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LITERATURE REVIEW

Potential therapy of umbilical cord mesenchymal stem cells (UC-MSC) in renal fibrosis

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ABSTRACT

Renal fibrosis (RF) is a severe kidney pathology defined by myofibroblast anomalies that create extracellular material on the interstitial and glomerular surfaces. The current therapy for treating renal disease has not achieved excellent results. A new theory about applying umbilical cord mesenchymal stem cells (UC-MSC) to treat renal fibrosis and other fibrosis-affected organs has been developed. This review aims to elucidate the role of UC-MSC in the therapy of renal fibrosis and summarize the numerous biological mechanisms involved. A search was undertaken using PubMed and Google Scholar from 2003 to 2021 to gather information regarding the Potential therapy with UC-MSC in renal fibrosis. Multiple studies on rat models of renal fibrosis have demonstrated a considerable improvement in fibrotic kidneys following UC-MSC treatment. It can transfer functional proteins and genetic information to recipient cells that suppress the fibrosis process. UC-MSC is considered a superior approach to MSC for therapeutic purposes due to its straightforward collection, minimum immunogenicity, and solid paracrine potency. The UC-MSC cellular treatment for renal impairment is a feasible option in the future.

1. Introduction

Renal fibrosis (RF) is the concluding pathological phase characterized by all chronic kidney injuries and maladaptive repairs. Renal fibrosis has few therapeutic options and is considered an advanced stage of chronic kidney disease (CKD). It is estimated that 10% of the world's population is affected by this condition (Eddy, 2014; François and Chatziantoniou, 2018; Humphreys, 2018). In over 100 countries, many individuals cannot afford these treatments, resulting in the deaths of over 1 million people every year due to untreated kidney failure. Chronic renal disease rated 27th among all causes of mortality worldwide in 1990 but rose to 18th by 2010, according to the Global Burden of Disease research (Couser *et al.,* 2011). Overwhelmed by the number of underlying renal impairments, which frequently remain obscure, fibrosis-targeting therapies, i.e. the final common pathway of progressive impairment, remain an intriguing and essential treatment option (Cho, 2010; Rockey, Bell and Hill, 2015; Panizo *et al.,* 2021).

Currently, medications and therapeutic strategies (ACE inhibitors, angiotensin receptor blockers) are utilized to postpone CKD continuation and avoid complications. However, these therapeutic strategies and treatments remain ineffective in treating RF (Zhuang *et al.,* 2019a; Liao *et al.,* 2022). Stem cells have been shown to treat chronic diseases that advance rapidly and effectively. There are various forms of mesenchymal stem cells (MSC), including: (1) umbilical cord mesenchymal stem cells (UC-MSC), (2) induced pluripotent stem cells and (3) embryonic stem cells. Adipose tissue, umbilical, bone marrow, and other perinatal tissues, including decidua placenta, Wharton colloids, and amniotic/chorionic membranes, are also

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sources of stem cells (Zhuang *et al.,* 2019a). MSC are formed from mesoderm cells capable of differentiating into several multidirectional cells and have significant concentrations of these cells. They demonstrate a therapeutic effect in fibrosis that can renew and repair tissue (Zhuang *et al.,* 2019a; Yu *et al.,* 2020; Liao *et al.,* 2022). Therefore, UC-MSC can substitute MSC in treating inflammatory and immune-related illnesses, including renal fibrosis. This review aims to describe the importance of UC-MSC in treating renal fibrosis, including diverse sources for various animal models and summarizes the possible molecular mechanisms elaborated.

2. Methods

Collecting data about the Potential therapy utilizing UC-MSC in Renal fibrosis, a search was conducted using PubMed and Google Scholar from 2003 to 2021. Included among the keywords are UC-MSC)", "renal fibrosis", "chronic kidney disease", "unilateral ureteral obstruction", and "ischemia-reperfusion injury". Research and original research were included, but only English-language articles were included.

3. Discussion

UC-MSC consist of a sponge-like structure interwoven with collagen fibres, stromal cells, and several proteoglycans. The UC-MSC is located in the centre, specifically in the subcortical endothelium, including the perivascular region and Wharthon's Jelly. UC-MSC is the preferable form of MSC primarily to its relatively straightforward collection technique, low immunogenicity, and high paracrine potential (Xiang *et al.,* 2020; Shang, Guan and Zhou, 2021).

The MSC is isolated from several compartments of the umbilical cord (UC) or the entire UC. This UC generally contains four compartments that have MSC:

1. The entire UC is sliced into minute pieces or fragments following enzymatic digestion or explant procedures.
2. UC vessels (arteries and veins) are eliminated to obtain Wharton's jelly (WJ) MSC. Additionally, the umbilical cord arteries (UCA) and veins (UCV) (umbilical vasculature) can be sliced into minute fragments and plated for the formation of MSC.
3. It is chopped into minute fragments after dislodging the sub-amnion portion of the lining membrane with a blade.
4. The vessels detached from the cord must be tied together at their two ends. The loops will be placed in an enzyme mixture for a predetermined time to dissociate the cell from the perivascular region.

The safety of UC-MSC

MSC is derived from the mesoderm and can be easily identified by self-renewal. MSC are multipotent and can generate several cell lineages. MSC developed from the umbilical cord (UC-MSC) offer more potential and advantages than stem cells derived from other sources (Figure 1). UC-MSC were obtained noninvasively, pathogen-free, and straightforward to isolate (Maitra *et al.,* 2004). According to multiple animal model-based research sources, UC MSC can bypass immune cell responses and have minimal immunological effects. Possible immunogenicity in UC-MSC was attributable to negligible primary histocompatibility complex class I (MHCI) and major histocompatibility complex class

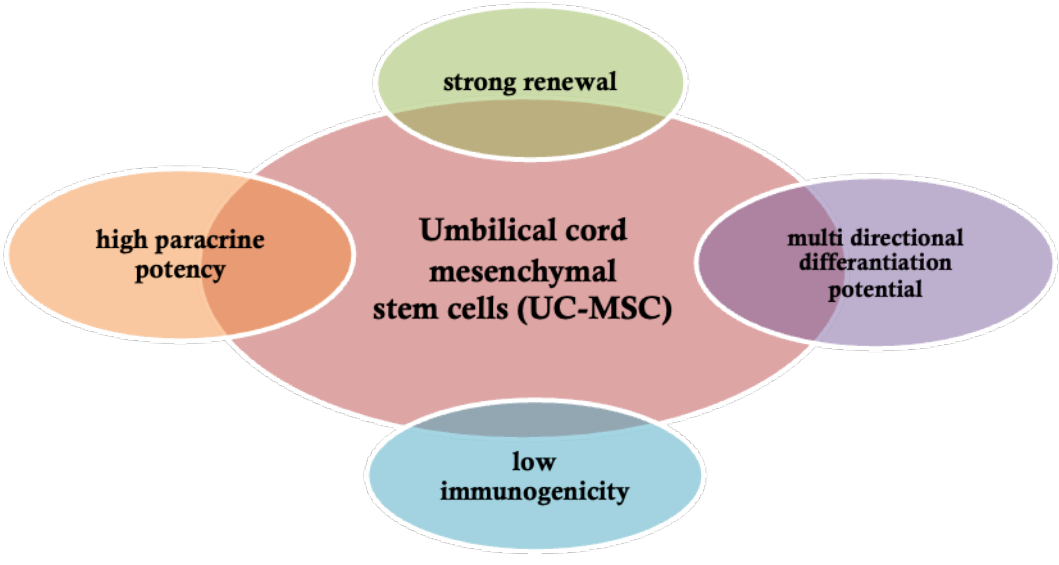

Figure 1. Specification of UC-MSC (Zhuang *et al.,* 2019a; Liao *et al.,* 2022)

Table 1. Literature overview of the antifibrotic mechanism of UC-MSC in fibrotic kidney

Author, year	Models	Cell/substance transferred	Fibrogenic signal pathway involvement	Delivery method	Reactions in cells or kidney
Oliva (2019)	Rat-IRI	Umbilical Cord Stem Cells	IGF-1	Left Carotid Artery Injection	↓ creatinine, blood urea nitrogen, apoptosis, -inflammation, ↓ kidney injury, ↑ cell proliferation
Rodrigues *et al.* (2017)	Rat-IRI	WJ-MSC	TGF- *1*	i.p.	↑ glomerular filtration, ↓ TGF-1, macrophage infiltration, protein–galactosidase
Du *et al.* (2013)	Rat-IRI	WJ-MSC	Akt and TGF-*β*1	Tail vein	Delaying EMT and Repair of renal fibrosis,
Liu *et al.* (2015)	Rat UUO	uUC-MSC CM	(TGF)-β	Renal artery	Inhibition of inflammation
Liu *et al.* (2018)	Rat UUO	uUC-MSC CM	TLR4/ *NF*- B	Renal artery	-extracellular matrix and inflammatory cell infiltration
Wu ***et al.***, in the article **by** Liu *et al.* (2018)	RAT IRI	WJ-MSC-MVs	Scr, BUN, vWF, IL-10, TNF α, α-SMA, andTGF-β1	Tail vein	Inhibits cell apoptosis and renal fibrosis,↑ Ki67 and HGF
Huang *et al.* (2013)	Rat UUO	uUC-MSC	Not mentioned	Tail vein	Repair of damaged kidneys (interstitium)
Fan *et al.* (2016)	Rat peritoneal dialysis- (PD) elicited fibrosis model	WJ-MSC	TGF-*β*	i.p.	Prevent methylglyoxal-induced abdominal cocoon peritoneal dialysis, ultrafiltration failure, and peritoneal membrane changes (peritoneal thickening, fibrosis, and inflammation)
Li *et al.* (2017)	Adenine-induced CRF rat model	WJ-MSC	TGF-*β*	Tail vein	- oxidative damage, ↓ inflammatory response, ↑ growth factor expression, and protect injured kidney tissue

II (MHCII) molecules (Devine *et al.,* 2003). It does not have an ethical difficulty because it is isolated from umbilical tissue and not from difficult-to-isolate or ethically problematic tissue arising from the internal body.

Additionally, UC MSC is straightforward to isolate and culture. This improves its application and makes it the safest alternative (Lu *et al.,* 2006). Administration of UC-MSC to humans or animal samples is guaranteed to be safe, as evidenced by previous studies indicating that UC-MSC is legitimate and practicable for intravenous transplantation into rats, as it did not incorporate alterations to biochemical parameters or histological lesions (Huang *et al.,* 2013).

Proliferation and Differentiation Potential of UC-MSC

The proliferation rate of UC-MSC, compared to adipose tissue-derived MSCs (AD-MSC) and bone marrow-derived MSCs (BM-MSC), was 3 to 4 times significantly greater. UC-MSC possesses multidirectional differentiation capabilities and the propensity to develop into adipose, cartilage, bone, and other tissues, providing a suitable germ cell for application in regenerative medicine to repair diverse tissues and organs. UC-MSC can be extracted in the perivascular, intravascular, and sub-amniotic areas. Study results have revealed that when tissues undergo ischemia-anoxia lesions or chronic inflammation, the injury releases chemokines, mobilizes and directs MSC migration to the injury site, and stimulates the diversification of several cellular processes (Yu *et al.,* 2018; Shen *et al.,* 2019; Hu *et al.,* 2020).

UC-MSC are an alternate form of MSC isolation that may be obtained noninvasively and could be easily cultivated, making them preferable candidates for cell transplantation than MSC from numerous sources. In vitro cultured UC-MSC can "trans-differentiate" in particular circumstances to get to be mesoderm cells, including cardiomyocytes, osteoblast and endothelial cells, and also differentiate, becoming neurons in the hepatocytes, ectoderm and pancreatic cells in the endoderm between the germ layers. UC-MSC are germ cells for cell replacement therapy attributable to their low immunogenicity, differentiation capacity, and intense proliferation (Van Pham *et al.,* 2016).

Potential Mechanisms of UC-MCS Decreasing Renal Fibrosis Progression; In vivo and In vitro

The function of UC-MSC in treating renal fibrosis was the subject of a specific study (Li *et al.,* 2017). UC-MSC can influence the stimulation phase of fibrogenic signals inside the organ level, such as TGF-1, TLR4/NF-B, ERK, and Akt signalling pathways (Table

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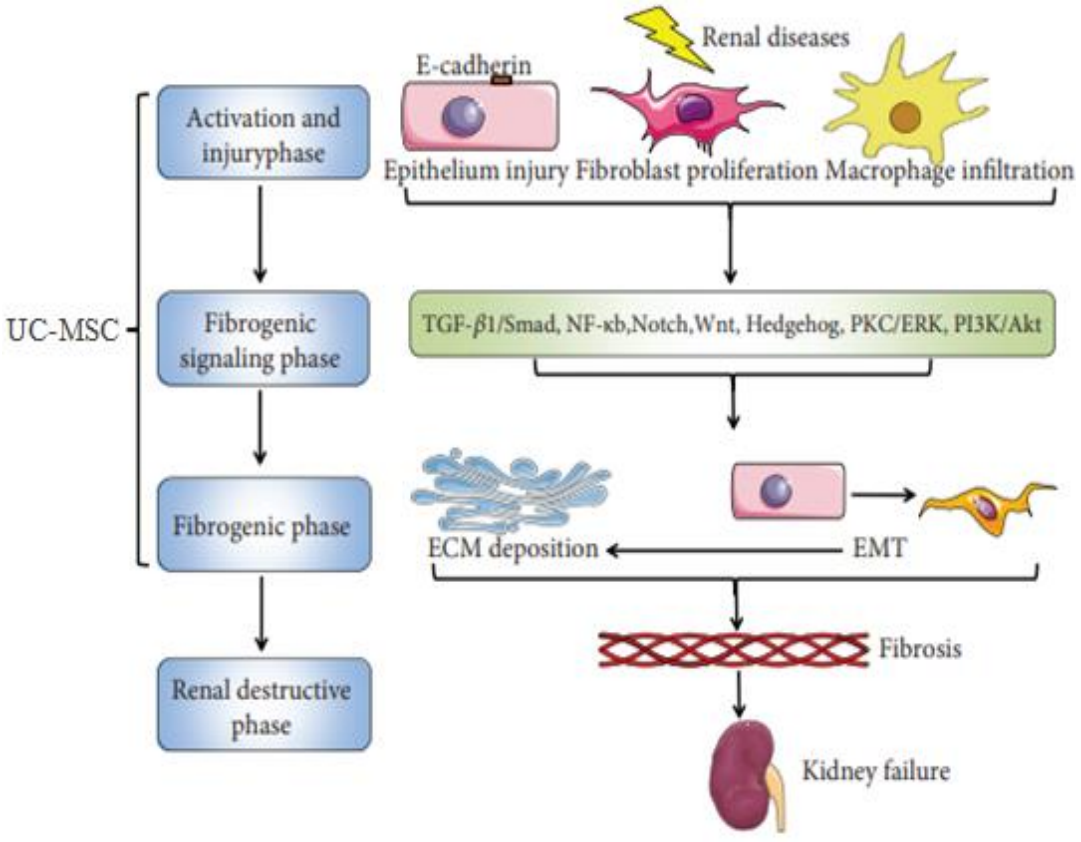

Figure 2. The relationship between renal fibrosis and UC-MSC (Zhuang *et al.,* 2019)

1) (Zhuang *et al.,* 2019a). Table 1 depicts the numerous publications concerning their immunosuppressive effect of UC-MSC (Fan *et al.,* 2016).

There are limited immunosuppressive effects attributed to UC-MSC. This is due to the regulation and interaction between cells and the interaction between dissolved chemicals. Prostaglandin E2 (PGE2), galectin-1, and human leukocyte antigen-G molecules (HLA-G5) are the immunosuppressive factors generated by UC-MSC. Another important immunosuppressive agent is indoleamine 2,3-dioxygenase, which interferon-γ (IFN-γ) activates to produce tryptophan-derived kynurenine. Tryptophan shortage will impede cell development under these circumstances. UC-MSC might generate immunosuppression due to early activation of proinflammatory cytokines, such as IFN-γ and interleukin-1 (IL-1) (Nagamura-Inoue and He, 2014)

Liu *et al.* (2018) reported that UC-MSC reduce inflammation in renal fibrosis and suppress epithelial migration to mesenchyme via the nuclear factor-κB (NF-κB) /Toll Like Receptor 4 (TLR4) signalling pathway. Unilateral ureteral obstruction (UUO) can stimulate extracellular matrix production and inflammatory cell infiltration in the kidney and release inflammatory mediators. Figure 2 shows the mechanism of UC-MSC therapy for kidney failure. UC-MSC inhibits cytokine proliferation and suppresses the epithelial-mesenchymal transition (EMT) process in UUO (Liu, F. X. Ding, *et al.,* 2018).

Application of UC-MSC to Model of Renal Fibrosis

Effects of UC-MSC on a mouse model of ischemia-reperfusion injury (IRI)

In a mouse model of ischemic acute kidney injury, UC-MSC can protect the kidney from damage. Oliva (2019) revealed that reducing creatinine, blood urea nitrogen, apoptosis, inflammation, renal injury, and increasing cell proliferation decreases apoptosis and reduces inflammation (Oliva, 2019). Rodrigues *et al.* (2017) created a mouse model of ischemia-reperfusion injury (IRI) receiving human UC-MSC intraperitoneal. They discovered that mice treated with UC-MSC exhibited improved tubular function, greater glomerular filtration, reduced TGF-1 level, ageing-associated protein-galactose, and macrophage infiltration. Minimal macrophage infiltration may be proportional to a diminished severity of fibrosis. Thus, mice treated with UC-MSC showed lower renal TGF- levels which may indicate decreased chronic kidney impairment and advancement of fibrosis (Rodrigues *et al.,* 2017).

Renal fibrosis caused by IRI was eliminated by treatment of UC-MSC with decreasing α-smooth

muscle actin (α-SMA) collagen levels. Additionally, the Akt signalling pathway is an integral part of this process. To further study the mechanism, the same team created an acute kidney injury (AKI) mouse model employing the same methodology, discovering one crucial tool: human UC-MSC can suppress tubular EMT and ameliorate renal fibrosis.

Initiation of the biochemical synthesis of exogenous and native hepatocyte growth factor (HGF) in disrupted tubular epithelial cells (TECs) during the initial phase of acute kidney injury leads to the repair of the transforming growth factor-β (TGF-β)/ HGF imbalance throughout renal scar formation (Du *et al.,* 2013; Zheng *et al.,* 2019). Injected human UC-MSC into IRI mice and found that UC-MSC can diminish IRI-induced fibrosis and strengthen kidney function. In addition, the outcomes demonstrated that WJ-MSC-MVs suppressed blood urea nitrogen (BUN), Scr, α-SMA, NADPH oxidases 2 (NOX2), reactive oxigen species (ROS), malondialdehyde (MDA), and Ki67 and reduced apoptosis (Zheng *et al.,* 2019; Hu *et al.,* 2020).

Effects of UC-MSC in a rat's model with unilateral ureteral obstruction (UUO)

Unilateral Ureteral Obstruction (UUO) has been utilized as an animal model for renal fibrosis, a disorder characterized by kidney damage. Injury to the renal tubules due to limited urine flow is the initial condition that UUO potentially induces. The UUO model in animals can mimic the state of obstructive nephropathy in humans, which is acquired relatively quickly. The benefit of the UUO model is that it is possible to eliminate obstacles and examine subsequent events. Chaabane *et al.* stated in the publication of Martnez-Klimova *et al.* (2019) that obstruction release did not overturn the downturn in nephron number and did not enhance tubular cellular proliferation, despite the normalization glomerular filtration rate (Martínez Klimova *et al.,* 2019).

After penetrating the UUO rat kidney, previous research has demonstrated that UC-MSC can play a crucial anti-inflammatory, anti-oxidative, and anti-fibrosis role. Researchers postulated that paracrine produced by UC-MSC plays an essential part in recovering from kidney injury (Huang *et al.,* 2013). According to the study, administration of UC-MSC condition medium via the renal artery decreases inflammation, collagen deposition, and oxidative stress, as well as decreases renal interstitial fibrosis, promotes tubular epithelial cell proliferation, slows the development of EMT, and inhibits its apoptosis in UUO rats. These findings suggest a viable treatment for chronic kidney diseases and renal fibrosis. However, the processes through which UC-MSC regulates renal responses are not entirely defined and require additional research (Liu, F. Ding, *et al.,* 2018).

4. Conclusion

Umbilical cord mesenchymal stem cells can inhibit inflammatory cell infiltration, inhibit cell apoptosis, reduce oxidative damage, and inhibiting EMT and increase cell proliferation. UC-MSC is considered a better choice of MSC for clinical applications because of its accessible collection, low immunogenicity, and high paracrine potency. It is expected to be regarded as the cellular therapy for Renal Failure.

Conflict of Interest

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