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Approach for extracellular vesicles in renal therapeutics: involvement of microRNAs

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ABSTRACT

Recently, special scientific efforts have been directed to investigate the role of small non-coding RNA (miRs) in different renal diseases. Extracellular vesicles (EVs) are small secretory vesicles released from almost all mammalian cells. EVs-miRs cargo plays a significant role in regulating various aspects of the biological machinery of the recipient cells. EVs-miRs may play an essential role in promoting cellular regenerative functions. miRs contained within the EVs fractions are capable of preserving their function throughout their journey from the cell of origin to the host cells. The current review discusses the role of EVs-miRs in different renal diseases as a novel approach for managing particular renal injuries. We tried to simplify the possible modulatory impact of miRs at the ultrastructural cellular pathological signaling, demonstrating the hazardous and the beneficial subtypes based on the previous research work. Further investigations are still needed in this regard, as miRs may have dual effects, as EVs-miR-23a could attenuate renal fibrosis through activation of Akt and inhibition of FoxO1 signaling. Whereas, EVs-miR-23a was upregulated by the hypoxia-inducible factor (HIF-1a) in the hypoxic TECs and activated macrophages to accelerate the renal inflammatory cytokine storm and promote interstitial fibrosis.

Keywords: extracellular vesicles, EVs, exosomes, microRNAs, kidney

INTRODUCTION

Extracellular vesicles (EVs) are cellular secretory vesicles released from almost all mammalian cells [3]. Independent of their cell of origin, EVs are membrane-surrounded particles secreting from the cells. EVs can be classified according to their size into three main subgroups: exosomes (ranging from 30–100 nm), microvesicles (100 nm to 1000 nm), and apoptotic bodies (50–5000 nm)**.** Exosomes are nanovesicles formed from intracellular multivesicular endosomes, while the microvesicles are shed buddings from the plasma membrane [23, 27, 32]. EVs are secreted in a wide range of biological fluids, including blood and urine [29].

EVs can transfer varieties of proteins, lipids, DNA, RNA (tRNAs, mRNAs), as well as microRNAs (miRs) strands. These biomolecules cargo transfer information from their original cells to the target cells and participate in cell-to-cell communication, which is important in regulating the biological machinery of the recipient cells. miRs are a newly discovered class of small, non-coding single RNA strands. Secreted miRs to the blood circulation or the urinary fluids favor EVs-encapsulated configuration [10], in which miRs are capable of preserving their function throughout their journey from the cell of origin to the host cell [1, 7]. The validity of stem cells in the treatment of renal injuries is still under research. The significance of the therapeutic potential of stem cells in tissue repair arises from their ability to secrete different factors, including EVs containing their miRs cargo. Paracrine transmission of miRs to the injured renal tissues may be responsible for modulating cellular biology [56]. The variety of miRs expression during renal diseases raises an important scientific question. Could patients with renal diseases benefit from the application of EVs-miRs? Therefore, this review discusses *in-vitro* and *in-vivo* studies suggesting significant values of EVs-miRs administration in the treatment of renal diseases. This work aims to collect data concerning the EVs-miRs role in different renal diseases and to discuss the relevance of EVs-miRs subtypes to renal injury. This review demonstrates the interrelation between different miRs subtypes at the ultrastructural cellular pathological signaling.

DISCUSSION

Possible mechanism of action of EVs-miRs in the renal pathogenesis

The interrelations between different miRs subtypes and the renal cell signaling pathways are complex and involve almost all axes, which may proceed into cell survival or death. The possible mechanism of miRs' actions on the renal signaling pathways is collected and

summarised in Figure 1. This review presents the modulatory role of miRs during different renal injuries. The significance of mesenchymal stem cell-secreting (MSCs) in tissue repair comes from its ability to secrete other factors, including EVs-miRs cargo. However, the validity and the therapeutic potential of MSCs-EVs in the treatment of renal injuries are still under research. The paracrine transmission of miRs to the injured renal tissues may be the mediator for tissue repair by modulating cellular biological pathways [56]. Here, we are discussing different *in-vitro* and *in-vivo* research suggesting significant values of MSCs-EVs-miRs administration in the treatment of renal diseases.

Ischemic renal injury and the treatment with EVs/miRs

The transfer of various miRs via EVs affects the pathophysiology of renal Ischemic renal injury (IRI) as EVs-miRs may be involved in the regulation of the immune system in renal IRI. miR-199a-5p, located within the MSCs, was transferred into the renal tubular epithelial cells (TECs) and was the mediator for inhibiting the IRI-induced endoplasmic reticulum stress [35]. Similarly, Zhu et al. [55] showed that exosomes-miR-199a-3p ameliorated renal IRI through the reduction of semaphorin 3A (Sema3A) and stimulation of the protein kinase (AKT) and extracellular-signal-regulated kinase (ERK) pathways. The intra-capsular administration of exosomes enriched with miR-93-5p improved renal structure and functions, decreased apoptosis inflammation, and activated the AKT pathway [49]. In the co-cultured renal artery-derived vascular progenitor cells and endothelial cells for 24 h, the secreted exosomes-miR-218 increased the migratory ability of the endothelial cells and improved renal vasculature [26]. Also, exosomes miR-20a-5p are protected against acute tubular injury *in vitro* by mitigating the mitochondrial functions [43]. Furthermore, miR-146a-5p enriched exosomes degraded the 3'UTR of interleukin-1 (IL-1) receptor-associated kinase-1 and prevented the nuclear factor (NFκB) activation in the renal HK2 cells exposed to hypoxia/reoxygenation [16]. Separated EVs from mesenchymal stem cells enriched with miR-21, 100, 99a, and 24 to the TECs promoted cell proliferation and inhibited apoptosis on exposure to hypoxia/reoxygenation [5]. On the contrary, the important participation miR-150 in the fibrosis initiation and progression was detected on the 12^{th} day following renal IRI in mice [8]. Exosomes-miR-374b-5p enhanced the polarization and activation of the M1 macrophage subtype through binding to Socs1 and, therefore, potentiated the inflammatory response and worsened renal IRI [6]. Also, EVs-miR-23a was upregulated by the hypoxia-

inducible factor (HIF-1a) in the hypoxic TECs and activated macrophages to accelerate the renal inflammatory cytokine storm [17].

EVs-miRs in the management of renal injury during sepsis

Intravenous administration of exosomes containing miR-126-5p and 3p ameliorated renal function in mice's sepsis model induced by cecal ligation and puncture (CLP). The protective response was mediated through inhibition of the high mobility group box 1 (HMGB1) and the vascular cell adhesion molecule 1 (VCAM1) levels [54]. Remote limb ischemic pre-conditioning 24 h before the onset of CLP released exosomes-miR-21 and circulated to target PTEN/AKT signals and inhibit renal inflammation and cell death [25]. Besides, exosomes-miR-146b aborted the mice's CLP renal injury through diminished IL-1 receptor-associated kinase and inhibition of the NF-kB activity [48]. Likewise, miR-342-5p levels were suppressed in patients with sepsis-induced AKI serum in mice exposed to CLP and human kidney-2 (HK-2) cells incubated with lipopolysaccharides. The diminished miR-342-5p was associated with inflammation and deteriorated renal functions. While MSCs-derived Exosome-transfected with lentivirus overexpressing miR-342-5p injection in mice enhanced autophagy suppressed inflammation and ameliorated kidney injury [18]

However, exosomes-miR-19b-3p were found to mediate tubulointerstitial inflammation through macrophage activation by targeting NF-κB/suppressor of cytokine signaling (SOCS-1) [20].

EVs and the unilateral ureteral obstruction induced fibrosis

Intramuscular injection of exosomes-miR-29a two weeks before unilateral ureteral obstruction (UUO) of mice diminished renal tissue fibrosis. Exosomes-miR-29a decreased the expression levels of TGFβ, fibronectin, alpha-smooth muscle actin (αSMA), and renal collagen deposition [36]. Similarly, exosomes-miR-26a attenuated renal fibrosis by inhibiting TGFβ and the connective tissue growth factor (CTGF) [46]. Furthermore, the overexpressed miR-let7c downregulated collagen IVα1, metalloproteinase-9, TGFβ, and its receptor [34]. Meanwhile, miR-133b overexpression complex injection significantly diminished renal interstitial fibrosis in aged mice subjected to UUO [4]. The ability of MSCs-EVs to prevent UUO-induced fibrosis is mediated via miR-294 and miR-133 transport. These miRs subtypes

were able to diminish SMAD2/3 and ERK1/2 signaling, thereby mitigating the TGFβ1-related EMT in HK2 [38]. A receptor-interacting protein kinase 1 (RIPK1) is the upstream of mixed-lineage kinase domain-like pseudokinase (MLKL), a necroptosis mediator. UUO mice model showed extensive necroptosis associated with promoted fibrosis. However, MSCs-Exo miR-874-3p therapy reduced renal tubular epithelial cell injury and renal fibrosis by suppressing necroptosis revealed by targeting RIPK1 and MLKL [44].

Diabetic nephropathy and the mediating role of EVs-miRs

Extracellular vesicles-miR-23a and 27a introduced intramuscularly to diabetic mice prevented diabetic nephropathy (DN) and attenuated renal fibrosis through activation of Akt and inhibition of FoxO1 signaling [45]. Furthermore, increased renal blood flow in chronic kidney-diseased mice was achieved through the remote transfer of exosomes-miR-181 from the acupunctured limb to the kidneys [14]. Application of EVs enriched with miR-15b-5p protected podocytes from inflammation and apoptosis, which was mediated through inhibition of the vascular endothelial growth factor [51]. Another promising molecule is miR-22-3p. Wang and co-workers revealed the effect of miR-22-3p in DN. They co-cultured podocytes with human umbilical MSCs derived Exo (UMSCs-Exo-miR-22-3p) in high glucose media (HG) and injected them into diabetic mice. UMSCs-Exo diminished the inflammation and depressed the activation of NLRP3 inflammasome in podocytes and diabetic mice. These beneficial effects were abolished when miR-22-3p was knocked down [39]. Conversely, Tsai and co-workers stimulated the proximal tubule epithelial cells by HG and induced exosomal miR-92a-1-5p secretion. The treatment of mesangial cell (MCs) with the driven exosomal miR-92a-1-5p promoted endoplasmic reticulum (ER) stress of MCs and its myofibroblast transdifferentiation, and in the same context, miR- 92a-1-5p inhibitor protected mice kidneys and prevented DN progression [33].

The precancerous/anticancer effects of EVs-miRs

Mesenchymal stem cells and human liver stem cells express vesicles enriched with miR-145 and miR-200. Both EVs-miR-145 and 200 enhanced apoptosis, inhibited proliferation, and reduced invasion in the renal cancer cells [2]. Lopatina and co-workers reported an anticancer effect mediated by the transmission of miR-15a, 181b, 320c, and 874 loaded within the EVs from the human liver stem cells to the renal tumor-derived endothelial cells [19]. Qin et al.

[28] observed the abundance of miR-224-5p in EVs extracted from patients with RCC urinary samples. miR-224-5p prevented the proliferation of RCC cells and induced cell cycle arrest by suppressing the CCND1 gene that encodes cyclin D1.

However, several research studies have linked the EVs-miRs expression to renal cancer proliferation. Exosomes-miR-19b-3p [37] and miR-210-5p [40] potentiated cell migration and metastasis of clear cell renal cell carcinoma. Hypoxia stimulates EVs secretion from the RCC cell lines and is found to be enriched with high levels of miR-155. The secreted EVs-miR-155 promoted cell proliferation and tumor progression through FOXO3 inhibition [22]. The elevated exosome-harbouring lncARSR mediates renal cancer resistance to treatment with sunitinib through competitively binding to miR-34, 449 and confers drug resistance [30]. Similarly, the resistant response to sorafenib is mediated through EVs-containing miR-31-5p by downregulating Mut L homolog 1 in RCC [9]. Furthermore, miR-142-3p functions as an oncogene in RCC, and miR-142-3p was upregulated in RCC, which promotes cancer progression and metastasis. By miR-142-3p suppression, RhoBTB3 protein expression was upregulated, and HIF1A, VEGFA, and GGT1 levels were mitigated, improving cancer prognosis [50].

EVs-miRs in miscellaneous renal studies

Researchers have noticed a significantly diminished hsa-miR-500a-3P in cisplatin-treated human HK2 cells, and application of hsa-miR-500a-3P attenuated P65 NF-kB phosphorylation and inhibited MLKL, the central mediator of necroptosis [13]. The endothelial progenitor cell-derived EVs (EPC-EVs) protected the glomerular membrane-like structure formed by glomerular endothelial cells and podocytes from inflammation-induced destruction. Analysis of the miRs content of EVs determined 16 protective subtypes miR-17-3p, 17-5p, 18a, 19a, 30a-3p, 30e-3p, 30a-5p, 30e-5p, 137, 142-3p, 142-5p, 324-3p, 425-5p, 484, 485-3p, and 650 [21]. The injured podocytes induced by puromycin secreted a group of EVs-miR-149-5p, 424-5p, 542-3p, 582-5p, and 874-3p. These miRs were cultured with renal TECs. The authors documented marked apoptosis in the TECs through activation of the cleaved poly (ADP-ribose) polymerase (PARP) [11].

To study the mediating role of macrophages in vascular calcification in chronic kidney disease (CKD), vascular smooth muscle cells (VSMCs) obtained from the arteries of CKD patients or mouse models were incubated with macrophage-derived exosomes. The results documented

an inhibited expression of let-7b-5p in VSMCs associated with vascular calcification [15]. The anti-fibrosis candidate molecule miR-26a expression was diminished in the kidney of aldosterone (ALD)-induced Renal tubulointerstitial fibrosis (TIF) mice model. When the diseased mice were injected with exomes-miR-26a, there was a significant inhibition in the epithelial-mesenchymal transition and extracellular matrix deposition through suppression of SMAD3 [52]. Yang and colleagues have studied the effect of hepatitis B virus (HBV) on podocyte viability and ferroptosis using HBx, a multifunctional protein encoded by HBV. They reported reduced podocyte viability following lentivirus transfection overexpressing HBx through ferroptosis activation. Meanwhile, MSCs-derived exosomes enriched with miR-223-3p protected the podocytes from ferroptosis cell death, which was proven when the miR-223-3p inhibitor reversed the protective effect of MSCs exosomes-miR-223- 3p [41]

Primed stem cells and EVs-miRs secretion improve their regenerative actions

Researchers tried to potentiate the beneficial effects of EVs by incubating their secretory cells with drugs. Melatonin has previously been known to improve MSCs' viability, proliferation, and differentiation [31]. When MSCs isolated from patients with CKD were treated with melatonin, upregulation of miR-4516-PrP^{C} was observed and enhanced the regenerative potential of the MSCs with reduced cellular senescence. Therefore, the pre-conditioned MSCs with melatonin mitigated the hind limb ischemia mice model of CKD [42]. Another factor is vasopressin, which activates the EVs-miR-503 uptake by the renal collecting duct cells and downregulates the vascular endothelial growth factor, fibroblast growth factor [24].

Interestingly, pre-treated HK-2 cells with exendin-4 inhibited the transfer of EV miR-192 from HG-induced renal TECs to normal cells and inhibited the expression of fibrosis markers fibronectin and type I collagen [12]. Furthermore, erythropoietin inhibited tubulointerstitial fibrosis in mice induced by UUO. The extended in-vitro research confirmed the role of transferred EVs-miR-144 from the bone marrow cells to the renal fibroblasts to suppress tPA expression [53]. Zhang and co-workers designed scaffold nanofibers containing Arginine-Glycine-Aspartate (RGD). RGD facilitated the uptake and stability of EVs to the injured renal tissues of mice by supporting the surface EVs integrins. The obtained EVs' protective effects seemed to be mediated through EVs-miR let-7a-5p, which regulated cell apoptosis and autophagy [47]. Therefore, the primed cells could be a promising strategy to potentiate beneficial types of miRs, which mediates renal tissue protection.

CONCLUSIONS

The non-coding RNA segments, miRs, participate in several biological processes, including inflammation, apoptosis, necroptosis, ferroptosis, fibrosis, and cancer progression. This review tried to collect and discuss EVs-harboured miRs as a new insight into the alteration of renal pathogenesis. This review attempted to simplify the possible modulatory effect of miRs at the cellular level. Further investigations are still needed as miRs may have dual effects; EVs-miR-23a attenuated renal fibrosis by activating Akt and inhibiting FoxO1 signaling. Whereas, EVs-miR-23a was upregulated by the hypoxia-inducible factor (HIF-1a) in the hypoxic TECs and activated macrophages to accelerate the renal inflammatory cytokine storm and promote interstitial fibrosis.

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Author contributions

Hend Ashour: Conceptualization, collection of data, writing, structuring the figure Mohamed H. Elsayed: Writing, finalization of the figure, language revision. Hind Zafrah: Writing, revision.

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Conflict of interest

No potential conflict of interest is reported by the authors.

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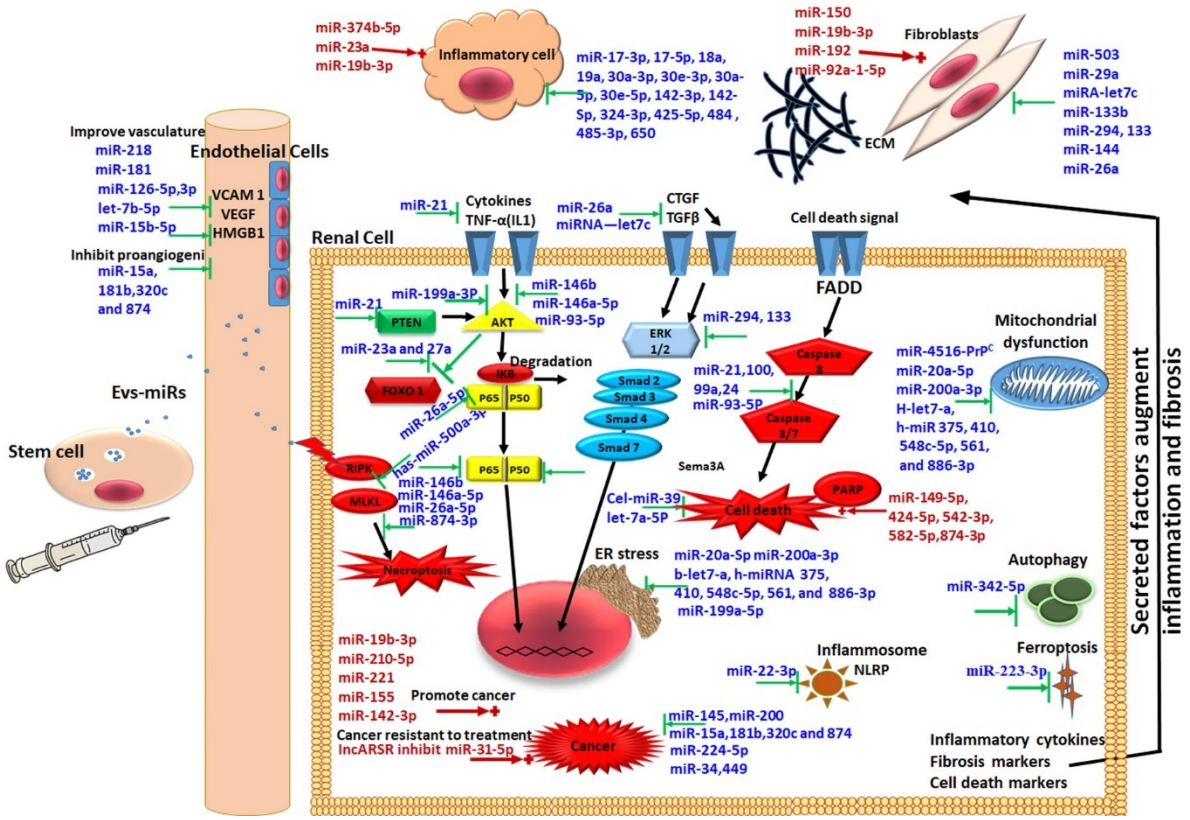

Figure 1. Schematic representation of the possible mediating role of miRs in renal pathogenesis. The figure demonstrates the interrelation between different miRs subtypes and the renal cell signaling pathways. The miRs in blue participate in beneficial effects while the miRs in red mediate harmful effects. EVs — extracellular vesicles-containing miRs. The inflammatory pathway begins by inflammatory cells' activation to secrete inflammatory mediators; TNF — tumor necrosis factor, IL — interleukin interaction which starts cell signalling through binding to their receptors. AKT — activated protein kinase, IKB — inhibitor of kappa light polypeptide, PTEN — phosphatase and tensin homolog, FOXO — forkhead transcription factors of the O class. The fibrosis signals involve CTGF — connective tissue growth factor, TGF — transforming growth factor and its downstream Smad, ERK — extracellular-signal-regulated kinase. Different cell death pathways are included in the modulatory functions of miRs. FADD — Fas-associated protein with death domain, PARP — poly (ADP-ribose) polymerase, the necroptosis mediators RIPK — receptor interacting protein kinase, and MLKL — mixed lineage kinase domain-like.