



# Exosomes: a potential key target in cardio-renal syndrome

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Exosomes have proven roles in regulating immune response, antigen presentation, RNA and protein transfer, and cell–cell (organ–organ) interaction/signaling. These microvesicles can be considered a mechanism of non-classical secretion of proteins, and they represent a subproteome, thus assisting in the difficult task of biomarker discovery in a biological fluid as urine, plasma, or serum. A potential role of exosomes in the cardio-renal syndrome is currently underexplored. Cardiovascular disease continues to be the leading cause of morbidity and mortality worldwide and, particularly, rates of cardiovascular events and death consistently increase as kidney function worsens. In other words, chronic kidney disease acts as a risk multiplier. Unfortunately, the relationship between markers of cardiovascular risk in kidney pathology often differs from that in the general population. Efforts in the search for novel action mechanisms simultaneously operating in both pathologies are thus of maximum interest. This article focuses to the role of exosomes in cardiovascular and renal diseases, in the search for novel key targets of interaction between heart and kidneys.

**Keywords:** exosomes, cardiovascular, kidney, proteomics

## THE CARDIO-RENAL SYNDROME

The term “cardio-renal syndrome” (CRS) encloses a scenario of clinical interactions in which cardiac and renal dysfunction coexists (1). The cross-talk between the heart and the kidneys is clearly evidenced but not fully understood. Observational and clinical data showed that acute/chronic worsening of kidney function directly contributes to acute/chronic cardiac disease and vice versa, constituting the CRS.

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem and its prevalence is continuously rising. Defined as an irreversible progressive loss of renal function for 3 months or longer, it is categorized into five stages of increasing severity (CKD1-5). In early stages, it develops silently and asymptomatic, which enormously difficult early diagnosis and intervention. In CKD patients, rates of cardiovascular events and death consistently increase as kidney function becomes worse. Thus, CKD acts as a risk multiplier. The risk of unfavorable cardiovascular prognosis increases as renal insufficiency progresses toward end stage renal disease (ESRD), reaches its maximum, and persists following successful renal transplantation. Subjects with mild to moderate renal dysfunction have a higher probability of dying by a cardiovascular event than due to the kidney disease itself before reaching ESRD. In fact, the American Heart Association (AHA) stated that CKD patients should be regarded as the highest risk group for subsequent cardiovascular disease (CVD) (2).

It may be thought that risk factors and misregulated molecules known to be acting in CVD in the general population can be directly translated into the renal disease frame. However, the relationship between risk markers and CV events in kidney pathology often differs from that in the general population. One of the main reasons is that traditional CV risk factors, e.g., age, male gender, hypertension, diabetes, dyslipidemia, smoking, overweight, and hyperhomocysteinemia are highly prevalent in CKD. Additionally,

contribution of risk factors specifically associated to kidney disease should be added, e.g., anemia, calcium-phosphate disorders, electrolyte imbalances, chronic inflammation, oxidative stress, hypercatabolism, uremic condition, and vitamin D deficiency (3). Some clinical trials focus on known drugs acting to control abovementioned risk factors (blood pressure management, lipid lowering, antiplatelet therapy, etc.). Unfortunately, the results are usually unexpected or not convincing, finding a non-clear response in the adequate direction. Additionally, most of the studies about CVD in CKD are carried out from a *post hoc* subgroup analysis of larger trials, which were not specifically designed to investigate effects on CKD population, so that final conclusions should be postponed until further evidence is found (4). In other cases, cardiovascular trials even excluded CKD patients from enrollment. Thus, despite of research efforts, active cardioprotective treatment is underemployed in renal disease patients, probably due to the uncompleted knowledge of the cardio-renal puzzle.

In this context, documented evidence exists to consistently prove that cardiovascular complications should be considered a key, unsolved and state-of-the art issue in kidney disease, in terms of early on-time diagnosis, accurate prognosis prediction, and in-depth understanding of underlying mechanisms.

## EXOSOMES REFLECT PATHOPHYSIOLOGICAL CHANGES IN THE KIDNEY

The classical pathway of exosome formation involves intraluminal vesicles (ILVs) formation within multivesicular bodies (MVBs) whose membrane fuses with the plasma membrane and release the ILVs, called exosomes once secreted (5). A potential role in the pathophysiology of the kidney has been attributed to exosomes, which may participate as mediators of intercellular communication, activate signaling mechanisms in the target cell, transfer their content in mRNAs, miRNAs and proteins, or just constituting a way of cellular contents disposal (6, 7) (Table 1).

**Table 1 | Overview of the main roles described for exosomes in cardiovascular and renal diseases.**

Sample	Disease	Main findings	Reference
<b>BIOMARKERS SOURCE</b>			
Urine	Aldosteronism	pNCC, marker of aldosteronism	(23)
Urine	AKI and podocyte injury	Transcription factors in urinary exosomes ATF3, marker of early AKI WT-1, marker of early podocyte injury	(11)
Urine	Diabetic nephropathy	WT-1, marker of DN	(20)
Urine	Diabetic nephropathy	VDAC1, AMBP, MLL3 markers of DN	(18)
Urine	Renal I/R injury	Aquaporin-1, novel exosomal marker in renal I/R injury	(22)
Urine	DGF in renal transplantation	Exosomal NGAL correlates with DGF patients	(17)
<b>INTERCELLULAR COMMUNICATION</b>			
Kidney cortical collecting duct cells		Functional Aquaporin-2 transfer between kidney cells by exosomes	(13)
Urinary exosome-like vesicles		PKD proteins, shed in urinary membrane particles, which interact with primary cilia	(6)
Model of kidney injury		Exosomes produced by injured epithelial cells activate fibroblasts by delivering TGF- $\beta$ 1 mRNA	(7)
Cardiomyocytes		HIF-1 $\alpha$ initiates expression of TNF- $\alpha$ mediated by exosomes in hypoxia	(38)
Vascular smooth muscle cells		VSMC-derived exosomes mediate vascular calcification	(39)
Endothelial cells		HSP70 secretion from endothelial cells is exosome-dependent	(40)
<b>CARDIOPROTECTION</b>			
MSCs		After ischemic preconditioning, MSCs secrete exosomes enriched with miR-22	(31)
Rats heart		Remote cardioprotection after ischemic preconditioning is mediated by heart extracellular vesicles	(41)
CPCs from mouse hearts		CPC-exosomes, as a therapeutic vehicle for cardioprotection	(34)

AKI: acute kidney injury; DN: diabetic nephropathy; DGF: delayed graft function; PKD: polycystic kidney disease; MSCs: mesenchymal stem cells; CPC: cardiac progenitor cells.

Representative examples.

In the kidney, exosomes can be released by cells as podocytes, pass through the renal tubule and they can either be uptaken by recipient epithelial cells of the collecting duct, or influence them through secretion of their content. Exosomes finally appear in urine (8, 9). Thus, these vesicles are direct messengers of what is happening in the kidney, both in acute and chronic damage, carrying molecular markers of renal dysfunction and structural injury (10, 11). More than a way of exocytic cell waste elimination, they should be considered as key molecular targets and a valuable source of potential biomarkers, particularly when kidney tissue is not available or as a non-invasive alternative to biopsy-based diagnosis (12). Aquaporin-2 present in exosomes released from collecting duct cells was shown to be physiological regulated and a close reflection of cellular expression, pointing to a novel mechanism of cell-to-cell communication inside the kidney (13). Another example of their role in intercellular communication is the observation that renal brush border-derived exosomes can induce crystallization in nephrolithiasis (14). In the same line, a still underexplored role in transplantation or protection against acute kidney injury (AKI) or toxics negative effect has been attributed to microvesicles in general and exosomes in particular (15, 16). A recent study shows a high presence of NGAL protein in urinary exosomes. This protein has been described as a good marker of AKI, and the reported correlation of urinary exosomal NGAL levels with delayed graft function after kidney transplantation point to the exosomal fraction as a more sensitive substrate to evaluate early biomarkers of prognosis in this context (17).

Zubiri et al. have recently published a panel of altered proteins composed by MLL3, AMBP, and VDAC1 in the urinary exosomes of patients with diabetic nephropathy (DN) compared to healthy controls (18). DN is the main cause of ESRD, but underlying mechanisms are not fully understood and renal damage observed in biopsied tissue does not always correlate with measurable indicators as microalbuminuria. In the search for novel and earlier indicators, urinary exosomes have been investigated in an animal model of DN finding Xaa-Pro dipeptidase and Major Urinary Protein 1 increased or decreased, respectively (19). Quantitation of damaged podocyte in urine has been proposed as an indicator of renal damage; however, it is not feasible for early detection of DN. Podocyte injury can be evaluated by means of Wilm's Tumor-1 protein levels, and although it could not be detected in urine from focal segmental glomerulosclerosis (FSGS) patients, Kalani et al. recently showed its predominant presence in urinary exosomes of diabetic patients and increased levels when renal function worsens (20). Markers of renal damage in the context of AKI have also been investigated in urinary exosomes pointing to Fetuin-A and Aquaporin-1 proteins (21, 22). The phosphorylated (active) form of the sodium chloride cotransporter (pNCC) was investigated in aldosteronism and discovered as an indicator of the biological activity of aldosterone and, potentially, as clinical biomarker for primary aldosteronism (23).

Thus, interest of exosomal research in kidney pathology is twofold: as a rich source of novel markers, which promisingly reflect what is happening in progressively or acute damaged kidney tissue, and as molecular messengers between the different parts

of the nephron contributing to its optimum functionality by the uptake and release of their content.

## EXOSOMES AND CARDIOVASCULAR DISEASE

Atherosclerosis develops silently and progressively. It is a multifactorial disease that starts with endothelium dysfunction, followed by accumulation of inflammatory cells (macrophages, lymphocytes), lipoproteins, lipids, and fibrous tissue in the wall of large arteries, leading to intima hyperplasia and proliferation of vascular smooth muscle cells (VSMC) within the intima. In advanced lesions, necrosis of macrophages derived foam cells and VSMC results in a lipid-rich core covered by a fibrous cap, which protects the lesions from rupture and consists mainly of collagen and extracellular matrix (ECM) proteins. Plaque rupture and the ensuing thrombosis commonly cause the most acute complications of atherosclerosis such as unstable angina or myocardial infarction (MI) (acute coronary syndrome) or stroke (24). The main problem is that we are facing an asymptomatic development of the pathology in which different cellular types are acting simultaneously.

Only recently, a potential implication of exosomes in CVDs has been raised (25) (Table 1). Similar to what has been described in pancreatic  $\beta$ -cells, exosomes could interact with the ECM via exosomal integrins (26) pointing to a role in plaque instability or, in the opposite way, in fibrous cap protection. Several studies show an increased amount of microvesicles released in CVD and, in particular, platelets are known to release exosomes, which may be involved in the complex cross-talk among different cell types during atherosclerosis development (27). The capacity of exosomes released by cardiomyocytes to transfer DNA and RNA to different cells has been shown (28). However, the exosomes involvement either in vascular diseases or in cardioprotection mechanisms has not been deeply investigated and fully unraveled. In this sense, preceded by studies showing that cardiac and circulating miRNAs are altered following MI, intercellular communication between heart and bone marrow through released exosomal miRNAs has been hypothesized as a protective/regeneration mechanism after ischemia (29–31). Apparently, similar mechanisms to those operating in preconditioning take place in cardioprotection conferred by exosomes (32–34).

Additionally, exosomal surface can be functionalized to direct them toward a specific target. In this way, they can be converted into therapeutic transporters as they may be acting on a solely cellular type (i.e., cardiac cells). The drug efficiency could be so increased and side effects could be minimized. In a similar way, exosomes have been proposed as ideal therapeutic agents in regenerative medicine, particularly in stem cell based therapies to treat acute MI (35).

## PERSPECTIVES: EXOSOMES, A NOVEL TARGET IN THE CARDIO-RENAL PUZZLE

Deeping insight the cardio-renal puzzle demands for expanded knowledge of many still missing pieces. This challenging multidisciplinary task should be accomplished in two main directions: discovery of novel markers of disease and understanding the underlying physiopathological mechanisms taking place. In general, biomarkers can be classified attending to the kind of

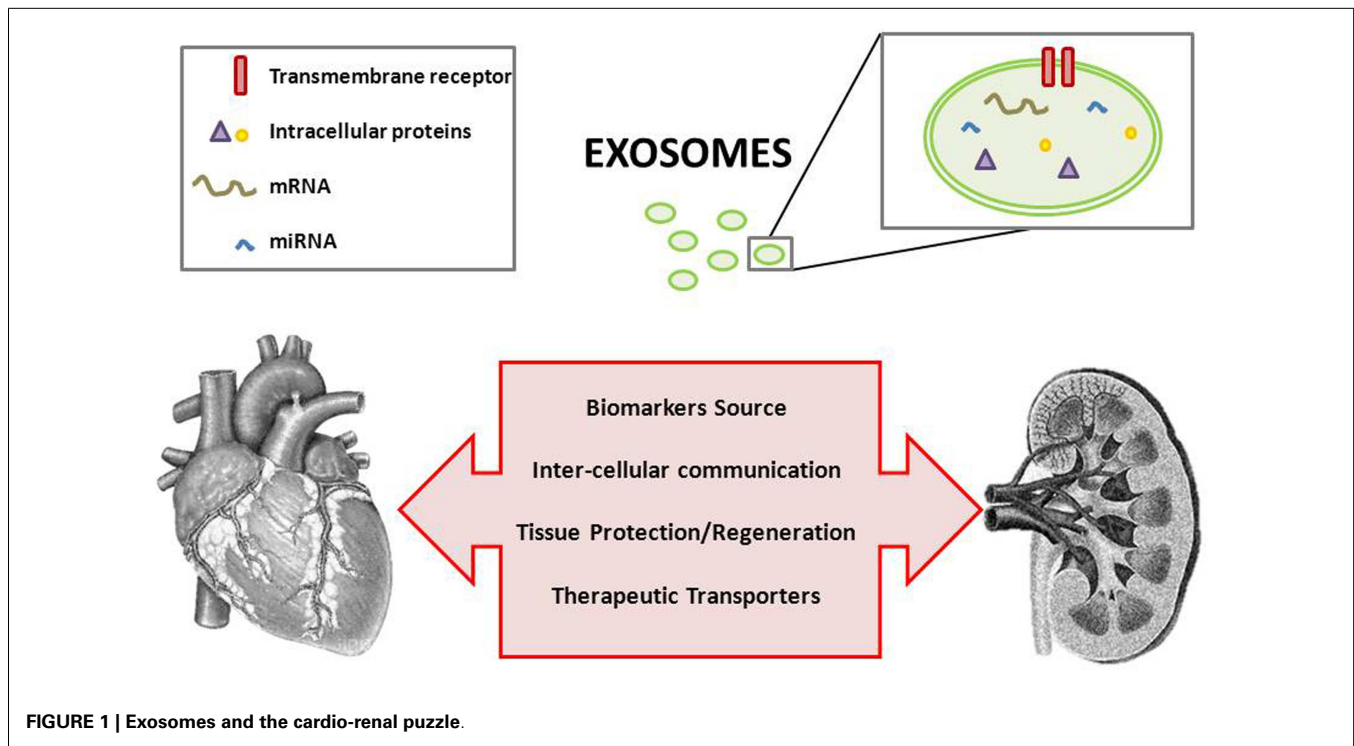
information provided in (a) risk assessment, (b) screening markers to distinguish between healthy and pathologic condition, (c) prognostic markers able to predict course of disease or therapy effect, (d) stratification markers to envisage responders and non-responders to drug, and (e) therapy monitoring, able to monitor the efficacy of treatment once the responder status is established (36). The difficulties behind novel biomarkers discovery make sense particularly in relation to approach cardiac or renal tissue.

Totally different from other diseases as cancer pathology in which biopsy procedures are routinely indicated, it is very much difficult, when not unfeasible, directly approach the heart or the kidney to investigate pathological changes of significance. In certain disorders as DN, a diagnosis based on clinical evidences usually takes place late in the course of disease or when damage at tissue level is already irreversible. Atherosclerosis silent and asymptomatic development results in the worst case in a fatal event, and there is lack of effective preventive markers to stratify risk and design preventive measurements individually.

Biological fluids such as serum, plasma, or urine are being explored in the different contexts in the search for diagnostic, prognostic, or risk markers. One of the main difficulties is the wide dynamic range of the sample when proteins are to be investigated. Fishing low-abundance molecules can be facilitated when approaching a certain subproteome such as the cellular or tissue secretome. In the same way, isolation of exosomal fraction from a biological fluid or secretome allows narrowing the complexity of the sample and focusing the search in a more specific target (37). Exosomal isolation from the original source (cell/tissue secretome, plasma, urine, platelets, etc.) is not a trivial task, and it should be carefully approached. Indeed, particular limitations has been pointed to in terms of “purity” of isolated exosomes, in the sense that care should be taken whenever a specific role is to be attributed specifically to these microvesicles instead of to microparticles or apoptotic blebs or mixtures of both. In urine, exosomes represent only a 3% of the whole proteome, thus they constitute an enriched subproteome with reduced complexity compared to the whole urine. In this way, low-abundance molecules that may have pathological significance are enriched against high-abundance ones. Their value as source of potential markers of disease is exemplified when the exosomal content can directly reflect the tissue situation.

Apart from a source of potential novel markers, they act as a way of intercellular communication, which although proved with sufficient evidence is currently underexplored. This exosomal role has been shown, for instance, in terms of proteins and miRNAs transfer from the origin cell and the target cell or acting as functionalized messengers to ensure specific drug delivery to the desired point of action. Related to cardioprotection following an acute cardiovascular event (e.g., MI) or to ameliorate the consequences of ischemia-reperfusion, there are evidences pointing to an active role for exosomes in ischemic signaling, myocardial repair, and communication between heart and bone marrow. This exosomal role acquires special significance in the context of CRS in which the cross-talk between heart and kidneys is known but not gone through.

Once overcome methodological difficulties, exosomal research in the context of cardio-renal pathology is therefore more than



justified (Figure 1). Exosomes are currently being of increased consideration and they constitute a promising field in this and other pathologies.

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