Chapter 7

Stem Cell Therapy in the Treatment of Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is one of the most serious complications of diabetes mellitus and a leading cause of end-stage renal disease (ESRD) worldwide. Current therapeutic strategies mainly focus on controlling blood glucose levels and slowing disease progression, but they are often unable to completely prevent renal damage. In recent years, stem cell–based therapy has emerged as a promising approach for the treatment of DN. Among the different types of stem cells, mesenchymal stem or stromal cells (MSCs) have gained considerable attention due to their regenerative potential, immunomodulatory properties, and ability to promote tissue repair. Several preclinical studies and early-phase clinical trials have demonstrated that MSC therapy may improve renal function, reduce inflammation, and inhibit fibrosis in diabetic kidneys. The therapeutic effects of MSCs are mainly attributed to their paracrine signaling, anti-inflammatory activity, and capacity to enhance cellular regeneration. This chapter reviews the recent advances in MSC-based therapy for diabetic

ISBN 978-816855389-7

nephropathy, highlighting the underlying mechanisms involved in renal protection and repair. In addition, the potential benefits, limitations, and possible risks associated with MSC therapy are discussed. Understanding these mechanisms may contribute to the development of novel therapeutic strategies and drug targets for the effective management of diabetic nephropathy.

Keywords: Diabetic nephropathy, Diabetes mellitus, End-stage renal disease, Stem cell therapy, Mesenchymal stem cells.

1. Introduction

Diabetic Nephropathy (DN) is a major microvascular complication of Diabetes Mellitus (DM) and a leading cause of End-Stage Renal Disease (ESRD) worldwide [1]. Persistent hyperglycemia in diabetes can damage several organs, particularly the kidneys, leading to progressive renal dysfunction [2]. Despite advances in glycemic control and the use of therapies targeting the Renin–Angiotensin–Aldosterone System (RAAS), current treatments mainly slow disease progression rather than completely preventing kidney failure [1]. Therefore, the development of new therapeutic strategies is essential. In recent years, regenerative medicine has emerged as a promising approach for the treatment of DN. Among these strategies, Mesenchymal Stem Cells (MSCs) have gained significant attention due to their ability to promote tissue repair, modulate immune responses, and secrete bioactive factors that support regeneration [3]. Preclinical studies and early clinical trials suggest that MSC-based therapy may help reduce renal inflammation, fibrosis, and structural damage, thereby offering a potential therapeutic option for slowing the progression of DN [4].

2. Diabetic Nephropathy

Diabetic Nephropathy (DN) is one of the most serious microvascular

complications of diabetes mellitus and a leading cause of End-Stage Renal Disease worldwide [1]. It develops due to long-term hyperglycemia, which progressively damages the renal microvasculature and glomerular structure [2]. The early clinical manifestation of DN is Microalbuminuria, followed by structural and functional alterations such as glomerular hypertrophy, thickening of the glomerular basement membrane, mesangial expansion, and renal fibrosis [2]. As the disease progresses, these pathological changes lead to glomerulosclerosis and gradual loss of kidney function. Current treatment strategies mainly focus on controlling blood glucose levels and inhibiting the Renin–Angiotensin–Aldosterone System using drugs such as ACE inhibitors and angiotensin receptor blockers [1]. However, these therapies primarily slow disease progression rather than completely reversing kidney damage. Therefore, novel therapeutic approaches, particularly regenerative medicine and stem cell therapy, are being explored as potential strategies to restore renal structure and function in DN [4].

3. Mesenchymal Stem Cells in Regenerative Medicine

Mesenchymal Stem Cells (MSCs) have become a major focus in regenerative medicine due to their therapeutic potential in treating various diseases [3]. First identified in the late 1960s in mesodermal tissues, MSCs are multipotent stromal cells capable of self-renewal and differentiation into multiple cell lineages [5]. They can be isolated from several tissues such as bone marrow, adipose tissue, umbilical cord blood, and amniotic fluid. MSCs possess several advantages for cell-based therapy, including easy isolation, rapid expansion in vitro, low immunogenicity, and the ability to migrate toward sites of tissue injury [3]. In addition, MSCs exert strong therapeutic effects through the secretion of bioactive molecules such as cytokines, growth

ISBN 978-816855389-7

factors, and extracellular vesicles including exosomes, which promote tissue repair and regeneration [6]. Due to these properties, MSCs have been widely investigated in preclinical and clinical studies for the treatment of various disorders, including neurodegenerative diseases, cardiovascular diseases, and organ failure [3]. These promising characteristics highlight the potential of MSC-based therapy as an emerging strategy in regenerative medicine.

4. Overview of MSC Therapy in Diabetic Nephropathy

Diabetic Nephropathy (DN) is one of the most serious complications of Diabetes Mellitus, and it is a major cause of End-Stage Renal Disease (ESRD) worldwide [1]. DN develops as a result of chronic hyperglycemia, leading to progressive kidney damage characterized by microalbuminuria, glomerular hypertrophy, mesangial expansion, and thickening of the glomerular basement membrane [2]. Current therapeutic approaches mainly focus on controlling blood glucose levels and regulating the Renin–Angiotensin–Aldosterone System (RAAS) using ACE inhibitors, angiotensin receptor blockers, and other antihyperglycemic agents [1]. However, these treatments only slow disease progression and do not completely prevent renal failure.

In recent years, regenerative medicine has emerged as a promising strategy for DN treatment. Among the various approaches, Mesenchymal Stem Cells (MSCs) have attracted significant attention due to their regenerative, immunomodulatory, and anti-inflammatory properties [3]. MSCs can migrate to injured tissues, secrete growth factors and cytokines, and promote tissue repair through paracrine signaling and extracellular vesicles such as exosomes [6]. Preclinical and early clinical studies suggest that MSC-based therapy may reducerenal inflammation, fibrosis, and oxidative stress, thereby

improving kidney function and slowing DN progression [4].

5. Mechanism of MSC Therapy in Treating DKD

Mesenchymal cells play a prominent role in treating Diabetic Kidney Disease (DKD) through strong immunomodulatory and anti-inflammatory effects [7]. They regulate the immune environment of the kidney through direct interaction with immune cells and secreting various cytokines. This decreases renal inflammation by suppressing pro -inflammatory cytokines such as IL-1β, IL-6, and TNF-α and decreasing infiltration of immune cells like dendritic cells, $CD8^+$ T cells, and macrophages [7]. MSC therapy also inhibits monocyte chemoattractant protein-1 (MCP-1), thereby limiting macrophage accumulation in kidney tissues.

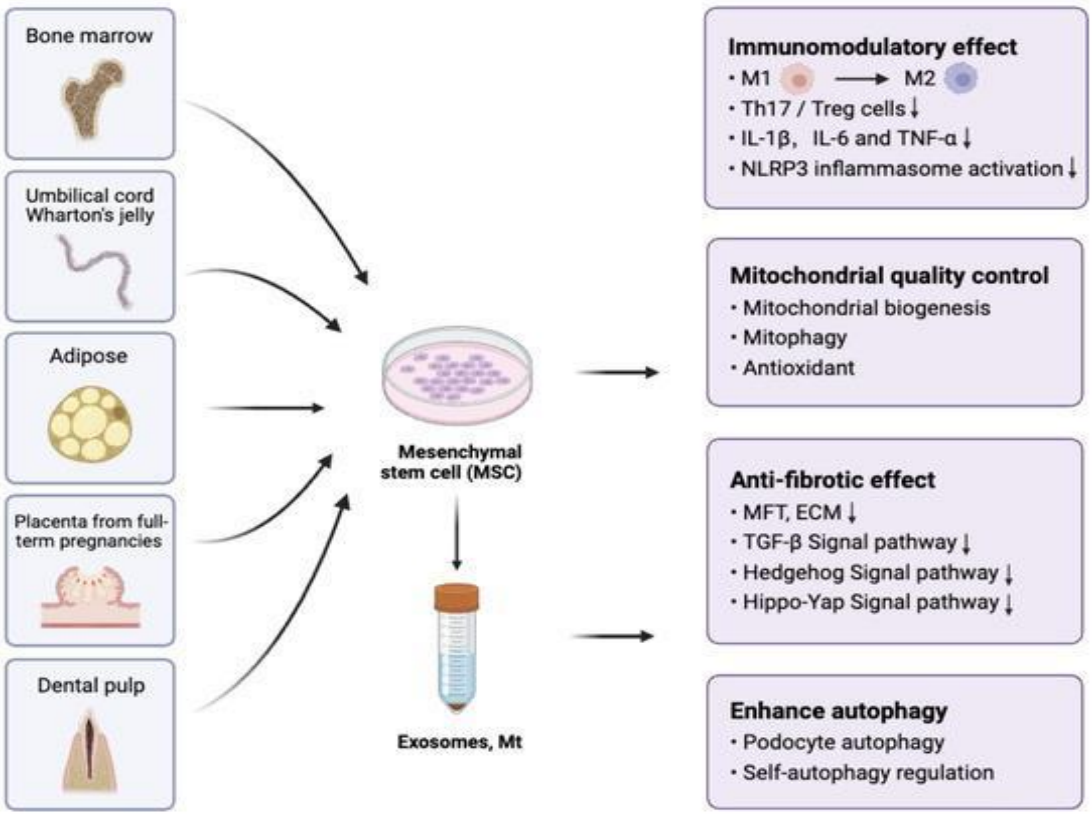

Figure 1: The therapeutic effects of MSCs and their derivatives from different sources in the treatment of DKD

ISBN 978-816855389-7

MSCs also help shift macrophages toward the anti-inflammatory M2 phenotype, which plays an important role in limiting tissue damage and promoting repair [8]. In addition to local effects in the kidney, MSCs influence systemic immune responses by lowering circulating inflammatory cytokines and restoring the balance between Th17 and Treg cells, which is often disturbed in DKD. Furthermore, MSCs and their released exosomes can suppress inflammatory signaling pathways such as Toll-Like Receptor Signaling and the NLRP3 Inflammasome [6], helping to protect kidney cells from further damage.

6. Mitochondrial Quality Control

Mitochondrial quality control plays an important role in maintaining normal cellular function by regulating processes such as mitochondrial DNA repair, mitochondrial fusion and fission, mitophagy, and mitochondrial biogenesis [9]. In Diabetic Kidney Disease (DKD), mitochondrial number and activity are often reduced, which contributes to kidney cell damage [9].

Mesenchymal Stem Cells (MSCs) can help restore mitochondrial function in damaged kidney cells. Studies have shown that MSCs are able to transfer mitochondria to injured cells through structures such as tunneling nanotubes or other cellular communication pathways [10]. This transfer improves cellular energy production, reduces oxidative stress, and limits apoptosis in kidney cells. MSCs also stimulate mitochondrial biogenesis and mitophagy, which help maintain mitochondrial balance and remove damaged mitochondria.

In addition, MSC therapy can improve the function of important kidney cells including tubular epithelial cells, glomerular endothelial cells, and podocytes by regulating mitochondrial signaling pathways.

Overall, MSCs support kidney repair in DKD by improving mitochondrial health and activating protective cellular mechanisms.

7. Antifibrotic Effect of MSC Therapy

Fibrosis and epithelial–mesenchymal transition are major pathological features of Diabetic Kidney Disease (DKD) [1]. These changes lead to excessive accumulation of extracellular matrix proteins in kidney tissue, resulting in glomerulosclerosis and reduced kidney filtration. Persistent hyperglycemia, cytokines, and advanced glycation end products stimulate myofibroblast formation and promote fibrotic changes in the kidney. Because the degree of fibrosis is closely associated with disease severity, preventing or reducing fibrosis is important for slowing the progression of DKD toward End-Stage Renal Disease (ESRD).

Mesenchymal Stem Cells (MSCs) and their secreted vesicles have been shown to reduce renal fibrosis by limiting extracellular matrix production and enhancing its breakdown. MSC therapy can suppress fibrotic signaling pathways and decrease the expression of proteins that promote matrix accumulation. In addition, MSC-derived factors can inhibit epithelial–mesenchymal transition and reduce collagen and fibronectin deposition in kidney tissue [8]. Since inflammation contributes to fibrosis, the anti-inflammatory actions of MSCs also indirectly help prevent fibrotic progression. Overall, MSC-based therapies may protect kidney structure and function by controlling fibrotic processes in DKD.

8. Conclusion

Mesenchymal Stem Cells (MSCs) have emerged as a promising therapeutic approach for the treatment of Diabetic Kidney Disease (DKD) due to their ability to regulate multiple biological processes

ISBN 978-816855389-7

involved in disease progression. Evidence from experimental studies shows that MSCs can reduce inflammation, limit fibrosis, improve mitochondrial function, and enhance cellular repair mechanisms such as autophagy. These effects are mainly achieved through the release of bioactive factors, exosomes, and the regulation of several important signaling pathways.

MSCs also help restore the balance of immune responses, reduce the accumulation of extracellular matrix proteins, and protect kidney cells from damage caused by chronic hyperglycemia. In addition, their ability to support mitochondrial quality control and activate protective cellular pathways contributes to improved kidney cell survival and function.

Although the current findings are encouraging, further research and large-scale clinical trials are required to better understand the safety, long-term effectiveness, and optimal application of MSC-based therapies. Overall, MSC therapy represents a potential regenerative strategy that may help slow the progression of DKD and improve future treatment options for patients.

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ISBN 978-816855389-7