Extracellular vesicles (EVs) released from different types of kidney cells under physiologic conditions contribute to homeostasis maintenance, immune-modulation, and cell-to-cell communications. EVs can also negatively affect the progression of renal diseases through their pro-inflammatory, pro-fibrotic, and tumorigenic potential. Inhibiting EVs by blocking their production, release, and uptake has been suggested as a potential therapeutic mechanism based on the significant implication of exosomes in various renal diseases. On the other hand, stem cell-derived EVs can ameliorate tissue injury and mediate tissue repair by ameliorating apoptosis, inflammation, and fibrosis while promoting angiogenesis and tubular cell proliferation. Recent advancement in biomedical engineering technique has made it feasible to modulate the composition of exosomes with diverse biologic functions, making EV one of the most popular drug delivery tools. The objective of this review was to provide updates of recent clinical and experimental findings on the therapeutic potential of EVs in renal diseases and discuss the clinical applicability of EVs in various renal diseases. [BMB Reports 2022; 55(1): 3-10]

INTRODUCTION

Extracellular vesicles (EVs) are endogenously produced, membrane-bound vesicles that are released from cells into the extracellular space (1). Exosomes and microvesicles (MVs) are major subtypes of EVs. They are known to serve important roles in homeostasis, immune modulation, and tissue regeneration under physiologic conditions (2, 3). EVs can also mediate inflammation, thrombosis, fibrosis, and tumorigenesis in pathologic conditions (4, 5). EVs contain various biologic materials including mRNA, microRNA (miRNA), proteins, and lipids. Their contents are determined by the type of host cells and microenvironments of host cells (6). The biologic function of EVs depends on their compositions and downstream responses of recipient cells.

EVs serve several pivotal roles in renal physiology including immune modulation, tissue proliferation/regeneration, antimicrobial effect, and electrolyte/water balance, which contributes to maintenance of renal homeostasis (3). In pathologic conditions, however, EVs can contribute to propagation of disease courses by enhancing inflammation, fibrosis, coagulation, and tumorigenesis in various renal disease conditions (3). The role of EVs as a novel biomarker gained a lot of attention and comprised a major proportion of EV studies in kidneys. This topic is well summarized in the review article by Karpman et al. (1) and will not be addressed further in this review as it is beyond the scope of our topic.

Based on the recent advancement of stem cell research and biomedical engineering technique on EV loading and modification (7), EVs have received a lot of medical attention for treatment of various kidney diseases including AKI, CKD, and transplant graft rejection even though further verification through human studies is limited. EVs serve a crucial role in intercellular communication by delivering biological cargo to recipient cells. The potential use of EVs as biocarriers has been exploited for the delivery of endogenous or exogenous therapeutic materials (3). Diverse cargos including miRNAs, proteins, and drugs, can be delivered to target cells by modulating EV production and cargo sorting. In this review, we will focus on the potential of EVs as intrinsic therapeutics, therapeutic targets, and drug carriers for various renal diseases.

EVs FOR TREATING VARIOUS KIDNEY DISEASES

More recently, both in vivo and in vitro studies have shown explosive advancements regarding the protective role of EVs in various types of renal diseases. Most EVs used in those studies originated from mesenchymal stem cells (MSCs). They can alleviate renal damage mainly through their paracrine effects rather than their differentiation potential (8). MSC-derived EVs can exert therapeutic effects by modulating various biological processes including tubular proliferation, angiogenesis, apoptosis,
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Acute kidney injury (AKI)
AKI is a clinical syndrome originating from acute loss of renal excretory function and typically results in accumulation of renal toxins or reduction in urine output. AKI can originate from various etiologies including dehydration, toxins, hemodynamic instability, or obstruction. AKI is associated with increased mortality and healthcare-related costs. Therefore, many studies have focused on finding novel therapeutics using EVs to prevent or improve AKI outcome which will be addressed more in detail below.

MSC-derived EVs have shown a profound protective effect on AKI through their anti-apoptotic, antioxidant, anti-inflammatory, and angiogenic activities. In a study by Chen et al. (9), MVs derived from human Wharton’s Jelly mesenchymal stromal cells (hWJMSCs) could ameliorate renal ischemia reperfusion injury (IRI) by enhancing the regeneration and decreasing the apoptosis of renal cells while mitigating IR-induced renal fibrosis. This protection was induced by G2/M cell cycle arrest via Erk1/2 signaling. Another study has shown that hWJMSC-derived MVs possess antioxidant effects in a rat ischemic AKI model (10). A single administration of hWJMSC-derived MVs into IR-injured kidneys decreased the expression of reactive oxygen species, reduced apoptosis, and enhanced proliferation of tubular cells in vivo. Renal fibrosis in the late stage of IRI was also significantly abrogated by MV delivery, leading to similar biochemical improvement (10).

As identification and characterization of noncoding RNAs become more widely available, several studies have shown therapeutic potentials of exosomal miRNAs in ischemic AKI by post-transcriptional regulation. Li et al. (11) have found that both human urine-derived stem cells (USC) and their exosomes could protect ischemic AKI in mice. Further sequencing and bioinformatics analysis showed that miR-146a-5p was the most abundant miRNA in USC-derived exosomes. They found that miR-146a-5p targeted interleukin (IL)-1 receptor-associated kinase 1 mRNA, subsequently inhibiting the activation of NF-κB signaling in vitro (11). Zhu et al. (12) have demonstrated that exosomes from human-bone-marrow-derived MSCs can induce anti-apoptotic effect in ischemic AKI by transferring miR-199a-3p to renal cells. This protective effect was mediated via modulation of protein kinase B and extracellular-signal-regulated kinase pathways (12). However, neither of these studies traced or targeted exosomes in vivo. Thus, direct visualization of exosome transfer into target renal cells could not be provided by these studies.

Several studies have shown therapeutic effects of EVs derived from various sources other than MSCs (13, 14). Pan et al. (13) have found that the protective effect of limb remote ischemic preconditioning (rIPC) is mediated by miR-21 transportation from preischemic limbs to remote organs via serum exosomes. Serum-derived exosomes from mice with limb rIPC or enhanced exosomal miR-21 from cultured myotubes with hypoxia and reoxygenation preconditioning integrated into renal tubular epithelial cells and targeted downstream PDCD4/NF-κB and
Table 1. Therapeutic application of extracellular vesicles from various origins in different kidney diseases

| Disease Model | Origin | EV type | Mechanism | Ref. |
|---------------|--------|---------|-----------|------|
| AKI           | hWJMSCs| MVs     | • hWJMSC-derived MVs improve renal function in ischemic AKI model by facilitating the proliferation of renal tubular cells and alleviating the apoptosis and fibrosis of renal cells in vivo (rats). | (9) |
|               | hWJMSCs| Not specified | • hWJMSC-derived EVs ameliorate ischemic AKI by inhibition of mitochondrial fission through miR-30 in vivo (rats). | (44) |
|               | hWJMSCs| MVs     | • hWJMSC-derived MVs alleviate the oxidative stress through suppressing NOX2 expression in both in vitro (HUVEC) and in vivo (rats) IRI model. | (10) |
|               | hWJMSCs| MVs     | • hWJMSC-derived MVs induce HGF synthesis in damaged tubular cells via RNA transfer, facilitating tubular cell dedifferentiation and regeneration in unilateral AKI model in vivo (rats). | (45) |
|               | hUC-MSCs| MVs | • hUC-MSC-derived MVs mitigate epithelial cell apoptosis in low oxygen environment in vitro (HK-2) and ameliorated renal IRI in vivo (rats) via delivery of miR-21. | (46) |
|               | hUSCs  | Exosomes | • hUSC-derived exosomes ameliorate ischemic AKI in vivo (rats). | (11) |
|               | hBM-derived MSCs | Exosomes | • Exosomes from hBM-derived MSCs play a protective role in H/R injury in vitro (HK-2) as well as in renal IRI in vivo (mice). | (12) |
|               | Mouse serum | Exosomes | • miR-199a-3p is involved in the renal protective effects of exosomes from hBM-derived MSCs by regulating Sema3A and activating the AKT and ERK pathways. | (47) |
|               | Human urine | Not specified | • Urinary EVs alleviate AKI generated by glycerol injection and accelerate renal recovery in vivo (mice). | (14) |
| Diabetic nephropathy | Human renal tubular cells | Exosomes | • Exosomes from human renal tubular cells prevent ischemic renal injury in Nude rats by preventing renal oxidant stress and apoptosis and suppressing pro-inflammatory and pro-fibrotic pathways. | (16) |
|               | Rat BM-derived MSCs | Exosomes | • BM-derived exosomes improve renal function, morphology, and fibrosis in streptozotocin-induced diabetic nephropathy model in vivo (rats) in parallel with increased autophagy markers, LC3 and Beclin-1, and decreased mTOR and fibrotic markers expression in renal tissue. | (18) |
|               | Rat BM-derived MSCs | Exosomes | • Exosomes from BM-derived MSCs ameliorate renal inflammation and fibrosis while protecting tight junction structure in streptozotocin-induced diabetic nephropathy in vivo (rats). | (19) |
|               | hUC-MSCs | Exosomes | • hUC-MSC-derived exosomes decrease the production of pro-inflammatory and profibrotic cytokines in high glucose-injured renal tubular epithelial cells and renal glomerular endothelial cells in vitro. | (48) |
|               | hBM-derived MSCs and HLSCs | Not specified | • EVs from hBM-derived MSCs and HLSCs alleviate renal fibrosis and proteinuria in streptozotocin-induced diabetic nephropathy model in vivo (mice). | (49) |
| Hypertensive nephropathy | Not specified | Adipose-derived MSCs | • Administration of exosomes from cardioplegic-derived cells attenuate renal injury and cardiac hypertrophy in angiotensin II-induced hypertension model in vivo (mice), which appears to be associated with changes in the expression of interleukin-10. | (21) |
|               | Cardiophasphere-derived cells | Exosomes | • Adipose-derived MSC-EVs improve renal function, decreased urinary protein excretion, and renal fibrosis while preventing cardiac tissue fibrosis and inducing better blood pressure control in DOCA-salt hypertensive model in vivo (rats). | (20) |
PTEN/AKT pathways. The delivery of those exosomes attenuated sepsis-induced AKI through their anti-inflammatory and anti-apoptotic effects. In a glycerol-induced AKI model, the delivery of urine-derived EVs (uEVs) from healthy volunteers alleviated biochemical and histological renal injury, improved tubular cell proliferation, and reduced tubular cell apoptosis (14). Biodistribution analysis confirmed the preferential localization of uEVs in damaged kidneys. Treatment with human uEVs could restore Klotho to normal levels in injured kidneys which is known to serve reno-protective role in AKI by inhibiting apoptosis, fibrosis

Table 1. Continued

| Disease Model | Origin | EV type | Mechanism | Ref. |
|---------------|--------|---------|-----------|------|
| Glomerulonephritis | hEPC | Not specified | • hEPC-derived EVs alleviate complement-mediated mesangial injury in anti-Thy.1.1-induced glomerulonephritis model in vivo (rats) by inhibiting mesangial cell activation, leukocyte infiltration, and apoptosis. • hEPC-derived EVs inhibit complement-mediated renal mesangial cell injury and C5b-9 deposition in vitro. | (22) |
| Other CKD | Adipose-derived autologous MSCs | Exosomes | • Autologous MSCs-derived EVs restore renal function through attenuation of renal inflammation, tissue hypoxia, and fibrosis in metabolic syndrome model in vivo (pigs). • These protective effects are blunted in pigs treated with interleukin-10-depleted EVs. | (23) |
| | hCB-MSCs | Exosomes | • Cell-free hCB-MSCs-EVs ameliorate the inflammatory immune reaction and transiently improve the overall kidney function in CKD patients. • Cell-free hCB-MSCs-EVs do not induce any significant adverse events throughout the study period (one year). | (24) |
| | hBM-derived MSCs | MV | • hBMSC-derived MVs improve survival rate and renal function after renal transplantation in vivo (rats). | (25) |
| | Human adipose-derived MSCs | Exosomes | • GDNF-modified human adipose-derived MSC ameliorate renal fibrosis in murine UUO model. • GDNF-modified human adipose-derived MSCs exert cytoprotective effect on HUVEC in hypoxia/serum deprivation injury model by promoting angiogenesis through activation of SIRT1/eNOS signaling pathway. | (26) |
| | Tregs | Exosomes | • Treg-derived exosomes can postpone allograft rejection and prolong the survival time of transplanted kidney in vivo (rats). • Treg-derived exosomes suppress T cell proliferation in vitro. | (27) |
| | Mouse immature DCs | Exosomes | • Immature DC-derived exosomes improve the survival in isograft mice by alleviating inflammatory response, reducing CD4 T cell infiltration, and increasing regulatory T cells in spleen and kidney tissues. • miR-682 is highly expressed in immature DC-derived exosomes which can promote regulatory T cell differentiation and immune tolerance in renal allograft in vivo (mice). | (28) |

EV: extracellular vesicles, AKI: acute kidney injury, hWJMSCs: human Wharton's jelly mesenchymal stromal cells, MVs: microvesicles, miR: microRNA, HUVEC: human umbilical vein endothelial cells, IRi: ischemia-reperfusion injury, HGF: hepatocyte growth factor, hUC-MSCs: human umbilical cord mesenchymal stem cells, HK-2: human tubule epithelial cells, hUSC: human urine-derived stem cells, H/R: hypoxia/reoxygenation, hBM: human bone marrow, MSCs: mesenchymal stem cells, AKT: protein kinase B, ERK: extracellular signal-regulated kinase, mTECs: mouse tubular epithelial cells, mTOR: mammalian target of rapamycin, hLSCs: human liver stem-like cells, CKD: chronic kidney disease, DOCA: deoxycorticosterone acetate, TGF-β1: transforming growth factor beta-1, hCB-MSCs: human cord blood mesenchymal stem cells, UUO: unilateral ureteral obstruction, GDNF: Gliacl cell line-derived neutrophic factor, SIRT1: Sirtuin 1, eNOS: endothelial nitric oxide synthase, hEPC: human endothelial progenitor cells, Tregs: regulatory T cells, DCs: dendritic cells.
and upregulating autophagy (15). However, uEVs from Klotho null mice did not show any renoprotective effect. On the other hand, Klotho engineered uEVs from Klotho null mice restored regenerative properties, suggesting the indispensable role of Klotho in the protective mechanism of uEVs. Dominguez et al. (16) have shown that exosomes from human renal tubules could reverse renal IRI in nude rats through maintenance of renal vascular and epithelial networks, protection from oxidative stress and apoptosis, and suppression of pro-inflammatory and pro-fibrotic pathways. Further comprehensive proteomic analysis on IR-injured kidneys showed that renal IRI induced significant and extensive changes in protein expression. However, treatment with human renal tubular exosomes could prevent most of these protein expression alterations (16).

**Chronic kidney disease (CKD)**

Renal fibrosis is a major contributor to CKD pathophysiology and can cause irreversible deterioration of renal function. The severity of renal fibrosis is significantly correlated with progression of CKD. Pathways, diagnostic potential, and therapeutic potential of EV-regulated renal fibrosis in CKD are well described in a review article by Brigstock (17). Here, we will review some representative in vivo studies regarding therapeutic actions of EVs in various experimental models of CKD.

The most common etiology of CKD is diabetic nephropathy, a microvascular complication from hyperglycemia-induced oxidative injury and inflammation that can ultimately lead to renal fibrosis. MSC-derived exosomes have shown renal-protective effects on diabetic nephropathy (18, 19), although the exact mechanism has not been completely understood. Using a rat model of streptozotocin-induced diabetes mellitus model, Elraham et al. (18) have reproduced improved biochemical and histological renal outcomes in a group treated with MSC-treated exosomes compared to a control group. Treatment with MSC-derived exosomes induced significant upregulation of autophagy markers, Beclin-1, and light chain-3, and downregulated mechanical target of rapamycin (mTOR) and fibrotic marker expression in renal tissues (18). The protective effect of MSC-derived exosomes was partially reversed by administration of autophagy inhibitors, suggesting that autophagy induction by exosomes could attenuate diabetic nephropathy (18). MSC-derived exosomes could also exert anti-apoptotic, anti-fibrotic, and anti-degenerative effects in tubular epithelial cells while protecting tight junction structure in streptozotocin-induced diabetic nephropathy model of rats (19).

Hypertension is the second leading etiology of CKD, causing damage to blood vessels and filtering function of the kidney. In a deoxycorticosterone acetate-salt hypertensive model, EVs from adipose-derived MSCs could ameliorate pro-inflammatory response and recruitment of immune cells into the kidney (20). Moreover, administration of these EVs could prevent cardiac tissue fibrosis and induce better blood pressure control. Further miRNA microarray profile suggested that EV administration could affect signaling pathway of epithelial-mesenchymal transition and prevent inflammation as well as fibrosis in the kidney. In an angiotensin II-induced hypertensive model, exosomes from cardiophaserived cells improved renal function and cardiac hypertrophy while diminishing inflammation and fibrosis in both kidney and heart in association with altered levels of IL-10 expression (21).

A study by Cantaluppi et al. showed that EVs from endothelial progenitor cells can decrease antibody- and complement-mediated injury in Thy1.1-treated glomerulonephritis model (22). This protective effect was significantly reduced by pre-treatment with a high dose RNase, suggesting a crucial role of RNA content in EVs. In a pig model of metabolic syndrome and renal artery stenosis, exosomes from autologous MSCs could preserve renal function by alleviating renal inflammation, tissue hypoxia, and fibrosis (23). This renoprotective capacity appeared to be mediated by exosomal IL-10, an anti-inflammatory cytokine. Song et al. (24) have shown that MSC-derived EVs from lean pigs are more effective in improving renal function and decreasing tubular injury and fibrosis than EVs from metabolic syndrome pigs. These beneficial effects were associated with enhanced anti-inflammatory transforming growth factor (TGF)-β signaling leading to regulatory T cell induction (24).

**Graft dysfunction after renal transplantation**

Renal transplant has become the treatment of choice for most of the advanced kidney disease by placing a healthy kidney from a donor into a recipient’s body. Transplant procedure itself induces some degree of ischemic-reperfusion damage as well as tissue damage which has significant impact on early graft function (25). Long-term immunosuppressive treatment is also crucial to prevent graft rejection and to prolong the graft survival as well as its function maintenance. EVs are known to serve a various role in transplanted kidney through their modulatory functions in innate immunity, complement system, and coagulation system, either by activating or inhibiting them depending on the microenvironment and EV content (25). EVs are also involved in allorecognition, IRI, and the autoimmune component of antibody-mediated rejections, affecting on the graft function and survival (25). Kidney endothelial- and tubular-derived EVs can trigger graft rejection by inducing alloimmune and autoimmune responses, while MSC-derived EVs have been investigated for their therapeutic potential in experimental transplant models (26-28). The role of EVs in the crosstalk between the renal graft and immune systems as well as the diagnostic and therapeutic role of EVs in renal transplantation are well summarized in the review article by Quaglia et al. (25).

In a rat model of kidney transplantation, exosomes derived from regulatory T cells could delay allograft rejection, prolong the survival time of transplanted kidney, and inhibit T cell proliferation (26). This protective effect was more prominent by using the exosomes collected from donors compared to those from recipients. Pang et al. (27) have shown that immature dendritic cells-derived exosomes could significantly improve
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Extracellular vesicles as a therapeutic tool in various renal diseases

Better understanding of biological mechanisms of EVs and simultaneous advancement of bio-engineering technology to modulate EV production and cargo sorting have made EV one of the most preferred drug delivery systems. There are multiple biological benefits of EVs as vectors over other methods, including their stability, reduced toxicity, biostability, and low immunogenicity (34). Specific cell surface molecules on EVs enable targeted delivery of therapeutics into subcellular structures including mitochondria and nucleus, while minimizing off-target effects (35). Exosomal delivery of biologic materials can modulate disease processes by altering genetic profiles and biological responses of recipient cells (36).

Several studies have investigated the therapeutic potential of EVs as a vector for drug delivery in various kidney diseases. Tang et al. (37) have successfully produced macrophage-derived dexamethasone containing MVs through co-incubation of macrophages with dexamethasone. Delivery of these MVs into inflamed kidneys showed significant suppression of renal inflammation and fibrosis in lipopolysaccharide- or Adriamycin-induced murine model most likely through inhibition of NF-κB activity. In contrast with the traditional systemic glucocorticoid treatment which can cause hyperglycemia, infection, osteoporosis, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, chronic glucocorticoid treatment through these MVs showed no significant effect on serum glucose, HPA axis, bone metabolism, or immune response.

More recently, Yim et al. (38) have shown significant advancements in exosome research regarding its production efficiency and biological compatibility using “exosomes for protein loading via optically reversible protein-protein interactions” (EXPLOR), a novel optogenetically engineered exosome technology. By using this EXPLOR technology, Choi et al. (39) have successfully delivered super-repressor IκB-containing exosomes and shown their protective effects in a murine septic AKI model by inhibiting nuclear translocation of NF-κB. Recently, our group also reproduced the protective effect of exosomal super-repressor IκB delivery treatment in an ischemic AKI model through its modulatory effect on inflammation and apoptosis (40).

As noncoding RNAs have gained more recognition for their important roles in various biological processes, delivery of noncoding RNAs as novel therapeutics for regulating renal disease progression using exosomes is in the limelight. Wang et al. (41) have shown that exosomal delivery of exogenous miRNA-let7c through engineered MSCs could alleviate renal fibrosis in a murine UUO model by suppressing TGF-β signaling pathway. Their group also showed that exosomal delivery of mir-R26a and mir-29 could attenuate renal fibrosis and muscle wasting in a murine UUO model (42, 43). These studies showed that exosomes-carried miR-26a could limit renal fibrosis by directly suppressing connective tissue growth factor, while delivery of exosomal miR-29 could down-regulate pro-fibrotic proteins in TGF-β pathway, attenuating the progression of renal fibrosis in UUO kidneys.

CONCLUSIONS

EVs carry high potentials as a novel therapeutic tool for modulation of disease courses and for drug delivery. However,
application of EVs to renal diseases is still in its infancy stage despite the explosive advancement in EV research during the past decade. Clinical application of exosomes as a therapeutic tool has been mainly focused on cancer therapy and related studies in the nephrology field are relatively scarce. There are also several technical challenges to be surmounted including retaining high yields of pure exosomes, enhancing the capability of loading various cargoes, and improving targeting specificity (35). Therefore, further advancements of therapeutic application of EVs in various renal diseases need a multidisciplinary approach harnessed with better understanding of renal pathophysiology, multi-omics studies to find a novel therapeutic target, and supplementation of bioengineering technique to enhance the quality of exosomes as biocarriers. Further optimization of EV isolation techniques and scrupulous manipulation of genetic or protein compositions of EVs are mandatory to expand the therapeutic applicability of EVs. Rigorous in vivo and in vitro studies to better characterize the exact biological role of each EV treatment and evaluate potential off-target effects from EV treatment are required for individualized therapeutic application. This achievement needs to be followed by further validation through clinical trials and large-scale cohort studies before entering clinical application. These efforts will further extend the clinical applicability of exosomes as novel therapeutics of various renal diseases.

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CONFLICTS OF INTEREST

Tae Hyun Yoo is a Scientific Advisory Board member at ILIAS Biologics Inc. The authors have no additional financial interests.

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