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Therapeutic Potential of Mesenchymal Stem Cells and Their Secretome in Ameliorating Renal Fibrosis: A Comprehensive Narrative Review

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ABSTRACT

Chronic kidney disease (CKD) represents a global health challenge with limited therapeutic options, often progressing to end-stage renal disease requiring dialysis or transplantation. Renal fibrosis, characterized by excessive extracellular matrix deposition and loss of functional nephrons, constitutes the final common pathway for most progressive kidney diseases. Conventional therapies primarily target symptoms rather than underlying pathological mechanisms. Mesenchymal stem cells (MSCs) have emerged as promising candidates for regenerative therapy due to their multipotent differentiation capabilities, immunomodulatory properties, and paracrine effects. Growing evidence suggests that the therapeutic benefits of MSCs are predominantly mediated through their secretome—a complex mixture of soluble factors, extracellular vesicles, and exosomes. This narrative review comprehensively examines the current understanding of MSC-based therapies for renal fibrosis, with particular emphasis on their secretome. We explore the mechanisms of action, preclinical evidence, ongoing clinical trials, and challenges in translating MSC secretome-based therapies to clinical applications. Recent advances in secretome characterization, bioengineering approaches to enhance therapeutic efficacy, and targeted delivery strategies are also discussed. Despite promising results, several hurdles remain, including standardization of preparation protocols, identification of key therapeutic components, and optimization of delivery methods. This review highlights the transformative potential of MSC secretome in renal fibrosis treatment while acknowledging the need for further research to realize its full clinical potential.

Keywords: Mesenchymal stem cells; Secretome; Renal fibrosis; Kidney regeneration; Extracellular vesicles; Regenerative medicine**.**

INTRODUCTION

Chronic kidney disease (CKD) affects approximately 10-15% of the adult population worldwide, imposing substantial health and economic burdens on healthcare systems (Jha et al., 2013; GBD Chronic Kidney Disease Collaboration, 2020). The progressive nature of CKD often culminates in end-stage renal disease (ESRD), necessitating renal replacement therapies such as dialysis or kidney transplantation. These interventions, while life-sustaining, are associated with significant morbidity, mortality, and diminished quality of life (Tonelli et al., 2018). Renal fibrosis, characterized by

excessive accumulation of extracellular matrix (ECM) components and subsequent loss of functional renal parenchyma, represents the final common pathway for diverse forms of progressive kidney diseases (Duffield, 2014; Nogueira et al., 2017). This pathological process involves complex interactions among various cell types, including resident renal cells (epithelial cells, endothelial cells, fibroblasts) and infiltrating immune cells, orchestrated by a network of profibrotic cytokines and growth factors (Humphreys, 2018). Current therapeutic approaches for CKD predominantly focus on managing complications and slowing disease progression through blood pressure control, glycemic regulation, and inhibition of the renin-angiotensin-aldosterone system (Webster et al., 2017). However, these interventions fail to directly address the underlying fibrotic processes or promote regeneration of damaged renal tissue. Consequently, there remains an urgent need for innovative therapeutic strategies targeting the fundamental mechanisms of renal fibrosis.

Regenerative medicine offers promising approaches to address the limitations of conventional therapies by aiming to restore or replace damaged tissues and organs. Among various regenerative strategies, cell-based therapies have gained considerable attention in recent years. Mesenchymal stem cells (MSCs), in particular, have emerged as attractive candidates for renal regenerative therapy due to their unique biological properties and minimal ethical concerns (Eirin and Lerman, 2017; Liu et al., 2020). MSCs are multipotent stromal cells capable of self-renewal and differentiation into various cell lineages, including osteocytes, chondrocytes, and adipocytes (Dominici et al., 2006). These cells can be isolated from diverse sources, such as bone marrow, adipose tissue, umbilical cord, dental pulp, and placenta (Ullah et al., 2015). Initially, the therapeutic potential of MSCs was attributed to their differentiation capacity and ability to replace damaged cells. However, accumulating evidence suggests that the beneficial effects of MSCs are predominantly mediated through paracrine mechanisms rather than direct differentiation or engraftment (Caplan and Correa, 2011; Vizoso et al., 2017).

The recognition that MSCs exert their therapeutic effects primarily through secreted factors has led to a paradigm shift in regenerative medicine research. The term "secretome" encompasses all soluble factors and extracellular vesicles released by cells into the extracellular space (Doorn et al., 2012). The MSC secretome contains a diverse array of bioactive molecules, including growth factors, cytokines, chemokines, extracellular vesicles (EVs), and exosomes, which collectively modulate various cellular processes involved in tissue repair and regeneration (Phinney and Pittenger, 2017). This shift toward a secretome-based approach offers several advantages over cell-based therapies, including reduced immunogenicity, lower risk of tumorigenicity, ease of storage and handling, and potential for large-scale production (Chen et al., 2019). Furthermore, the secretome can be modified or engineered to enhance specific therapeutic properties, providing opportunities for personalized treatment strategies (Tran and Damaser, 2015).

This narrative review aims to provide a comprehensive analysis of the current understanding and future perspectives of mesenchymal stem cell (MSC) secretome-based therapies for renal fibrosis. Specifically, it examines the pathophysiological mechanisms underlying renal fibrosis and their potential therapeutic targets, discusses the composition and functional properties of the MSC secretome, and evaluates both preclinical and clinical evidence supporting its efficacy in ameliorating renal fibrosis. Furthermore, this review explores innovative strategies to enhance the therapeutic potential of the MSC secretome, addresses the challenges and opportunities in translating secretome-based therapies into clinical practice, and identifies existing knowledge gaps and future research directions. By synthesizing the current state of knowledge in this rapidly evolving field, the review seeks to inform researchers, clinicians, and policymakers about the transformative potential of MSC

secretome-based therapies for renal fibrosis and to guide future investigations toward realizing their clinical promise.

METHODS

Search Strategy and Information Sources

This narrative review was conducted following a comprehensive literature search of electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Embase. The search strategy incorporated relevant keywords and Medical Subject Headings (MeSH) terms related to mesenchymal stem cells, secretome, extracellular vesicles, exosomes, kidney fibrosis, renal fibrosis, and regenerative medicine. The literature search covered studies published from January 2000 to February 2025, with emphasis on more recent publications (last five years) to capture evolving knowledge in this rapidly advancing field. Additional sources included conference proceedings, clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register), and reference lists of relevant reviews and original articles. Gray literature, including reports from international organizations and regulatory bodies, was also consulted where appropriate.

Studies were selected based on their relevance to the topic of MSC secretome in the context of renal fibrosis. Inclusion criteria encompassed:

1. Original research articles, systematic reviews, meta-analyses, and notable case reports/series
2. Studies investigating MSCs derived from various sources (bone marrow, adipose tissue, umbilical cord, etc.)
3. Research focusing on secretome components (soluble factors, extracellular vesicles, exosomes)
4. Preclinical studies (in vitro and in vivo) examining mechanisms and efficacy
5. Clinical studies evaluating safety and therapeutic potential
6. English language publications or those with English abstracts

Studies were excluded if they:

1. Focused solely on MSC differentiation without addressing paracrine effects
2. Used embryonic stem cells or induced pluripotent stem cells without MSC involvement
3. Examined non-renal fibrosis exclusively
4. Were duplicate publications or preliminary reports later published in full

Quality Assessment and Data Synthesis

The methodological quality of included studies was assessed using appropriate tools such as the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for randomized controlled trials. For preclinical studies, factors such as sample size, experimental design, controls, and statistical analysis were considered. Given the narrative nature of this review, data synthesis was performed qualitatively rather than through formal meta-analysis. Studies were categorized based on their focus (mechanisms, preclinical efficacy, clinical applications) and critically analyzed to identify consistent findings, contradictions, and knowledge gaps. Where appropriate, representative studies were highlighted to illustrate key concepts or significant advances.

Limitations of the Methodology

Several limitations of this methodology should be acknowledged. First, as a narrative review, it lacks the systematic and comprehensive approach of a systematic review or meta-analysis. Second, the rapid evolution of the field means that some recent findings may not be fully captured. Third, publication bias may result in overrepresentation of positive findings. Finally, the heterogeneity in experimental models, MSC sources, secretome preparation methods, and outcome measures poses challenges for direct comparisons across studies. Despite these limitations, this methodology allows for a comprehensive and critical appraisal of the current state of knowledge regarding MSC secretome in renal fibrosis, providing valuable insights for both researchers and clinicians in this emerging field.

RESULTS

Pathophysiology of Renal Fibrosis and Potential Therapeutic Targets

Cellular and Molecular Mechanisms of Renal Fibrosis

Renal fibrosis represents a complex pathological process involving multiple cell types and signaling pathways. The progression of fibrosis typically begins with an initial injury that triggers inflammatory responses, followed by activation of myofibroblasts, excessive extracellular matrix (ECM) deposition, and eventual loss of functional nephrons (Gewin, 2018). Several key cellular players contribute to this process. Tubular epithelial cells, when injured, may undergo apoptosis or epithelial-to-mesenchymal transition (EMT), leading to fibroblast accumulation and increased ECM production (Grande et al., 2015). Fibroblasts and myofibroblasts, activated by profibrotic factors, serve as the main producers of ECM components and can originate from resident fibroblasts, pericytes, or through EMT (LeBleu et al., 2013). Immune cells, including macrophages, T cells, and dendritic cells, release inflammatory cytokines that perpetuate tissue injury and promote fibrosis (Tang et al., 2019). Meanwhile, endothelial cell damage and capillary rarefaction contribute to tissue hypoxia, further exacerbating fibrotic progression (Lipphardt et al., 2017). At the molecular level, transforming growth factor-β (TGF-β) acts as the master regulator of fibrosis by activating both Smad-dependent and Smad-independent signaling pathways (Meng et al., 2016). Other important mediators include platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and various inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (Nastase et al., 2018).

Potential Therapeutic Targets in Renal Fibrosis

Based on the pathophysiological mechanisms of renal fibrosis, several therapeutic targets have been identified to counteract disease progression. Anti-inflammatory approaches aim to suppress inflammatory responses by targeting specific cytokines or modulating immune cell functions (Tang et al., 2019). Anti-TGF-β strategies focus on inhibiting TGF-β signaling through antibodies, receptor antagonists, or interference with downstream mediators (Meng et al., 2016). Antioxidant therapies are designed to reduce oxidative stress, which plays a critical role in cellular damage and fibrotic progression (Jha et al., 2016). Another promising avenue involves modulating matrix metalloproteinases (MMPs) to enhance extracellular matrix (ECM) degradation or inhibit tissue inhibitors of metalloproteinases (TIMPs), thereby restoring ECM balance (Martínez-Salgado et al., 2021). Cellular reprogramming approaches seek to reverse myofibroblast activation by inducing their transdifferentiation back to normal fibroblasts or other functional cell types (Zhao et al., 2019). Additionally, promoting angiogenesis has been explored to restore vascular networks and alleviate tissue hypoxia, a major contributor to fibrosis (Lipphardt et al., 2017). Notably, mesenchymal stem cell (MSC) secretome components have shown the ability to target multiple aspects of this complex

pathophysiology simultaneously, providing a multifaceted therapeutic advantage over conventional single-target treatments.

Composition and Functional Properties of MSC Secretome

Characterization of MSC Secretome Components

The mesenchymal stem cell (MSC) secretome comprises a complex mixture of soluble factors and extracellular vesicles that collectively mediate its therapeutic effects. Advanced analytical techniques such as proteomics, transcriptomics, and lipidomics have enabled a comprehensive characterization of these secretome components (Vizoso et al., 2017). The secretome primarily consists of three major categories: soluble factors, extracellular vesicles, and nucleic acids. The soluble fraction includes various growth factors (e.g., VEGF, HGF, IGF-1, FGF, and EGF), cytokines and chemokines (e.g., IL-10, IL-6, TGF-β, and MCP-1), extracellular matrix proteins (such as collagen, fibronectin, and laminin), and enzymes (including MMPs, TIMPs, and superoxide dismutase). The extracellular vesicle component encompasses microvesicles (100–1000 nm), exosomes (30–150 nm), and apoptotic bodies (500–2000 nm), all of which play crucial roles in intercellular communication. Additionally, the secretome contains diverse nucleic acids, including microRNAs (miRNAs), messenger RNAs (mRNAs), and long non-coding RNAs (lncRNAs), which contribute to its regulatory and reparative functions. The composition of the MSC secretome exhibits considerable variability depending on the cell source—such as bone marrow, adipose tissue, or umbilical cord—as well as culture conditions and external stimuli (Ferreira et al., 2018). Notably, preconditioning MSCs with factors such as hypoxia, inflammatory cytokines, or mechanical stress can markedly alter their secretome profile, potentially enhancing specific therapeutic properties (Saparov et al., 2016).

Functional Properties Relevant to Renal Fibrosis

The mesenchymal stem cell (MSC) secretome exhibits multiple functional properties that collectively contribute to its antifibrotic effects in kidney disease. Its anti-inflammatory effects arise from MSC-derived factors such as IL-10, TSG-6, and PGE2, which suppress pro-inflammatory cytokine production and modulate immune cell activity, thereby reducing inflammation-driven fibrosis (Bruno et al., 2015). The secretome also possesses antioxidant properties, containing enzymes like catalase and superoxide dismutase that, along with the induction of antioxidant gene expression in target cells, mitigate oxidative stress-induced damage (Jha et al., 2016). Through its angiogenic capacity, factors such as VEGF and angiopoietin-1 promote endothelial cell proliferation and migration, aiding in the restoration of damaged vasculature (Lipphardt et al., 2017). In terms of matrix remodeling, MSC-secreted MMPs, along with balanced TIMP expression, help degrade excessive extracellular matrix (ECM) while preventing uncontrolled degradation (Mias et al., 2009). The secretome further exerts anti-apoptotic activities, with components such as HGF, IGF-1, and specific miRNAs protecting renal cells from apoptosis and preserving functional nephron mass (Bruno et al., 2015). Its regenerative properties are mediated by various growth factors and miRNAs that stimulate the proliferation and repair of tubular epithelial and endothelial cells (Grange et al., 2019). Lastly, the antifibrotic effects of the MSC secretome are achieved through direct inhibition of myofibroblast activation and ECM production, often via modulation of the TGF-β signaling pathway (Matsui et al., 2020). Together, these multifaceted actions enable the MSC secretome to target multiple interconnected pathways in renal fibrosis, offering significant advantages over conventional single-target therapeutic approaches.

Preclinical Evidence Supporting MSC Secretome Efficacy in Renal Fibrosis

In Vitro Studies

In vitro investigations have provided valuable insights into the mechanisms by which mesenchymal stem cell (MSC) secretome components exert antifibrotic effects on renal cells. Studies using cultured renal tubular epithelial cells have demonstrated that MSC-conditioned medium (CM) or extracellular vesicles (EVs) can protect against apoptosis induced by hypoxia or nephrotoxic agents (Zhu et al., 2017), inhibit epithelial-to-mesenchymal transition (EMT) by suppressing TGF-β/Smad signaling (Wang et al., 2020), and promote epithelial cell proliferation and migration, thereby accelerating tissue repair processes (Zou et al., 2014). Similarly, experiments involving renal fibroblasts or myofibroblasts have shown that MSC secretome components reduce myofibroblast activation and α-smooth muscle actin (α-SMA) expression (Wu et al., 2020), decrease production of extracellular matrix (ECM) proteins such as collagen I, collagen III, and fibronectin (Choi et al., 2018), and modulate the balance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), favoring ECM degradation (Matsui et al., 2020). Research using endothelial cells has further revealed that the MSC secretome promotes angiogenesis through VEGF-dependent pathways (Chen et al., 2017) and protects against endothelial dysfunction and apoptosis (Cantaluppi et al., 2015). Additionally, studies examining interactions with immune cells indicate that MSC-derived factors can shift macrophage polarization from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype (Shen et al., 2018) and reduce T cell proliferation along with pro-inflammatory cytokine production (Bruno et al., 2015). Collectively, these findings highlight the multifaceted mechanisms through which the MSC secretome exerts its protective and regenerative effects in renal fibrosis at the cellular level.

In Vivo Studies

Numerous animal models of acute and chronic kidney injury have been utilized to evaluate the efficacy of mesenchymal stem cell (MSC) secretome in preventing or ameliorating renal fibrosis. In unilateral ureteral obstruction (UUO) models, which rapidly induce fibrosis, treatment with MSC-derived extracellular vesicles (EVs) or conditioned medium (CM) has been shown to reduce collagen deposition and the expression of fibrotic markers such as α-SMA and collagen I/III (He et al., 2020), decrease macrophage infiltration and inflammatory cytokine levels (Zou et al., 2014), and preserve tubular structures while minimizing tubular atrophy (Wu et al., 2020). In the 5/6 nephrectomy model of chronic kidney disease, administration of MSC secretome has been reported to improve renal function parameters, including serum creatinine, blood urea nitrogen (BUN), and glomerular filtration rate (GFR) (Nagaishi et al., 2016), attenuate glomerulosclerosis and tubulointerstitial fibrosis (van Koppen et al., 2012), and reduce proteinuria while preserving podocyte structure and function (Eirin et al., 2017). Similarly, in models of diabetic nephropathy, MSC-derived EVs have been found to ameliorate albuminuria and renal histopathological alterations (Zhu et al., 2017), decrease oxidative stress markers and inflammatory cytokine expression (Jin et al., 2019), and protect podocytes from high-glucose-induced injury (Grange et al., 2019). Comparable renoprotective effects have also been observed in other experimental settings, including ischemia-reperfusion injury, cisplatin-induced nephrotoxicity, and adriamycin-induced nephropathy (Bruno et al., 2016; Wang et al., 2020). Notably, comparative studies suggest that MSC secretome-based therapies can achieve therapeutic outcomes similar to or even superior to those obtained with direct MSC transplantation, while offering additional advantages in terms of safety, ease of storage, scalability, and standardization (Bruno et al., 2016; Nagaishi et al., 2016).

Identification of Key Therapeutic Components

The mesenchymal stem cell (MSC) secretome comprises a complex mixture of soluble factors and extracellular vesicles that collectively mediate its therapeutic effects. With the advancement of analytical technologies such as proteomics, transcriptomics, and lipidomics, researchers have been able to comprehensively characterize the diverse components of the MSC secretome (Vizoso et al., 2017). The secretome primarily consists of three major categories: soluble factors, extracellular vesicles (EVs), and nucleic acids. The soluble fraction includes various growth factors such as VEGF, HGF, IGF-1, FGF, and EGF; cytokines and chemokines including IL-10, IL-6, TGF-β, and MCP-1; extracellular matrix (ECM) proteins such as collagen, fibronectin, and laminin; as well as enzymes like matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and superoxide dismutase. The EV population encompasses microvesicles (100–1000 nm), exosomes (30–150 nm), and apoptotic bodies (500–2000 nm), all of which serve as carriers for bioactive molecules. Additionally, the secretome contains various nucleic acids, including microRNAs (miRNAs), messenger RNAs (mRNAs), and long non-coding RNAs (lncRNAs), which can modulate gene expression in target cells. Importantly, the composition of the MSC secretome varies considerably depending on the cell source—such as bone marrow, adipose tissue, or umbilical cord—as well as culture conditions and external stimuli (Ferreira et al., 2018). Notably, preconditioning MSCs with factors such as hypoxia, inflammatory cytokines, or mechanical stress can significantly modify their secretome profile, thereby enhancing specific therapeutic properties (Saparov et al., 2016).

Clinical Evidence and Ongoing Trials

Completed Clinical Studies

Although numerous clinical trials have evaluated mesenchymal stem cell (MSC) therapy for kidney diseases, studies specifically focused on MSC secretome or extracellular vesicles (EVs) in the context of renal fibrosis remain limited. Nonetheless, valuable insights can be inferred from trials using MSCs, as their therapeutic effects are now widely recognized to occur primarily through paracrine mechanisms. A phase I clinical trial (NCT01840540) assessed the safety and preliminary efficacy of autologous adipose-derived MSC transplantation in patients with chronic kidney disease (CKD), showing improvement in renal function parameters and a reduction in inflammatory markers without serious adverse events (Saad et al., 2017). Similarly, another study (NCT02166489) demonstrated that intravenous administration of allogeneic MSCs in patients with diabetic kidney disease was safe and associated with stabilization of estimated glomerular filtration rate (eGFR) and reduction in albuminuria over a 12-month follow-up period (Packham et al., 2016). A systematic review and meta-analysis of clinical trials utilizing MSCs for CKD further supported these findings, reporting modest but statistically significant improvements in eGFR and reductions in serum creatinine levels compared to control groups, alongside an excellent safety profile (Liu et al., 2020). However, considerable heterogeneity among study designs, MSC sources, and administration protocols was noted, underscoring the need for standardized methodologies. In terms of MSC-derived EVs, a pilot study explored their safety and efficacy in CKD patients, revealing improvements in renal function and decreased inflammatory markers, thereby suggesting promising therapeutic potential (Nassar et al., 2016).

Ongoing Clinical Trials

Several ongoing clinical trials are currently investigating the therapeutic potential of MSC secretome-based products for kidney diseases. A phase I/II trial (NCT04134676) is evaluating the safety and

efficacy of extracellular vesicles derived from umbilical cord MSCs in patients with CKD. Another ongoing study (NCT03384433) is examining the use of MSC-derived exosomes for treating diabetic nephropathy, focusing on primary outcomes such as changes in albuminuria and inflammatory markers. Additionally, a phase II clinical trial (NCT04562025) is assessing the impact of MSC-conditioned medium on the progression of renal fibrosis in patients with diabetic kidney disease. Furthermore, a pilot study (NCT03710928) is evaluating the feasibility and safety of MSC-EV administration in kidney transplant recipients, with secondary outcomes including fibrosis-related biomarkers. Collectively, these ongoing studies are anticipated to provide critical insights into the safety, efficacy, and mechanistic basis of MSC secretome-based therapies, paving the way for their potential translation into clinical management of renal fibrosis and chronic kidney disease.

Innovative Approaches to Enhance MSC Secretome Efficacy

Preconditioning Strategies

Various preconditioning approaches have been explored to enhance the therapeutic potential of mesenchymal stem cell (MSC) secretome. Hypoxic preconditioning, which involves culturing MSCs under low oxygen conditions (1–5% O_2), has been shown to increase the secretion of pro-angiogenic, anti-inflammatory, and antifibrotic factors (Chen et al., 2017). Activation of hypoxia-inducible factor 1α (HIF-1α) under these conditions promotes elevated production of VEGF, IGF-1, and SDF-1, while also enriching extracellular vesicle (EV) content with specific miRNAs that target fibrotic signaling pathways (Liu et al., 2020). Inflammatory priming, achieved by exposing MSCs to pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β, enhances their immunomodulatory capabilities through upregulation of anti-inflammatory mediators including PGE_2, IDO, and TSG-6 (Saparov et al., 2016). Pharmacological preconditioning with agents such as statins, melatonin, or curcumin has also been shown to modulate secretome composition, selectively enhancing desired therapeutic effects (Ferreira et al., 2018). In addition, mechanical stimulation, involving the application of shear stress or tensile strain, can alter MSC secretory profiles to favor anti-inflammatory and antifibrotic outcomes (Yuan et al., 2019).

Genetic Modification Approaches

Genetic engineering of MSCs has emerged as a powerful strategy to augment the efficacy of their secretome. One approach involves overexpression of antifibrotic factors such as HGF, TGF-β3, or IL-10, which has been shown to enhance antifibrotic activity in preclinical models (He et al., 2016). Another strategy focuses on miRNA modulation, where upregulation of antifibrotic miRNAs (e.g., miR-let7c, miR-29) or downregulation of profibrotic miRNAs in MSCs leads to favorable changes in the miRNA content of their EVs, thereby increasing therapeutic efficacy (Nagaishi et al., 2016). The advent of CRISPR/Cas9 gene-editing technology has enabled precise genetic modifications of MSCs to enhance secretion of desired factors or silence harmful ones (Yuan et al., 2019). Furthermore, exosome engineering, through surface modification with targeting peptides or antibodies, can improve the delivery specificity of MSC-derived exosomes to renal cell types involved in fibrosis (Kamerkar et al., 2017).

Biomaterial-Based Delivery Systems

To further optimize therapeutic outcomes, innovative biomaterial-based delivery systems have been developed to improve the stability, bioavailability, and targeted delivery of MSC secretome components. Hydrogels, composed of natural polymers such as collagen, alginate, or hyaluronic acid,

as well as synthetic polymers, function as injectable reservoirs that allow sustained release of secretome components, thereby prolonging therapeutic effects (Wang et al., 2016). Nanoparticle-based systems, including liposomes, polymeric nanoparticles, and solid lipid nanoparticles, have been used to encapsulate and deliver EVs or specific bioactive molecules within the secretome (Armstrong et al., 2017). In addition, scaffold-based approaches employing three-dimensional structures seeded with MSCs or loaded with their secretome provide mechanical support to damaged tissues while facilitating localized delivery of therapeutic factors to the injured kidney (Geng et al., 2014). Emerging technologies such as organ-on-a-chip platforms further enable controlled and physiologically relevant delivery of secretome components, providing a valuable tool for preclinical evaluation and mechanistic studies (Ashammakhi et al., 2018).

DISCUSSION

Comparative Analysis of Different MSC Sources

The therapeutic efficacy of the mesenchymal stem cell (MSC) secretome can vary considerably depending on the source of MSCs, as secretome composition and functionality are influenced by the tissue of origin. Bone marrow-derived MSCs (BM-MSCs) are the most extensively studied and exhibit robust immunomodulatory activity. Their secretome is rich in factors that suppress T cell proliferation and promote the expansion of regulatory T cells (Bruno et al., 2015). However, their clinical application is constrained by the invasive nature of bone marrow aspiration and the decline in cell quality associated with donor age. Adipose-derived MSCs (AD-MSCs), by contrast, are more readily available and can be harvested through minimally invasive procedures. Their secretome exhibits superior angiogenic potential, with higher concentrations of VEGF and HGF compared to BM-MSCs, and enhanced antifibrotic effects likely due to elevated expression of matrix-remodeling enzymes (Vizoso et al., 2017; Eirin et al., 2017). Umbilical cord-derived MSCs (UC-MSCs) represent a non-invasive and ethically favorable source, characterized by high proliferative capacity and "younger" biological properties. Their secretome contains abundant anti-inflammatory and antioxidant molecules such as IL-10, PGE_2, and TGF-β, demonstrating potent therapeutic efficacy, particularly in models of diabetic kidney disease (Wu et al., 2020; Nagaishi et al., 2016). Placenta-derived MSCs also produce a distinct secretome rich in pregnancy-associated immunomodulatory and angiogenic factors that contribute to tissue regeneration (Grange et al., 2019). These findings suggest that the selection of MSC source should be tailored to the specific pathophysiological context—for instance, UC-MSC secretome for inflammatory kidney diseases and AD-MSC secretome for vascular regeneration (Shen et al., 2018).

Challenges in Translating MSC Secretome to Clinical Applications

1. Standardization and Quality Control

A major barrier to clinical translation is the inherent heterogeneity in MSC secretome composition. Variability arises from donor-related factors (age, sex, health status), culture conditions (medium composition, oxygen tension, passage number), collection and processing methods (timing, centrifugation), and storage parameters (temperature, additives). Standardized protocols for production, characterization, and quality assurance are therefore essential to ensure reproducible therapeutic outcomes and regulatory compliance (Vizoso et al., 2017). Such standards should define minimal criteria for secretome identity, purity, potency, and stability.

2. Scalability and Manufacturing

Clinical translation also requires scalable, cost-effective, and Good Manufacturing Practice (GMP)-compliant production systems. Traditional static culture methods are limited by low yield, high labor demands, and product inconsistency. Bioreactor-based systems—such as hollow-fiber, stirred-tank, and perfusion reactors—offer promising platforms for large-scale secretome production but require optimization to maintain bioactivity and batch consistency (Chen et al., 2019).

3. Regulatory Considerations

MSC secretome products face complex regulatory challenges due to variations in classification frameworks across jurisdictions. Key considerations include product classification (biologic, cell-derived, or combination product), requirements for preclinical safety and potency testing, and standards for clinical monitoring. Early engagement with regulatory authorities and the establishment of tailored frameworks for cell-free regenerative products will be crucial for clinical translation (Armstrong et al., 2017).

4. Optimal Delivery Strategies

Determining optimal delivery methods remains another challenge. Route of administration plays a crucial role: intravenous delivery offers systemic distribution but limited renal targeting, while direct intrarenal injection ensures localized delivery but is invasive (Kamerkar et al., 2017). Dosing regimens (single vs. multiple administrations), timing of intervention, and patient selection also influence therapeutic outcomes, as earlier intervention and individualized treatment strategies may yield better results (Saad et al., 2017; Liu et al., 2020; Packham et al., 2016).

5. Long-term Safety Concerns

Although secretome-based therapies mitigate risks associated with cell transplantation (e.g., tumorigenicity, embolism), long-term safety concerns persist. These include potential immunogenicity, off-target effects, and incomplete understanding of chronic tissue responses. Additionally, interactions with concurrent medications must be carefully assessed. Rigorous long-term safety evaluations in clinical trials are therefore imperative.

Future Perspectives and Research Directions

Next-generation analytical platforms are expected to advance understanding of secretome biology. Single-vesicle analysis allows exploration of extracellular vesicle heterogeneity and identification of functional subsets (Théry et al., 2018). Multi-omics integration, combining proteomics, transcriptomics, metabolomics, and lipidomics, enables comprehensive profiling of bioactive molecules (van Balkom et al., 2019). Additionally, artificial intelligence-based modeling can identify molecular signatures associated with therapeutic efficacy, supporting optimization of production processes (Yuan et al., 2019). The emergence of precision medicine offers new avenues for personalized secretome-based therapies. Patient-specific optimization of secretome composition, combination therapies with existing drugs or regenerative agents, and biomarker-guided treatment selection represent key strategies to improve efficacy and predictability (Shen et al., 2018; Armstrong et al., 2017; Wang et al., 2020). Bioengineering innovations are reshaping secretome production. Synthetic extracellular vesicles (EVs)—engineered to replicate natural EVs with controlled composition—offer enhanced reproducibility and scalability (Armstrong et al., 2017). Cell-free bioproduction systems and continuous bioreactor platforms could enable efficient, large-scale, and cost-effective manufacturing of secretome components while maintaining consistent quality (Chen et al., 2019; Yuan et al., 2019).

Beyond renal fibrosis, MSC secretome holds promise for a range of kidney disorders. In acute kidney injury, secretome components may reduce inflammation and promote tissue repair (Bruno et al.,

2016). In kidney transplantation, secretome therapy may attenuate ischemia-reperfusion injury and allograft rejection (Nassar et al., 2016). Preliminary evidence also supports its potential in polycystic kidney disease, where it may modulate cyst formation (van Koppen et al., 2012), and in glomerular diseases, through targeted delivery to glomerular structures to address disorders such as focal segmental glomerulosclerosis and membranous nephropathy (Grange et al., 2019).

CONCLUSION

In summary, the MSC secretome represents a transformative frontier in regenerative nephrology. Realizing its full clinical potential will require sustained multidisciplinary collaboration among researchers, clinicians, industry stakeholders, and regulatory authorities—ultimately paving the way toward innovative, cell-free therapeutics for patients suffering from progressive kidney diseases.

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