes-related immune responses. Similarly, Ozay *et al.* [85] noted that iPSC-MSCs have tri-lineage differentiation capacity similar to BM-derived MSCs and significantly extend graft survival time in transplantation models. This suggests that iPSC-MSCs may be an effective strategy for treating diabetic complications, including DN. Wang *et al.* [75] compared the therapeutic effects of iPSC-MSCs and adult MSCs, and in acute kidney injury. The results showed that iPSC-MSCs are comparable to adult MSCs and, in some cases, exhibit superior tissue repair capabilities and promote angiogenesis. Lee *et al.* [86] demonstrated that iPSC-MSCs can prevent the progression of DN by improving mitochondrial function and inhibiting inflammation, indicating their potential in regulating metabolic processes and providing therapeutic effects.

5.3 Personalized Therapy and Disease Modeling

Another significant advantage of iPSCs is their ability to generate patient-specific cells, thereby avoiding immune rejection reactions. Päth *et al.* [87] emphasized that iPSCs can produce patient-specific renal cells, offering a more personalized treatment approach, which is especially important for chronic diseases like DN. Moreover, iPSCs hold substantial value in disease modeling and drug development. Liu and Tang [88] pointed out that iPSCs can not only be used to construct disease models but also directly treat kidney injuries by generating renal cells. Wu *et al.* [89] highlighted the potential of iPSCs in generating specific types of renal cells, providing possibilities for future personalized DN therapies. Additionally, Himeno *et al.* [90] found that iPSC-derived MSC-like cells can significantly improve DN, demonstrating their potential in treating diabetic complications. The ability of iPSCs to generate specific cell types for repairing damage underscores their multifunctionality compared to MSCs.

5.4 Treatment Time and Complexity

The differentiation process of iPSCs is complex, involving multiple stages of cell culture and induction. Compared to MSCs, the use of iPSCs demands a higher level of operational complexity, presenting technical bottlenecks and longer timelines for clinical translation. To improve the differentiation efficiency and cell maturity, optimizing culture systems is essential. Technologies such as 3D bioreactors and microfluidic chips allow for better simulation of

Table 1. MSCs from different sources.

Research (author and year)	Mechanism/Principle	Research results
Bone marrow-derived MSCs, BM-MSCs		
Zhou *et al.* (2009) [55]	BM-MSCs colonization in kidneys without sustained proliferation	Reduction in urinary protein and renal mass index
Lang and Dai (2016) [56]	Inhibition of TGF-β1/Smad3 signaling to reduce renal fibrosis	Reduction in 24-hour urinary protein, serum creatinine, and renal mass index
Luznik *et al.* (2008) [57]	Promotion of pancreatic β-cell regeneration, reducing renal fibrosis	Lowered blood glucose, preventing DN onset
Mousa *et al.* (2016) [70]	Regulation of metabolic markers, reducing inflammation	Improvements in renal, hepatic, and glucose levels
He *et al.* (2020) [71]	Promote insulin-secreting cell regeneration, activating GSK-3β/β-catenin pathway	Improved renal function, reduced urinary protein
Lin *et al.* (2020) [72]	Activation of GSK-3β/β-catenin pathway, enhancing renal function	Reduction in urinary protein and renal damage
Akagun *et al.* (2017) [73]	Improvement of metabolic abnormalities in diabetes patients	BM-MSCs improve blood glucose and metabolic irregularities, aiding diabetes management
Adipose tissue-derived MSCs, AD-MSCs		
Takemura *et al.* (2020) [58]	Direct transplantation of AD-MSC cell sheets into kidney	Suppression of renal injury progression
Alicka *et al.* (2019) [59]	Comparative study on AD-MSC function in diabetic vs. non-diabetic patients	Reduced proliferation, secretion, and mitochondrial function in diabetic AD-MSCs may affect therapeutic potential
Timper *et al.* (2006) [74]	AD-MSCs differentiated into insulin-secreting cells	Potential for AD-MSCs as cell replacement therapy in diabetes
Wang *et al.* (2018) [75]	AD-MSCs improve insulin sensitivity, reduce inflammatory responses	Lowered inflammatory markers, improved insulin resistance in diabetic models
Ni *et al.* (2015) [76]	AD-MSCs reduce inflammation, improve metabolism	Improved glucose metabolism through inflammation reduction
Habib *et al.* (2021) [77]	Synergistic effect of AD-MSCs combined with other therapies	Enhanced efficacy in diabetes treatment with combined therapies, indicating synergy
Umbilical cord-derived MSCs, UC-MSCs		
Park *et al.* (2012) [60]	Paracrine action reducing TGF-β1-induced epithelial-mesenchymal transition	Renal protection in DN, reducing renal injury
Montanucci *et al.* (2016) [61]	Restoration of Treg/Th17 balance, improving immune dysfunction	Microencapsulated UC-MSCs improve immune dysfunction in type 1 diabetes
Chen *et al.* (2020) [62]	Inhibition of ASK1 and P38 MAPK pathways, reducing apoptosis	Enhanced renal function, reduced renal cell apoptosis
Li *et al.* (2020) [42]	Inhibition of TGF-β1-mediated myofibroblast transformation, reducing renal fibrosis	Reduction in fibrosis, improvement in DN pathology
Guan *et al.* (2015) [78]	UC-MSCs differentiate into insulin-secreting cells, enhancing pancreatic function	Increased insulin secretion, lowered glucose in diabetes models
Zang *et al.* (2023) [79]	UC-MSCs improve glucose metabolism, reduce insulin resistance	Reduced or discontinued insulin use in some type 2 diabetes patients post-transplantation
Placenta-derived MSCs, PL-MSCs		
Jiang *et al.* (2011) [63]	Intravenous PL-MSC infusion to assess safety and efficacy	Reduced insulin use, increased C-peptide levels, improved renal function
Han *et al.* (2023) [64]	Activation of SIRT1-PGC-1α-TFAM pathway regulating mitochondrial autophagy	Alleviated podocyte damage in DN, showing potential in DN treatment
Liang *et al.* (2017) [80]	Promotion of angiogenesis through pro-angiogenic and immune factors	Improved ischemia in diabetic rats; essential in treating diabetes complications

Table 1. Continued.

Research (author and year)	Mechanism/Principle	Research results
Dental pulp-derived MSCs, DP-MSCs		
Rao *et al.* (2019) [65]	Inhibition of AGEs-induced epithelial-mesenchymal transition, reducing renal fibrosis	Improvement in renal damage in DN models, protective effects
Kanafi and Bhonde (2024) [66]	Differentiation into insulin-secreting cells, promoting pancreatic regeneration	Therapeutic potential in diabetes treatment
Yamada *et al.* (2019) [81]	Pluripotency and self-renewal for systemic disease treatments	Broad application prospects in regenerative medicine; potential in DN
Amniotic fluid-derived MSCs, AF-MSCs		
Feng *et al.* (2018) [67]	SIRT3 regulates mitochondrial autophagy, enhancing AFSCs tolerance in high glucose	SIRT3-modified AFSCs improved glucose metabolism, reduced renal fibrosis and injury, showing therapeutic potential in DN
Kim *et al.* (2012) [68]	Promotes angiogenesis and re-epithelialization, accelerating wound healing	Accelerated wound healing in diabetic NOD/SCID mice; strategy for chronic diabetic wound treatment
Harrell *et al.* (2019) [69]	Highlighted AF-MSCs' therapeutic potential in degenerative and inflammatory diseases	Emphasizing their differentiation capacity and immunomodulatory effects, especially in DN

MSCs, mesenchymal SCs; GSK-3β, Glycogen synthase kinase 3 beta; MAPK, mitogen-activated protein kinase; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; Th17, T helper 17; TFAM, mitochondrial transcription factor A; AFSCs, amniotic fluid stem cells.

the *in vivo* microenvironment, providing more physiologically relevant conditions that enhance the functionality of the derived cells for DN treatment [91]. Dynamic monitoring with single-cell RNA sequencing (scRNA-seq) allows real-time tracking of differentiation, while precise modulation of signaling pathways like Wnt, BMP, and Notch improves differentiation accuracy and iPSC therapeutic potential [92]. MSCs, on the other hand, offer a simpler therapeutic approach with rapid efficacy, particularly advantageous in the acute or early stages of DN, where their effects can be swiftly realized through intravenous infusion [43]. However, for iPSCs, optimizing cell delivery methods remains a challenge. Techniques such as renal artery injection, tail vein injection, and local tissue implantation have been explored to improve cell engraftment and ensure their long-term survival in the kidney [93]. Furthermore, the success of iPSC-based therapies depends on immune and inflammation modulation. Gene editing to reduce the expression of major histocompatibility complexes (MHC) or the use of immunosuppressive agents can minimize immune rejection and enhance integration with host tissues [94]. Finally, improving the renal microenvironment using biomaterials (e.g., hydrogels and scaffolds) along with local delivery of pro-angiogenic or anti-inflammatory factors can support the long-term functionality of transplanted cells [95].

5.5 Tumorigenic Risk

The risk of tumorigenesis is a significant concern in the clinical application of iPSCs. Han *et al.* [96] reported a case in which a diabetic patient developed an immature teratoma following an injection of iPSC-derived β cells. The patient exhibited a locally invasive tumor with lymph node metastasis, underscoring the potential tumorigenic risks associated with iPSC therapies and highlighting the need for stringent safety evaluations in clinical trials. Seno and Nostro [97] further discussed the inherent risk of undifferentiated iPSCs adopting cancerous phenotypes, emphasizing the importance of stringent control during the differentiation process to minimize tumor formation. In a related study, Tajiri *et al.* [98] demonstrated the potential of iPSCs derived from dialysis patients to regenerate renal tissue; however, they also stressed the need to ensure that these cells do not lead to tumor formation or other adverse effects in patients with chronic kidney disease. To mitigate these risks, Kuang *et al.* [99] proposed an innovative approach involving alkaline phosphatase-mediated synthetic peptide aggregation to selectively eliminate undifferentiated iPSCs, thereby significantly reducing the risk of tumorigenesis and enhancing the safety of iPSC-based therapies.

5.6 Immune Rejection

hPSCs also present a substantial risk of immune rejection, particularly when using allogeneic cells, which may necessitate prolonged immunosuppressive therapy. By contrast, MSCs exhibit inherently low immunogenicity, resulting in better compatibility for allogeneic transplantation and a reduced risk of immune rejection [100]. Pellegrini and Sordi [100] pointed out that despite the significant potential of iPSCs in regenerative medicine, their application is still hindered by challenges such as immunogenicity and

tumorigenic risk. They suggested that the implementation of more rigorous differentiation and purification protocols is essential to enhance the safety of iPSC-based treatments.

5.7 Uncertain Long-Term Efficacy

The long-term efficacy of hPSCs in treating DN remains uncertain, necessitating further research and validation. By contrast, the application of MSCs in chronic kidney disease has been well documented, with numerous clinical studies demonstrating their effectiveness, particularly in enhancing renal function and slowing disease progression [101]. Liu and Tang [88], in their comprehensive review, highlighted both the potential and limitations of iPSCs in treating chronic conditions such as DN. They emphasized that, despite the promise shown by iPSCs in terms of differentiation potential and immunomodulatory capacity, issues related to tumorigenesis and immune rejection remain major obstacles that must be addressed before broader clinical application.

iPSCs show considerable promise for treating DN, but their clinical application is hindered by several significant challenges, including risks of tumorigenesis, immune rejection, low differentiation efficiency, difficulties in large-scale production, and issues with genetic and epigenetic stability. Additionally, the complex and time-consuming differentiation process of iPSCs presents obstacles, particularly in scenarios where rapid therapeutic intervention is required, making MSCs a more favorable option in such cases. To advance the use of iPSCs in DN treatment, it is crucial to enhance differentiation protocols, employ precise gene-editing tools [102], and implement stringent quality control measures, thereby ensuring a safe and effective approach to personalized therapy.

6. Potential of hPSCs in the Treatment of DN

hPSCs show substantial promise in the treatment of DN, particularly in personalized therapy, genetic correction, and tissue engineering. With advancements in gene editing and bioengineering technologies, hPSCs are expected to offer safer and more effective treatments for DN in the near future (Fig. 3).

6.1 Personalized Therapy and Disease Modeling

hPSCs possess high pluripotency, allowing differentiation into various renal cell types, which provides an opportunity for personalized therapy. Patient-specific iPSCs can be used to prevent immune rejection associated with allogeneic transplantation, thereby enhancing therapeutic efficacy [103]. For instance, Lim *et al*. [104] corrected gene mutations in iPSCs derived from patients with Gitelman syndrome using clustered regularly interspaced short palindromic repeats (CRISPR) technology, leading to the development of functional renal organoids with restored normal function, highlighting the potential of iPSCs in treating genetic kidney diseases. Furthermore, hPSCs have demonstrated significant value in disease modeling. Shamshirgaran *et al*. [105] used CRISPR/Cas9 to generate iPSC-derived kidney organoid models, accurately recapitulating the polycystic kidney disease (ADPKD) phenotype, thus providing an effective platform for target validation and treatment strategy exploration.

hPSCs also play a crucial role in disease modeling. iPSC-derived kidney organoids can partially mimic glomerular diseases, providing valuable tools for studying disease mechanisms and drug screening [106]. Rota *et al*. [107] highlighted the significant potential of iPSCs in generating kidney-specific cells like podocytes and tubular epithelial cells, though challenges such as post-transplant cell survival and functional integration remain. Moreover, iPSC-derived kidney organoids can effectively mimic pathological processes in diabetic nephropathy (DN), such as foot cell damage and tubulointerstitial fibrosis, providing an important model for DN research [105]. High-throughput drug screening platforms utilizing these organoids can more accurately replicate the human kidney's response to drug treatments compared to traditional monolayer cell cultures or animal models, making them ideal for drug screening [108]. By integrating kidney organoids into microfluidic chips, multiple drug combinations can be screened in parallel in small volumes across multiple channels. This approach, combined with assays for cell viability, inflammatory markers, and histological staining, enables a comprehensive evaluation of drug effects and toxicity [109].

6.2 Application of Gene Editing in hPSCs for Enhanced Therapeutic Effectiveness

The application of CRISPR gene editing in hPSCs has shown remarkable potential, particularly in repairing disease-specific gene mutations. Through CRISPR technology, researchers can modify specific genes in hPSCs to correct gene mutations associated with renal diseases, thereby improving therapeutic outcomes [110]. For example, Brandão *et al*. [111] introduced specific mutations in human iPSCs using CRISPR/Cas9, which provides an efficient tool for modeling genetic kidney diseases. Further advances in gene editing have enabled multiplex editing and large-scale gene correction, which could be crucial for treating complex genetic conditions. Ma [112] utilized CRISPR-Cpf1 for simultaneous multi-gene editing, improving the modeling efficiency of complex kidney diseases. This capability enhances the accuracy of the models, making it feasible to treat conditions with complex genetic backgrounds. Maguire *et al*. [113] developed a CRISPR/Cas9 gene editing method combining two oligonucleotide repair templates to achieve high precision during specific gene modifications, thereby enhancing the therapeutic potential of hPSCs. CRISPR has also been used to enhance the immune evasion capability of hPSC-derived renal organoids, further improving their ther-

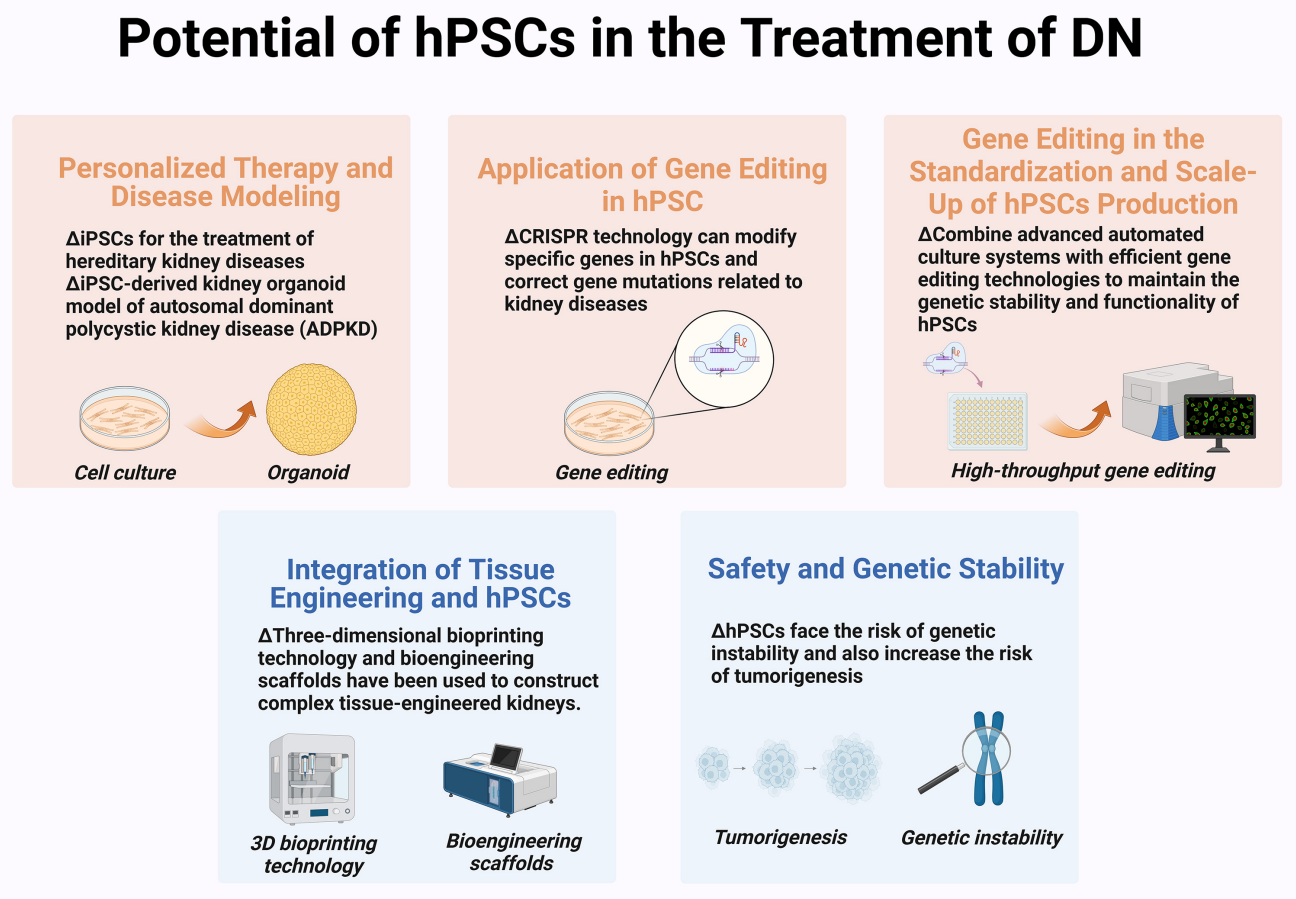

Fig. 3. Potential of hPSCs in the treatment of DN. Therapeutic potential of hPSCs is mainly reflected in their ability to provide personalized, targeted treatments, enhance efficacy through gene editing, enable large-scale standardized production, integrate with tissue engineering, and offer reliable safety and genetic stability. (Created with BioRender.com).

apeutic effectiveness. Gaykema *et al.* [114] knocked out β-2-microglobulin, eliminating human leukocyte antigen (HLA) class I expression and significantly reducing immune rejection *in vitro*. Nevertheless, since HLA class II molecules still existed after transplantation, additional modification of HLA class II molecules is necessary for complete immune evasion.

6.3 Role of Gene Editing in the Standardization and Scale-Up of hPSCs Production

The production of hPSCs is complex and faces challenges regarding standardization and scale-up, particularly in maintaining genetic stability and ensuring batch-to-batch consistency. To meet clinical demands, it is critical to combine advanced automated culture systems with efficient gene editing technologies to maintain the genetic stability and functionality of hPSCs [115]. Jurlina *et al.* [116] developed a tetracycline-inducible high-fidelity CRISPR platform by integrating high-fidelity Cas9 into the adeno-associated virus integration site 1 (AAVS1) safe harbor locus, which significantly improved editing efficiency and reduced quality variations between batches during large-scale production. This high-precision gene editing technique ensures that hPSCs maintain genetic stability during mass production, thus reducing tumorigenic risk. Wang *et al.* [117] demonstrated the feasibility of using CRISPR/Cas ribonucleoproteins for high-throughput gene editing, providing a rapid and efficient approach to repairing genetic defects in hPSCs, which is beneficial for producing stable cells on a large scale for therapeutic purposes. These developments will help address challenges in production, particularly regarding the consistency and safety of cells during large-scale production.

6.4 Integration of Tissue Engineering and hPSCs

The integration of tissue engineering technologies with hPSCs further expands their application potential. For instance, 3D bioprinting has been utilized to construct complex tissue-engineered kidneys, enhancing the integration and regenerative capabilities of hPSCs *in vivo* [115]. In another study, Kim *et al.* [118] used decellularized ECM hydrogels to improve the vascularization and maturation of hPSC-derived renal organoids, which successfully recapitulated the renal pathology of Fabry disease, promoting clinical feasibility. Additionally, the use of bioengineered scaffolds can provide an ideal microenvironment for the growth

of hPSCs, thereby improving cell integration and overall therapeutic efficacy post-transplantation [119,120]. Hammad *et al*. [121] successfully used CRISPR/Cas to introduce a fluorescent biosensor gene into iPSCs, enabling real-time monitoring of cellular behaviors during the generation of kidney organoids. This technology allows more precise tracking of cell differentiation and maturation processes, thus paving the way for further optimization of hPSC-based therapies.

6.5 3D Bioprinting and hPSCs

During large-scale *in vitro* expansion, hPSCs face the risk of genetic instability, which affects therapeutic efficacy and safety [115]. Genetic instability not only compromises therapeutic reliability but also increases tumorigenic risk. Therefore, the development of efficient and precise gene editing methods is essential for maintaining genetic stability in hPSCs. For example, CRISPR/Cpf1-mediated multigene editing can effectively reduce the accumulation of genetic mutations, thereby decreasing tumor risk and enhancing cellular safety [112].

To mitigate genetic instability, researchers have also explored non-integrative CRISPR/Cas9 knockout methods to avoid random integration of exogenous gene segments. Mamun and Bukhari [122] proposed a simplified CRISPR/Cas9 gene editing method that effectively avoids foreign DNA integration, improves editing efficiency, and enhances the applicability of hPSCs for clinical use. High-fidelity CRISPR variants and base editing offer advanced solutions for precise genetic manipulation. Modifying the Cas9/Cpf1 protein structures significantly reduces off-target effects while improving gene editing efficiency [116]. Base editing, which allows base substitution without causing double-strand breaks, reduces the risk of large-scale genomic rearrangements, making it a safer approach for gene correction. Additionally, prime editing further extends the editing potential by handling complex base substitutions and small insertions [123]. The concept of a "body-on-a-chip" offers a novel approach to studying the effects of drugs on multiple systems in patients with DN. By interconnecting multiple microphysiological systems, researchers can more comprehensively simulate drug metabolism and toxicity within the human body. This integrated approach provides a holistic perspective, aiding in the accurate assessment of drug safety and efficacy in DN research [124]. To ensure the safety and consistency of hPSCs, large-scale culture and quality control are essential. Techniques such as digital PCR and next-generation sequencing (NGS) can be employed to monitor off-target edits and genomic structural changes, ensuring the consistency and safety of cell products [125]. *In vivo* experiments and long-term monitoring are also critical to verifying the stability and functionality of transplanted cells. Animal models can be used to track whether transplanted cells exhibit chromosomal abnormalities or tumorigenic tendencies. Regular assessments of kidney function markers are also necessary to confirm the clinical potential of the cell therapies [108,126].

7. Conclusion

DN remains a major complication of diabetes with limited therapeutic options, especially in advanced stages. hPSCs, particularly iPSCs, offer promising avenues for both treatment and research. Their ability to differentiate into kidney-specific cells and enable personalized therapies makes them valuable tools in regenerative medicine. Advances in CRISPR-based gene editing further enhance their therapeutic potential by allowing precise correction of genetic abnormalities. Additionally, hPSC-derived kidney organoids serve as effective models for disease mechanism studies and drug screening. Compared to mesenchymal stem cells, hPSCs provide broader differentiation capabilities, particularly when integrated with tissue engineering strategies such as 3D bioprinting and bioengineered scaffolds. Despite ongoing challenges like tumorigenicity and genomic instability, continued advancements in stem cell biology, gene editing, and biomaterial technology are paving the way for the clinical application of hPSC-based therapies in DN, potentially transforming the future of diabetic kidney disease management.

Author Contributions

JY and CZ designed the study; FY and WX drafted the manuscript, HL, XZ and ZS performed literature selection and drew the figures; YD and WZ revised the manuscript. WX, FY, YD, and WZ contributed to the literature selection and acquisition. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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