
REVIEW ARTICLE

Exosomes: Development, advancement and possible treatment options for diabetic nephropathy: A literature review

Zhangsuo Liu, Lixue Yin, Xinghua Xu

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ABSTRACT

According to this literature review, Exosomes are nanoscale vesicles that are expelled by practically all cell types through invagination of the endosomal membrane pathway and are a significant kind of Extracellular Vesicles (EVs). Exosomes are essential for intercellular communication in both health and sickness. This is due to their ability to carry cargoes like DNA, mRNA, proteins, and microRNA to nearby or distant cells, which in turn controls the biological activity of the recipient cells. A prominent cause of end-stage renal disease and a critical microvascular consequence of diabetes mellitus, Diabetic Nephropathy (DN) places a heavy financial burden on both people and

society but despite significant efforts, there are no therapeutic strategies that stop DN from progressing, indicating the need for new strategies. Exosomes may serve as novel indicators and therapeutic targets for DN, according to a growing body of research suggesting their involvement in the pathophysiological mechanisms linked to the disease. Due to their potential as indicators and therapeutic targets, exosome processes in DN have seen recent improvements that are summarized in this review.

Key Words: *Exosomes; Diabetic nephropathy; Intercellular communication; Biomarkers Therapies*

INTRODUCTION

End-Stage Renal Disease (ESRD), which has a high rate of morbidity and mortality, is frequently brought on by DN, a severe microvascular consequence of diabetes that is a chronic, progressive condition. 40% of those with type 2 diabetes and 30% of those with type 1 diabetes, respectively, will acquire DN. The presence of proteinuria, a decline in Estimated Glomerular Filtration Rate (eGFR), and a long history of diabetes are the main criteria for the clinical diagnosis of DN. The prognosis is further improved by the presence of diabetic retinopathy and the exclusion of other chronic kidney diseases. However, in reality, renal function is compromised or even degraded before the microalbuminuria is discovered. In particular, microalbuminuria has been recognized as a traditional predictor for renal disorders, including DN [1].

Renal biopsy, the gold standard for kidney disease diagnosis, also has the drawbacks of being an invasive technique and being unable to

monitor disease progression. As a result, new accurate and sensitive biomarkers are needed for the diagnosis of DN. Currently, DN treatment plans focus on comprehensive management, which includes reducing albuminuria, hyperglycemia, and hypertension, administering RAAS inhibitors, and using novel renoprotective medications such Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) [2]. Even with these treatments, there is still a high rate of ESRD. In conclusion, it is critical to investigate fresh methods for DN diagnosis and care. Exosome involvement in DN is being suggested by more and more studies. We discuss the possible effects of exosomes on the pathophysiology, biomarkers, and treatments of DN in our review.

Using a transmission electron microscope, Trams et al. made the initial discovery of exosomes in the early months of 1981, however at this point, only minor structural characteristics (such as vesicle-like characteristics) were revealed. Six years later, Johnstone et al.

Editorial Office, *Journal of Kidney Treatment and Diagnosis*, Windsor, Berkshire, England

Correspondence: Lixue Yin, Editorial Office, *Journal of Kidney Treatment and Diagnosis*, Windsor, Berkshire, England, e-mail kidney@clinicalsci.org

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conducted a study on the procedures connected with sheep reticulocyte maturation where they first provided a more precise definition of exosomes. However, they received little attention from scientists at the time and were viewed as little more than "waste" that cells excreted. Exosomes are currently understood to be Extracellular Vesicles (EVs) that are released by a number of cell types and have a diameter ranging from 40 nm to 160 nm (on average, 100 nm). Exosomes often come from the endosomal system through processes including internal budding and plasma membrane invagination, and they frequently co-form with Multivesicular Bodies (MVBs). Early-Sorting Endosomes (ESEs) and Late-Sorting Endosomes are the first endosomes to form after the plasma membrane internally budding (LSEs). MVBs are then created following sequential or double inward invagination of the plasma membrane, which permits MVBs to be created that include Intraluminal Vesicles, which are precursors of exosomes (ILVs) [3]. As a result of the MVBs outer membrane joining the cellular plasma membrane and exocytosis, exosomes are expelled into the extracellular area. Endosomal sorting complexes necessary for transport are the mechanism that regulates the production of exosomes. Additionally, involved in exosome formation include Ral GTPases, Rab GTPases, and exosome markers such CD9, CD81, CD63, TSG101, and flotillin. Exosomes were first thought to exclusively be involved in the clearance of extracellular materials like proteins and lipids. However, the growth of this field's study over the last few decades has demonstrated that exosomes play a role in the control of intercellular communication.

Review of Literature

Exosomes carry complex molecules, such as proteins, lipids, RNA, non-coding RNA, microRNA, and short RNA, which are carefully regulated by the parent cell. This allows information about certain biological functions to be transferred from the parent cell to the acceptor cell. Exosomes have a high degree of selectivity for certain receptor cells due to the wide variety of cells from which they arise in their surface molecules. Exosomes are often internalized by acceptor cells after being targeted by specific molecules on their surface, internalization induced by membrane fusion with acceptor cells, and endocytosis. Exosomes are heterogeneous in that they come in a range of sizes, contents, functions, and cellular origins. Exosome-focused research is still active and extensive, despite the fact that our understanding of exosome biogenesis, release, uptake, and function is not entirely clear. This is because exosomes may be useful in the detection and treatment of a variety of diseases, including cancer, metabolic disorders, cardiovascular dysfunction, and neurodegeneration. Exosomes have also been widely used in targeted drug delivery using surface engineering techniques, which offers efficient methods for cancer diagnosis and treatment. Exosomes can be found in a variety of body fluids and tissues, including urine, blood, saliva, and adipose tissue. Exosomes are released into the extracellular space by the majority of cell types. Exosome isolation and purification serve as the cornerstone for research into exosome function. Exosomes have been isolated and purified using a number of sophisticated methods, including size exclusion chromatography, immunoaffinity capture, density gradient ultracentrifugation, and polymer precipitation [4]. Every method offers a different set of benefits and drawbacks. For exosome extraction, ultracentrifugation is the most popular and regarded as the "gold standard" isolation

technique since it can simultaneously extract huge sample volumes. However, there are drawbacks to this approach, including extended operational durations and high instrument needs. Additionally, adopting this technique frequently results in the exclusion of microvesicles, producing impure isolated exosomes. When used to isolate exosomes from certain sources, immunoaffinity capture techniques rely on the precise binding of markers and antibodies. However, they have a low productivity and need expensive antibodies. As a result of exosome heterogeneity, no exosome isolation technique has been consistently advised by researchers up to this point. Numerous variables, such as the starting matrix (cell culture media versus biofluid), starting volume, downstream analysis, and research topic, influence the procedure selection. Exosome characterisation utilizing a combination of transmission electron microscopy and protein markers including CD63, CD9, and CD81 is also necessary following exosome isolation. In conclusion, researchers must continue to make improvements to the extraction of exosomes. Functional (such as proteinuria and a decrease in glomerular filtration rate) and structural (extracellular matrix accumulation, glomerular basement membrane thickening, podocyte injury and depletion, tubulointerstitial inflammation, and fibrosis) changes are the primary pathological hallmarks of renal injury in diabetes. Unfortunately, little is known about the various and intricate pathogenic mechanisms [5,6]. The main factor for long-term hyperglycemia is diabetes mellitus, however careful glycemic control may not necessarily stop or slow the development of DN. Inflammation, fibrosis, mitochondrial dysfunction, decreased autophagy, and oxidative stress are additional variables that contribute significantly to the course of DN. Additionally, recent research links aberrant renal cell communication to the pathophysiology of DN. However, the residual risk of DN progression remains significant despite the currently available medications, indicating additional potential molecular processes contributing to DN progression that need further exploration. High glucose concentrations that stimulate renal cells change their composition and communication, which further affects and damages intact cells. This suggests that exosomes may be involved in the pathophysiological pathways of diabetic kidney disease. Exosomes are membrane-bound transport vesicles that are generated from cells. They are essential in the regulation of cellular biofunction because they facilitate cell-to-cell communication by carrying cargos such microRNA, mRNA, and proteins [7]. There is proof that these cargos are transported into nearby or distant cells to influence their biofunction. Exosomes carry their cargo across the kidney cells, according to recent investigations. Glomerular Endothelial Cells (GECs), an essential element of the glomerular filtration barrier, have been implicated in the pathophysiology of DN through interplay with other glomerular cells such Gomerular Mesangial Cells (GMCs) and podocytes. However, little is known about the complex chemical mechanisms that underlie these interactions. Exosomes produced by high glucose-induced GECs have recently been discovered to transfer circRNA or mRNA to GMCs, which promotes renal fibrosis by activating, proliferating, and overproducing Extracellular Matrix (ECM) proteins in GMCs. Similar to this, the Wnt/ β -catenin signaling pathway, which is produced by GECs, causes the Epithelial-Mesenchymal Transition (EMT) and malfunction of the podocyte under high glucose circumstances. Furthermore, podocyte death and depletion are distinctive feature of DN because they lack the ability to proliferate when faced with damage. Earlier work showed that TGF/ β -PI3K-AKT signaling may be involved in the process by which HG-activ-

-ated GMCs interact with podocytes by secreting exosomes, leading to podocyte death. Additionally, in kidney illnesses like DN, Tubular Epithelial Cells (TECs) and their interactions with fibroblasts lead to interstitial fibrosis. The ability of exosomes recovered from HG-treated renal tubular cells to promote the differentiation of fibroblasts into myofibroblasts in the kidney suggests that exosomes may play a role in the communication between the two cell types, according to the authors. Interstitial fibrosis is also greatly influenced by dedifferentiation of renal Proximal Tubular Epithelial Cells (PTECs). Podocyte-derived EVs caused dedifferentiation of PTECs after treatment with high glucose by trafficking miR-221-3p through the Wnt/catenin signaling pathway. It has been shown that the TECs exosomal miR-19b-3p targets Nuclear Factor B (NF-B)/SOCS-1, which is responsible for tubulointerstitial inflammation, and may facilitate the crosstalk between TECs and macrophages as well as contribute to the activation of M1 macrophages. Additionally, TECs release EVs, which trigger an inflammatory response via NF-B and harm GECs. Release of pro inflammatory cytokines, chemokines, adhesion molecules, and inflammatory signal transduction are frequently used to describe inflammatory responses. Initially thought to be a non-inflammatory condition, chronic inflammatory stimulation appears to play a role in the development and maintenance of the damage brought on by DN, according to growing body of research. In particular, macrophages, which are types of immune inflammatory cells directly related to the regulation of inflammatory processes, can be divided into M1 macrophages (which primarily generate pro-inflammatory mediators) and M2 macrophages (that exhibit anti-inflammatory properties) [8]. During the early stages of DN, macrophages move into and infiltrate the kidney tissue, which encourages the release of TGF- β , Reactive Oxygen Species (ROS), Vascular Endothelial Growth Factor (VEGF), and cytokines like IL-1 and TNF, ultimately speeding up the development of DN; however, the mechanisms need to be clarified. In contrast, stimulation of TGF-1 and IL-1 promotes the accumulation and activation of macrophages, creating a negative feedback loop. EVs may also mediate these pathways, according to recent investigations. After being exposed to high hyperglycemia, mouse macrophage-derived EVs (miR-21-5p) increased NLRP3 and IL-1 levels, which in turn caused podocyte pyroptosis via targeting A20 in DN model mice and in vitro. Uncommon transcription factor NF-B is a key element in inflammatory responses. According to research, in the presence of high glucose levels, macrophage-related exosomes cause macrophage activation, proliferation, and the release of inflammatory mediators and pro-fibrotic cytokines, such as IL-1, TNF- β , and TGF-1, which cause inflammation and kidney injury. The same research team found in another study that these exosomes can be ingested and internalized by mesangial cells and cause mesangial cell activation, excessive Extracellular Matrix (ECM) deposition, and the release of inflammatory factors like IL-1 and TNF- through TGF-1/Smad3 signaling, suggesting that these changes contribute to mesangial expansion and renal fibrosis. Exosomes generated from mouse TECs also drive activating macrophage by targeting NF-B, resulting in tubulointerstitial inflammation in mice models of acute and chronic kidney injury. The frequency of ESRD linked to diabetes is still high, despite the fact that current treatments have a major impact on DN progression, and there is a dearth of efficient instruments to stop (oreven reverse) DN progression. Therefore, it is imperative to investigate and identify novel, effective renoprotective treatment approaches to halt the course of DN. Recent studies have

demonstrated the potential of exosomes as therapeutic delivery systems for the treatment of DN. Due to the majority of their positive effects being mediated through paracrine processes, stem cells, which can self-renew and evolve into a wide variety of functional cells, have been suggested as potential treatment agents for DN. Exosomes produced from stem cells, which can deliver exogenous miRNAs to recipient cells, are effective and safe for the treatment of kidney disorders in rat and mouse models, according to a growing body of compelling evidence [9,10].

CONCLUSION

DN is a significant economic burden and has a high incidence, making it a global public health issue. Effective, focused therapy approaches for DN remain elusive despite decades of effort. Nephrologists and endocrinologists are constantly looking for fresh therapeutic methods through investigation of the molecular causes of DN as well as for new instruments to help them quickly and reliably identify renal damage brought on by diabetes using noninvasive methodology. Exosomes have a number of characteristics, as described in this review, including the ability to modulate cell-to-cell communication, deliver specific cargo to target cells, and change the biofunction of acceptor cells. These characteristics have a significant impact on the pathogenesis, detection, and management of DN. Exosomes therefore hold great promise for the advancement of DN therapies, even though several prospective exosome biomarkers and therapeutic approaches for renal disorders related to diabetes are still in their infancy and need to be further validated in extensive fundamental and clinical studies. We anticipate that the intrinsic qualities of exosomes will soon be completely understood and put to use, benefiting more individuals with diabetic kidney disease.

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