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Exosomal miR-126: Unveiling Its Diagnostic and Therapeutic Potential in CKD

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Abstract. Chronic kidney disease (CKD) represents a significant global health challenge, with a prevalence estimated to affect 8-19% of the global population. The pathogenesis of CKD involves intricate interactions among various cellular and molecular mechanisms, with exosomes playing a crucial role. Exosomes are small extracellular vesicles that facilitate intercellular communication by transporting biomolecules, including microRNAs (miRNAs), between cells. This review highlights the crucial function of exosomes in CKD, with a particular focus on the role of miR-126, a microRNA encapsulated within exosomes, which has shown promise both as a diagnostic biomarker and a therapeutic target for CKD. We elaborate on the nature, function, and altered expression patterns of exosomes in CKD, underscoring the diagnostic and prognostic significance of urinary exosomes. Furthermore, we delve into the regulatory role of miR-126 in vascular integrity and angiogenesis, its association with CKD progression, and its potential therapeutic implications. Our comprehensive analysis aims to illuminate the intricate mechanisms by which exosomes and miR-126 contribute to CKD pathophysiology, offering insights into their utility in developing novel diagnostic tools and therapeutic strategies. This synthesis of current research underscores the importance of further investigation into exosomal miR-126, paving the way for innovative approaches to tackle CKD.

Keywords: CKD, Exosomes, MicroRNA-126 (miR-126), Diagnostic Biomarkers, Therapeutic Targets.

1. Introduction

CKD stands as a formidable global health challenge, affecting an estimated 8-19% of the world's population. This range not only highlights the disease's widespread prevalence, but also underscores the variability in its detection and diagnosis across different regions and populations. The under diagnosis of CKD by both patients and physicians further complicates the landscape, allowing the disease to progress unnoticed until it reaches more advanced and less manageable stages[1,2]. The criteria for diagnosing CKD include; one or more of: a) albuminuria (albumin to creatinine ratio ≥ mg/g, b) urine sediment abnormalities, c) persistent hematuria d) electrolyte abnormalities e) structural abnormalities detected by imaging f) history of kidney transplantation in addition to that factors combined with low GFR <60 ml/min per 1.73 m[2,3]. These clinical features provide a framework for detecting CKD but also indicate the disease's complexity and the need for vigilant monitoring.

The disparity in CKD prevalence between high-income and low- to middle- income countries reveal the influence of socio-economic factors on disease distribution. In wealthier nations, access to healthcare and early diagnosis may contribute to lower prevalence rates, whereas in less affluent areas, limited access to healthcare and higher exposure to risk factors

may result in increased incidence[4]. The risk factors for CKD are diverse, encompassing diabetes, hypertension, glomerulonephritis, infections, environmental exposures, and genetic predispositions, such as sickle cell disease and the presence of two APOL1 risk alleles. This array of risk factors underscores the multifaceted nature of CKD and the necessity for comprehensive approaches to its prevention and management[2,5,6].

The prevalence of CKD in Saudi Arabia was 5.7% in young Saudi adults with a mean age of 37.4±11.3 in a single study[7]. Another study demonstrated that the prevalence of CKD is(13.8%) which is higher in relatives of patients with CKD than the reported prevalence in the Saudi population[8], suggesting a potential genetic or environmental component to disease susceptibility within families. Furthermore, the differentiation between actual CKD prevalence and the incidence of mildly decreased kidney function highlights the importance of nuanced diagnostic criteria and the need for early detection strategies to prevent disease progression.

The suggested risk of CKD in populations, particularly in regions with varying socio-economic statuses, emphasizes the need for increased awareness, better diagnostic tools, and more accessible treatment options. As the global community continues to grapple with the rising tide of CKD, understanding its epidemiology, risk factors, and the challenges associated with its diagnosis becomes paramount. Only through a concerted effort to address these issues can we hope to mitigate the impact of CKD on affected individuals and healthcare systems worldwide. This requires not only medical and technological advancements but also a commitment to improving the socio-economic determinants of health to reduce the burden of CKD on a global scale.

1.1 Etiology of CKD

The etiology of CKD is a complex and multifaceted issue, with causative agents varying widely across different populations and regions, reflecting the interplay of genetic, environmental, and lifestyle factors. Globally, the predominant causes of CKD include Type 1 and Type 2 diabetes mellitus, hypertension (HTN), various forms of glomerulonephritis, chronic tubulointerstitial nephritis, hereditary or cystic diseases, vasculitis, plasma cell neoplasia, and sickle cell nephropathy. Each of these conditions contributes to the overall burden of CKD through distinct pathophysiological mechanisms, necessitating a tailored approach to prevention, diagnosis, and management.

- **Type 1 and Type 2 Diabetes Mellitus** are leading causes of CKD, given their role in inducing hyperglycemia-induced damage to the nephrons. High blood sugar levels in diabetes lead to glomerulosclerosis and interstitial fibrosis, culminating in the loss of kidney function over time. The high prevalence of diabetes worldwide, coupled with its increasing incidence, underscores the critical need for effective glycemic control measures to mitigate CKD risk in diabetic populations.
- **Hypertension (HTN)** is another significant contributor to CKD, with elevated blood pressure causing damage to the blood vessels in the kidneys. This can lead to a reduction in kidney function as the organ's delicate filtration system becomes impaired. Controlling blood pressure is therefore paramount in slowing the progression of CKD in hypertensive patients.
- **Glomerulonephritis**, including both primary and secondary forms, refers to a group of diseases that cause inflammation and damage to the glomeruli, the filtering units of the kidneys. Primary glomerulonephritis originates within the kidney, while secondary glomerulonephritis is a consequence of other systemic diseases like lupus or vasculitis. These conditions can lead to significant kidney damage and eventual failure if not adequately addressed.

- **Chronic Tubulointerstitial Nephritis** is a condition characterized by inflammation and fibrosis of the tubules and interstitial tissue of the kidneys. It can result from long-term exposure to toxins, medications, or infections, highlighting the importance of identifying and eliminating potential nephrotoxic exposures in at-risk populations.
- **Hereditary or Cystic Diseases**, such as polycystic kidney disease (PKD), account for a portion of CKD cases. These genetic disorders are marked by the growth of numerous cysts in the kidneys, which can significantly disrupt kidney function and lead to CKD.
- **Vasculitis**, an inflammation of the blood vessels, can affect the kidneys by damaging the renal arteries and arterioles.
- **Plasma cell neoplasia**, including multiple myeloma, can lead to kidney damage through the overproduction of abnormal proteins that can deposit in the kidneys, causing damage.
- **Sickle Cell Nephropathy**, associated with sickle cell disease, involves the sickling of red blood cells within the kidney's microvasculature, leading to vaso-occlusion and ischemic damage to the renal medulla. This can result in a range of renal complications, further exacerbating the risk of developing CKD.

Given the diversity of CKD causes, a comprehensive approach to prevention and management is essential. This approach includes early detection and control of diabetes and hypertension, reduction of exposure to nephrotoxic substances, and specific treatments for diseases like glomerulonephritis and hereditary kidney conditions. Moreover, understanding the genetic and environmental factors contributing to CKD's global variation can guide public health strategies and individualized patient care, ultimately aiming to reduce the incidence and impact of this chronic condition worldwide[9].

1.2 Pathophysiology of CKD

The pathophysiology of CKD is a complex and multifaceted process, involving various pathways and mechanisms that lead to the progressive loss of renal function over time. At the core of CKD's pathophysiology are three critical processes: glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis. Each of these conditions contributes to the decline in kidney function by affecting different parts of the renal architecture, leading to the impaired ability of the kidneys to filter blood and perform their essential roles in maintaining homeostasis.

- **Glomerulosclerosis** refers to the scarring or hardening of the glomeruli, the kidney's filtering units. Glomeruli are composed of tiny blood vessels (capillaries) that filter waste and excess substances from the blood. Glomerulosclerosis results from long-standing, uncontrolled hypertension or diabetes, or primary kidney diseases such as focal segmental glomerulosclerosis (FSGS). The damage leads to a decrease in the glomeruli's filtering capacity, causing proteins such as albumin to leak into the urine (proteinuria) and a reduction in the effective clearance of waste products from the blood. Over time, the loss of functional glomeruli forces the remaining healthy glomeruli to work harder, leading to hyperfiltration injury and further progression of glomerulosclerosis.
- **Tubulointerstitial Fibrosis** involves the scarring and hardening of the kidney tubules and the surrounding interstitial tissue, where the filtered fluid from the glomeruli is processed into urine. This condition can result from chronic exposure to toxins, infections, drug reactions, or as a consequence of chronic glomerular diseases. Tubulointerstitial fibrosis disrupts the tubules' ability to reabsorb water and essential solutes, leading to electrolyte imbalances, acidosis, and further loss of kidney function. The fibrotic process also involves the infiltration of inflammatory cells and the deposition

of extracellular matrix proteins, which can obstruct urine flow and increase intratubular pressure, exacerbating kidney damage.

- **Vascular Sclerosis** is the hardening and thickening of the blood vessels within the kidneys, including the small arterioles that supply blood to the glomeruli. This process is primarily driven by hypertension and diabetes, which cause high pressure and glucose levels in the blood, leading to damage and sclerosis of the renal vasculature. Vascular sclerosis results in reduced blood flow to the kidney tissues, ischemia, and hypoxia, further impairing kidney function and promoting the progression of glomerulosclerosis and tubulointerstitial fibrosis.

The interplay between glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis creates a vicious cycle of ongoing kidney damage and functional decline. The progression of CKD is also influenced by systemic factors, including the activation of the renin-angiotensin-aldosterone system (RAAS), chronic inflammation, oxidative stress, and the accumulation of uremic toxins. These systemic effects not only contribute to the direct damage to kidney tissues but also exacerbate cardiovascular risk, which is a major cause of morbidity and mortality in patients with CKD.

Understanding the pathophysiology of CKD is crucial for developing targeted interventions to halt or slow the progression of kidney damage. Current strategies focus on controlling blood pressure and blood sugar levels, reducing proteinuria, and addressing the underlying causes of kidney damage. Advances in our understanding of the molecular and cellular mechanisms underlying CKD pathophysiology hold promise for the development of novel therapeutic approaches aimed at preventing or reversing kidney fibrosis and preserving kidney function [9].

1.2.1 Treatment of CKD

While there is no complete cure for CKD, several key treatments can effectively manage its complications. These include regular visits to a nephrologist, using anti-glycemic and antidiabetic medications, avoiding certain painkillers, preventing smoking, and adhering to a specific diet. Treatment plans are tailored to the individual patient's condition and may involve diuretics, erythropoietin (to treat anemia), cholesterol-lowering medications, vitamin D, and calcium supplements to address calcium loss. For patients with end-stage renal failure, renal dialysis and transplantation are viable options.

- **Angiotensin Receptor/Neprilysin Inhibition:** This treatment is used for patients with heart failure and reduced ejection fraction, reducing the risk of death by 20%[10].
- **Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors:** These drugs reduce glucose reabsorption in the proximal tubules of the kidney, leading to high glucose excretion in the urine and lower blood glucose levels[11].
- **Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists:** These medications increase levels of cytosolic cAMP and calcium, which induce insulin release from the pancreas[12].
- **Selective Mineralocorticoid Receptor Antagonists:** These are added as a therapeutic option for patients with type 2 diabetes mellitus but are poorly tolerated due to the risk of side effects[13].

1.3 Extracellular Vesicles

Extracellular vesicles (EVs) represent a diverse group of cell-derived membranous structures that play pivotal roles in intercellular communication, impacting a wide range of biological and pathological processes. They are released by virtually all cell types into the

extracellular environment and can be found in various bodily fluids, including blood, urine, saliva, and cerebrospinal fluid. These vesicles encapsulate a variety of molecular constituents of their cell of origin, such as proteins, lipids, DNA, mRNA, and microRNA (miRNA), allowing them to transfer these molecules between cells and thereby modulate recipient cell behavior and function. The classification of EVs is based on their size, biogenesis pathways, and release mechanisms (Fig. 1).

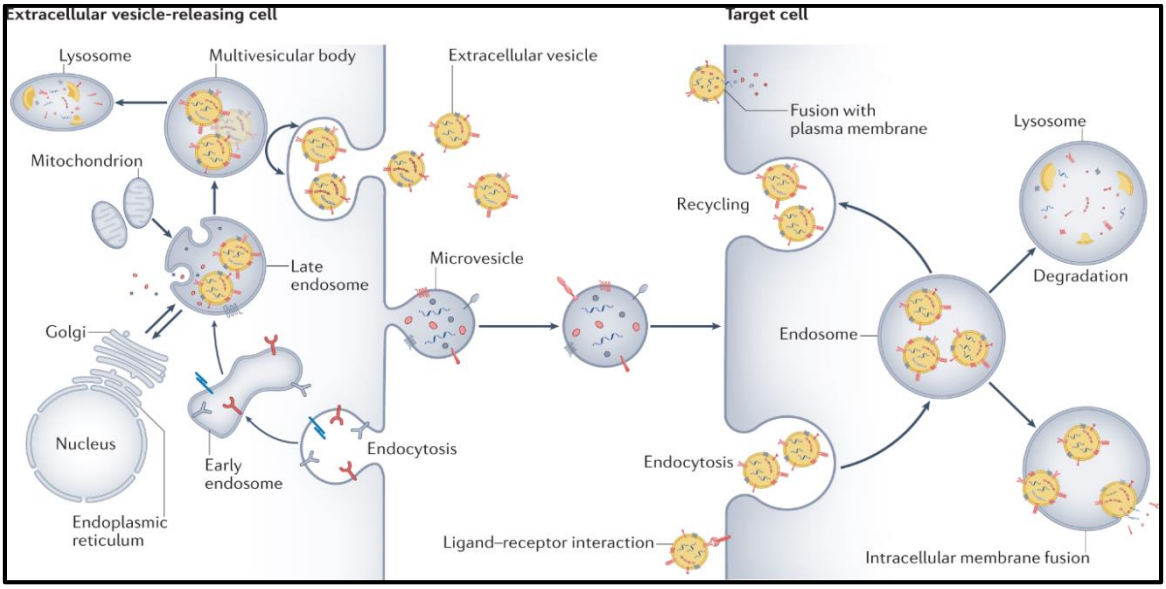

Fig. 1. Schematic illustration of the exosomes[14].

Exosomes are typically small, ranging in size from about 30 to 150 nanometers (nm) in diameter, with 100 nm being a common size mentioned in the literature. They are formed within the endosomal network of a cell. The process begins with the inward budding of the plasma membrane to form early endosomes, which then mature into late endosomes. During this maturation, parts of the late endosome membrane invaginate to form small vesicles within the endosome, known as intraluminal vesicles (ILVs). The late endosome filled with ILVs is referred to as a multivesicular body (MVB). Exosomes are released into the extracellular space when the MVB fuses with the plasma membrane, a process facilitated by the cellular machinery involved in membrane fusion and transport. The molecular composition of exosomes is reflective of their cellular origin and the physiological or pathological context of the cell, making them valuable for diagnostic and therapeutic applications, particularly in cancer and neurodegenerative diseases.

Ectosomes, also known as microvesicles or shedding vesicles, are generally larger than exosomes, with sizes ranging from about 50 nm to 1 micrometer (μm). Unlike exosomes, ectosomes are formed by the outward budding and fission of the plasma membrane. This process can be triggered by various stimuli, including cell activation, stress, or apoptosis. The shedding of ectosomes from the cell surface involves the reorganization of the cytoskeleton and changes in lipid distribution within the plasma membrane. The composition of ectosomes is also influenced by their cellular origin and the microenvironment, containing a subset of proteins, lipids, and genetic material from the parent cell. Ectosomes have been implicated in numerous biological processes, such as coagulation, inflammation, and the progression of diseases like cancer and cardiovascular disorders.

Both exosomes and ectosomes serve as essential mediators of cell-to-cell communication, capable of influencing the behavior and fate of recipient cells in both local and distant tissues. This communication can be beneficial, as in the case of tissue repair and regeneration, or detrimental, as observed in the spread of cancer metastases or the progression of

neurodegenerative diseases. The unique properties of these vesicles, including their stability in bodily fluids, their ability to cross biological barriers, and their capacity to carry and protect complex cargoes, have spurred interest in their potential as biomarkers for disease diagnosis and prognosis, as well as their use as vehicles for targeted drug delivery. Ongoing research aims to further elucidate the molecular mechanisms underlying the biogenesis, release, and uptake of exosomes and ectosomes, as well as their roles in health and disease, paving the way for novel diagnostic and therapeutic strategies [15,16].

In addition to the well-characterized exosomes and ectosomes, the extracellular vesicle (EV) landscape includes a variety of other vesicular entities, each with distinct origins, compositions, and functions. Among these are apoptotic bodies, tumor-derived vesicles, and mitochondria-derived vesicles, all of which play critical roles in intercellular communication, cellular homeostasis, and disease pathogenesis.

Apoptotic Bodies are one of the largest types of EVs, typically ranging in size from 1 to 5 micrometers. They are released during the late stages of apoptosis, a programmed cell death process. As a cell undergoes apoptosis, its nucleus fragments and the cell shrinks and buds off to form apoptotic bodies. These vesicles can contain cellular organelles, DNA, RNA, and proteins. Apoptotic bodies are primarily involved in clearing cellular debris and preventing the release of potentially harmful or immunogenic intracellular contents into the extracellular space. They can be recognized and phagocytosed by macrophages and other phagocytic cells, facilitating the removal of dying cells without inducing an inflammatory response.

Tumor-Derived Vesicles, particularly those originating from the endosomal compartment (often referred to as tumor-derived exosomes), are released by cancer cells and carry a wide range of biomolecules, including proteins, lipids, and nucleic acids that reflect the malignant nature of their cell of origin. These vesicles can influence the tumor microenvironment, promote angiogenesis, suppress the immune response, and enhance the metastatic potential of cancer cells by facilitating communication between tumors and their surrounding tissues, as well as distant organs. The presence of tumor-derived vesicles in body fluids makes them attractive targets for cancer biomarker discovery and disease monitoring.

Mitochondria-Derived Vesicles (MDVs) are a specialized type of microvesicle that originates from the mitochondria. These vesicles are involved in the selective elimination of damaged or dysfunctional mitochondrial components, thereby contributing to mitochondrial quality control and cellular homeostasis. MDVs can also play a role in intercellular communication by transferring mitochondrial components to other cells, which may have implications in metabolic regulation, immune responses, and the propagation of mitochondrial DNA mutations.

The biogenesis and release of exosomes, a subset of EVs, occur through a sophisticated and highly regulated process. Initially, the plasma membrane undergoes inward budding, engulfing extracellular and cytosolic components to form early endosomes. As these early endosomes mature, intraluminal vesicles (ILVs) are generated within them by further inward budding of the endosomal membrane, leading to the formation of multivesicular bodies (MVBs). The sorting of cargo into ILVs is mediated by endosomal sorting complexes required for transport (ESCRT), which include key components such as TSG101 and ALIX. These complexes, along with other proteins like SNAREs and HSP90, are crucial for the selection of cargo, vesicle formation, and the fusion of MVBs with the plasma membrane to release exosomes into the extracellular space.

Migrasomes are a newly identified type of EV formed during cell migration, distinct from exosomes and ectosomes. Discovered in 2015, migrasomes emerge at the ends or intersections of retraction fibers and involve integrins and tetraspanins (TSPANs). These

vesicles are found in various cell types, such as immune and metastatic tumor cells, and are present in organisms like humans and mice, particularly in dynamic areas such as blood vessels and alveoli. Migrasomes are essential for intercellular communication, maintaining homeostasis, supporting embryonic development, and contributing to disease processes. They facilitate the transfer of cellular materials, including mRNA and proteins, thus affecting cellular behavior and function. Additionally, migrasomes are involved in mitochondrial quality control and cholesterol metabolism. In embryogenesis, they play roles in organ and tissue formation. Migrasomes are also significant in diseases, especially cancer, due to their involvement in cell migration and metastasis, as well as in cardiovascular, neurological disorders, and infections. They can be detected using methods like total internal reflection fluorescence (TIRF) microscopy and live cell imaging. Future research aims to uncover the detailed mechanisms of migrasome formation, their roles in various physiological and pathological settings, and their potential as therapeutic targets, paving the way for innovative diagnostic and treatment approaches [17].

Exosomes can be classified based on their size into small (less than 100 nm), medium (100-200 nm), and large (more than 200 nm) categories. This classification reflects the heterogeneity in exosome populations, which may have implications for their biological functions and utility as biomarkers. Specific proteins, such as tetraspanins (CD9, CD81, and CD63), are commonly used as biomarkers to identify and characterize exosomes. These proteins are involved in exosome formation, cargo sorting, and interactions with recipient cells, highlighting the complexity and specificity of exosome-mediated communication.

Understanding the diverse roles of miscellaneous EVs, including apoptotic bodies, tumor-derived vesicles, and MDVs, as well as the intricate processes governing exosome biogenesis and function, is essential for unraveling the complexities of cellular communication and exploiting EVs for therapeutic and diagnostic applications. Advances in this field may lead to novel approaches for treating diseases, including cancer, neurodegenerative disorders, and metabolic conditions, by targeting or harnessing the unique properties of these vesicles [18].

The Minimal Information for Studies of Extracellular Vesicles (MISEV2023) guidelines provide a comprehensive and updated framework to standardize EV research practices. These guidelines emphasize the use of precise terminology and robust methodologies for the isolation and characterization of EVs, incorporating advanced techniques to ensure their purity and integrity. They address critical aspects such as pre-analytical variables, optimal separation methods, and detailed protocols for both *in vitro* and *in vivo* studies, with a particular focus on the functional aspects of EVs. The guidelines highlight the importance of quality control and transparent data reporting to enhance reproducibility and comparability in EV studies. Moreover, they encourage interdisciplinary collaboration and data sharing within the EV research community to promote scientific innovation and rigor. In order to properly study and understand extracellular vesicles, it is crucial for researchers to adhere to the latest guidelines published by the International Society for Extracellular Vesicles (ISEV), such as MISEV2023[19].

1.4 Exosomes Functionalities

1.4.1 Intracellular communication

The processes of exosome secretion and absorption involve interactions with a diverse mixture of exosomes, both naturally produced within and recycled by cells. The particular ways in which exosomes are taken up by cells, coupled with the inherent specificity of exosomes across various cell types, add layers of complexity to their role in facilitating communication within cells. This complexity is illustrated through several examples: a) In human pancreatic cancer, oncogenic signals triggered by the expression of mutant KRAS enhance the uptake of

exosomes via macropinocytosis. b) Human melanoma cells incorporate exosomal content by merging the exosomes with their own plasma membrane[20].

Until 2020, it remained unclear how various models of exosome uptake by recipient cells affect the localization, degradation, or functional outcomes of exosomal contents. Additionally, the impact of administering exosomes, which are externally generated by diverse cell types, into mice-particularly in terms of organ specificity or retention-was not well understood, especially when compared to exosomes produced within the organism (*de novo*)[21].

An experiment involving mice, which utilized *in vivo* exosomes, revealed that these vesicles successfully deliver mRNA to target cells.

In summary, the research into exosomes, particularly their secretion, uptake, and functional roles within cells, has unveiled significant complexities in intracellular communication mechanisms. Studies up to 2020 have revealed that not all aspects of exosome behavior, such as the consequences of their uptake on recipient cells and the effects of externally introduced exosomes in animal models, are fully understood. Experimental findings have shown that. These insights highlight the intricate role of exosomes in cellular processes and disease, pointing towards the need for further research to unravel the full spectrum of their functions and applications in medicine.

1.4.2 Reproduction and development

Plasma exosomes play a pivotal role in sperm maturation, a necessary step for the successful fertilization of an egg. These tiny vesicles carry proteins, lipids, and RNA molecules that can influence the functionality and viability of sperm cells, promoting their maturation and enhancing their ability to fertilize an egg effectively. This interaction between exosomes and sperm cells underscores the importance of exosomal communication in the earliest stages of human development.

Moreover, exosomes are instrumental in protecting the placenta from infections. The placental barrier is a critical interface between the mother and the developing fetus, and its protection is paramount for a healthy pregnancy. Exosomes contribute to this protection by transporting immune-modulating molecules that can help prevent infections from reaching the placenta and the fetus. This protective role of exosomes is crucial for maintaining a sterile environment around the fetus during its development.

Additionally, plasma exosomes are associated with the process of childbirth (delivery). They carry signals that can influence the timing of labor and the initiation of birth, acting as messengers that communicate between the fetus and the maternal body to prepare for delivery. Understanding how exosomes contribute to the onset of labor could provide insights into mechanisms underlying preterm and overdue pregnancies.

1.4.3 Immunological role

The documented role of exosomes in modulating the immune response highlights their significance in immune regulation[22]. Numerous studies have shown that administering low doses of exosomes to mice over a period of time did not significantly alter their immune response[23].

A recent study reported that injections of genetically engineered exosomes, derived from antigen-presenting cells (APCs) and loaded with major histocompatibility complex-2 (MHC-II) alongside tumor peptides, demonstrated no inherent functions in the innate immune system yet contributed to the eradication and growth delay of tumors in mice[24].

1.4.4 Metabolic and cardiovascular diseases (CVD)

Exosomes play a crucial role in metabolic diseases by facilitating the transfer of metabolites and supporting intracellular communication. This involves the exchange of exosomal microRNAs (miRNAs) among key metabolic organs and tissues, such as the pancreas, adipose tissue, skeletal muscles, and liver. In a mouse model, the mediation of the leptin gene knockout by exosomes has implicated retinol binding protein-4 (RBP4) in the stimulation of macrophage activity and the development of insulin resistance, highlighting the complex interplay between exosomes and metabolic regulation[25,26].

The relationship between cancer, exosomes, and cachexia highlights the potential for these vesicles to serve as both biomarkers and therapeutic targets. Understanding the specific contents and signaling pathways modulated by cancer-derived exosomes could lead to new strategies to mitigate the effects of cachexia. For instance, blocking the release of certain exosomal contents could alleviate muscle wasting and improve patient outcomes.

Moreover, the role of exosomes in cachexia contrasts with their emerging involvement in obesity, where they have been found to facilitate metabolic dysregulation in different ways, such as by promoting adipose tissue inflammation or insulin resistance. This dual role underscores the versatility of exosomes in modulating metabolic processes and the potential for leveraging their unique properties in the treatment of both cachexia and obesity. Further research into the molecular details of exosome signaling in these conditions will be crucial for developing targeted interventions aimed at improving patient care in a range of metabolic diseases[27].

Exosomes, abundant in heat shock proteins 70 and 90, have been implicated in muscle wasting in mice[28]. Moreover, exosomes derived from both mouse and human cells have been linked to conditions such as metabolic syndrome, cardiovascular diseases including atherosclerosis, diabetes-related cardiovascular complications, and metabolic adaptations associated with heart failure[29]. The protective role of exosomes against atherosclerosis was demonstrated in mice, where platelet-derived exosomes decreased macrophage scavenger activity, thereby reducing the uptake of detrimental cholesterol[30].

1.4.5 Neurodegeneration

The interplay between exosomes and the regulation of secretory vesicles in neural cells presents a potential link to the development of neurodegenerative disorders. Within the brain, exosomes play a role in both promoting and restricting the folding and unfolding of proteins, thereby influencing the progression of such disorders[31]. Exosomes serve diverse functions in the context of neurodegenerative disorders. Firstly, they are involved in the clearance of misfolded proteins, acting as a mechanism for cellular quality control by removing aberrant protein aggregates. This process helps maintain cellular homeostasis and prevents the accumulation of toxic protein species.

Secondly, exosomes exhibit detoxifying and neuroprotective functions within the central nervous system. They can encapsulate and transport harmful molecules or metabolic by-products away from neurons, thereby mitigating cellular damage and promoting neuronal survival in stressful environments.

Thirdly, exosomes contribute to the propagation and aggregation of misfolded proteins, a hallmark feature of many neurodegenerative diseases. By carrying and releasing protein aggregates, exosomes can facilitate the spread of pathological proteins between neurons, leading to the amplification of disease pathology and the progression of neurodegenerative processes.

In neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, exosomes play a pivotal role in modulating the formation and toxicity of neurotoxic oligomers. They can either impair the formation of toxic protein aggregates within neurons or transport these aggregates outside of cells, influencing disease progression and the spread of pathology throughout the brain. Overall, exosomes represent intricate regulators of neurodegenerative processes, participating in both protective and pathogenic mechanisms within the central nervous system[32,33].

1.4.6 Cancer

Research on the role of exosomes in cancer has advanced rapidly, surpassing investigations in other disease areas. Exosomes are intricately associated with numerous hallmarks of cancer, encompassing tumor growth, metastasis, para-neoplastic syndrome, and resistance to chemotherapy. The specific functions are elaborated in Table 1 [34].

Numerous instances highlight the involvement of exosomes in tumors. For instance, exosomes derived from pancreatic cancer cells have been demonstrated to initiate cell transformation by inducing mutations in NIH/3T3 recipient cells. Similarly, in breast cancer, exosomes facilitate neoplasia through the transfer of miRNA cargo[35]. In prostatic carcinoma, miR-155, miR-130, and miR-125b play a significant role in neoplastic reprogramming and the formation of tumors in adipose stem cells[36].

Exosomes have been observed to play a role in modulating the efficacy of chemotherapy in cancer treatment. For instance, in lymphoma, exosomes carrying CD20+ act as decoys by binding to CD20, which can potentially reduce the effectiveness of CD20-targeted therapies. Similarly, in cancers characterized by overexpression of HER2 (human epidermal growth factor receptor 2), such as breast cancer, HER2-positive exosomes can act as decoys, diverting anti-HER2 therapies away from their intended targets and potentially diminishing their therapeutic effects.

This phenomenon highlights the complex interplay between exosomes and therapeutic interventions in cancer treatment, underscoring the need for further research to elucidate their precise mechanisms and implications[37,38].

Table 1. Role of micro-RNA in tumors.

Role of Micro-RNA in tumors		
miR-423[39]	Carcinoma (Ca) of the Breast	Human Progesterone Receptor (PR)
miR-2011[40]	Ca mammary gland B-cell lymphoma	CHOP
miR-1236[41]	Ca Bladder	p21
miR-205[42]	Ca prostate	IL24 IL32
miR-124[43]	Ca Breast And Ovary	P27
miR-2478[44]	Breast cancer	TGFβ1
miR-138[45]	Prostate cancer	β-catenin
miR-877[46]	Bladder cancer	p16
miR-6734[47]	Ca Colon	p21

2. Urinary Exosomes

Urinary exosomes play a pivotal role in reflecting the health status of the renal system, owing to their stability and diverse cellular origins. Compared to soluble proteins and RNA in urine, those encapsulated within urinary exosomes exhibit enhanced stability, making them valuable biomarkers for assessing kidney diseases. These exosomes are sourced from various cell types within the urinary system, including the glomerulus, renal tubule, prostate, and bladder cells, highlighting their multifaceted cellular origins.

In-depth RNA sequencing analyses conducted at the organ level have elucidated the intricate composition of urinary exosomes. These analyses have revealed the involvement of bladder cells, endothelial cells, basal cells, monocytes, and dendritic cells in the formation and secretion of urinary exosomes. Consequently, it becomes evident that urinary exosomes are not solely derived from renal cells but also originate from other cellular constituents of the urinary system, underscoring their comprehensive representation of renal health.

As research into exosomes continues to expand, numerous studies have underscored the utility of urinary exosomes as diagnostic and prognostic tools for kidney diseases. Table 1 provides a comprehensive overview of these studies, emphasizing the specificity and accuracy of protein profiles within urinary exosomes in delineating various kidney pathologies. The utilization of urinary exosomes in clinical settings holds significant promise for advancing the early detection, monitoring, and management of kidney diseases, thereby improving patient outcomes and healthcare practices[48].

2.1 Urinary Exosomes as a Biomarker of Kidney Diseases

Urinary exosomes serve as crucial biomarkers in the diagnosis, prognosis, and monitoring of various renal and urinary tract disorders, encompassing conditions ranging from acute renal injury (AKI) to renal fibrosis and urinary cancers.

In the realm of AKI, urinary exosomes have emerged as valuable indicators of renal damage. Numerous studies have identified specific proteins within exosomes, including Aquaporin-1 (AQP1), Aquaporin-2 (AQP2), ATF3, and fetuin A, as biomarkers for AKI. These biomarkers aid in the early detection and assessment of renal injury, enabling timely intervention and management strategies to mitigate further damage and promote renal recovery.

Renal fibrosis, a hallmark of CKD, can be effectively diagnosed and monitored through exosomal studies. Early detection of renal fibrosis holds immense therapeutic potential, as it allows for interventions that can halt or even reverse the progression of the disease. Proteins and microRNAs encapsulated within urinary exosomes, such as CD2 associated protein (CD2AP), serve as valuable biomarkers for assessing renal fibrosis severity and progression in patients with nephropathy.

Diabetic nephropathy, a common complication of diabetes mellitus, poses significant challenges in diagnosis and management. Traditional diagnostic tests like microalbuminuria lack sensitivity and specificity. However, urinary exosomes offer a promising alternative for the early detection and monitoring of diabetic nephropathy. Exosomes carry a repertoire of proteins, including Voltage-Dependent Anion Channel 1 (VDAC1), whose upregulation in diabetic nephropathy reflects the disease pathology, providing insights into disease progression and treatment responses.

Furthermore, urinary exosomes play a pivotal role in the diagnosis and management of urinary cancers, including prostate cancer, renal cell cancer, and bladder cancer. The analysis of exosomal content enables the identification of specific biomarkers associated with these malignancies, facilitating early detection, prognostication, and personalized treatment strategies for affected individuals as in Table 2.

In summary, urinary exosomes represent a rich source of biomarkers for various renal and urinary tract disorders, offering unparalleled insights into disease pathogenesis, progression, and treatment responses. Their utility extends across diverse clinical contexts, from acute kidney injury to chronic conditions like renal fibrosis and diabetic nephropathy, as well as in the realm of urinary cancer diagnostics and management. Continued research efforts in this field hold immense promise for enhancing our understanding of these diseases and improving patient outcomes through targeted interventions[49].

Table 2. Summary of Studies Utilizing Urinary Exosomes in Various Kidney Diseases.

Urinary exosome	Specific effect
Futon A	Increased significantly in patients with AKI than in healthy volunteer
AFT3 and WT1	Increased in early AKI and not increased in CKD
AQP1	Renal ischemia/perfusion
AQP2	Gentamycin increases the excretion of AQP2 on day one and decreases in day 7
CD26	Significantly lower in AKI than control
NGAL	Urinary exosomes increased in patients with DGF
Cystatin C	highly expressed and upregulated in renal cortex
miR-21	inversely correlated WITH GFR
miR-16-miR-24	Increased in the injury state
CD2AP	Inversely correlated with 24 Hours protein, tuberuinterstesial fibrosis and glomerulosclerosis
miR-29 and miR-200	Reduced level in CKD than control
miR-29c	Decrease with the progress of renal fibrosis
miR-200b	Lower in CKD group than normal group
Wt-1	Positive in 33 diabetics out of 48 and only positive in 1 healthy control
PEPD and MUP1	PEPD increased and MUP1 decreased in diabetic fatty rats
Regucalcin	Reduced expression in CKD than the control group
Ceruloplasmin	Exossomal CP is 10-20 times higher in CKD than in control
AQP5 and AQP2	Upregulated in diabetic nephropathy
CD63	Higher in normoalbuminuria than micro-albuminuria
miR-145	Were enriched in type-1 DM
miR-15b, miR-34a, and miR-30a	Expressed in TYPE 2 diabetic nephropathy than healthy control
miR-320c	up-regulated in diabetic nephropathy
Let-7i-5p	Significantly up-regulated in diabetic nephropathy

3. Micro RNA-126

MiR-126 has been previously documented to exhibit altered expression in CKD. Elevated levels of miR-126 have been linked to the preservation of vascular function and correlated with a reduced risk of CKD development. Conversely, decreased levels of miR-126 have been observed during the late stages of CKD and in individuals with atherosclerosis[50]. Furthermore, studies have reported the protective function of miR-126 in kidney tissue[50].

miR-126 has been demonstrated to have potential therapeutic effects by promoting endothelial regeneration in blood vessels[51]. Furthermore, miR-126 contributes to the protection of kidney tissue and helps limit atherosclerosis and kidney damage[52].

MiR-126 is linked to CKD-related complications as evidenced by studies. A lower median level of miR-126 is correlated with poorer survival rates in late-stage CKD (Stages 3, 4, and 5)[53]. MiR-126 exhibits reduced expression in CKD Stages 4 and 5. However, this downregulation disappears after renal transplant, even in cases with low GFR[54].

Furthermore, miR-126 is downregulated across various CKD stages compared to healthy controls, except in CKD G1[55]. Moreover, miR-126 is typically downregulated in CKD compared to normal kidney function. However, another study demonstrated no significant difference in the expression of miR-126[56]. The expression of miR126 is lower in diabetic nephropathy compared to the control group, and this decreased expression is negatively correlated with albuminuria levels[57]. MiR-126 is found in higher abundance in glomerular extracts[58]. A study reported an increase in plasma levels of miR-126 in diabetic nephropathy[59].

A recent study conducted by Zietar et al. highlighted alterations in miR-126 levels, which mediate vascular intracellular communication, in patients with CKD compared to control subjects. This finding was further corroborated by an experimental study in septic rats, demonstrating that miR-126 regulates TH17/Treg (T-helper 17/regulatory T cell) balance and improves organ function, such as the kidneys, thereby mitigating damage[60].

In a community-based study conducted in South Africa, researchers observed that the expression of whole blood miR-126-3p was elevated in individuals with CKD compared to those without CKD. Interestingly, within the subset of patients with type 2 diabetes mellitus (T2DM), those with proteinuria exhibited higher levels of miR-126 compared to diabetic patients without proteinuria. This distinction sheds light on the specific role of miR-126 in the context of diabetic nephropathy, suggesting its potential involvement in the pathogenesis and progression of renal complications associated with diabetes. These findings, found in Table 3, underscore the importance of further investigating the mechanistic underpinnings of miR-126 in diabetic kidney disease and its potential as a biomarker for disease progression and prognosis[61].

Table 3. Various Effects of miR-126 on CKD.

MiR 126 specific effect	Effect on CKD
High level of miR-126	Reduced risk of CKD
Low level of MIR-126	Late stage of CKD with atherosclerosis
Down regulation	In CKD compared to control
Low miR-126	Diabetic nephropathy
High serum miR-126	Elevated in CKD than control group

4. Conclusion

The intricate dance of molecular interactions underpinning CKD is increasingly coming into focus, with exosomes playing a central role. These nanoscale extracellular vesicles, once thought to be mere cellular debris, are now recognized as key players in intercellular communication, carrying a rich cargo of bioactive molecules including proteins, lipids, and nucleic acids. Among these, miRNAs - small non-coding RNAs that regulate gene expression - have garnered significant attention. Particularly, miR-126, encapsulated within exosomes, has emerged as a critical modulator of pathways involved in CKD pathogenesis, offering promising avenues for diagnostic and therapeutic intervention.

The contribution of exosomes to CKD extends beyond their role as molecular couriers. They serve as a mirror, reflecting the physiological and pathological states of their cells of origin, including those in the renal system. In CKD, changes in the content and concentration of exosomal cargo, such as miR-126, offer insights into the disease's progression, severity, and the underlying mechanisms driving it. These insights have profound implications, not just for understanding CKD but for diagnosing and treating it.

miR-126, in particular, has been highlighted for its regulatory role in vascular integrity and angiogenesis - processes that are often compromised in CKD. Its potential as a diagnostic biomarker lies in its altered expression levels in patients with CKD compared to healthy individuals. Elevated or diminished levels of exosomal miR-126 can indicate the onset and progression of CKD, providing a non-invasive means of disease detection and monitoring. Beyond diagnosis, the therapeutic implications of miR-126 are profound. By modulating miR-126 levels or activity, it might be possible to influence the course of CKD, offering hope for interventions that could slow, halt, or even reverse kidney damage.

Yet, the road from discovery to clinical application is fraught with challenges. The mechanisms of exosome formation, secretion, and uptake, as well as the specific roles of exosomal miR-126 in CKD, are complex and not fully understood. Questions remain about how best to harness the diagnostic and therapeutic potential of exosomal miR-126. For instance, strategies to modulate miR-126 levels in a targeted manner, ensuring delivery to the kidneys while minimizing off-target effects, require further innovation and refinement.

Moreover, translating these findings into practical clinical tools and therapies will necessitate rigorous clinical trials to establish efficacy, safety, and feasibility. Despite these

challenges, the potential rewards are immense. Unraveling the role of exosomes and miR-126 in CKD could lead to breakthroughs in how we diagnose, monitor, and treat this chronic condition, ultimately improving patient outcomes.

In conclusion, the journey into the molecular intricacies of CKD has revealed exosomes and miR-126 as pivotal elements in its narrative. The path ahead is complex, demanding continued research, collaboration, and innovation. As we delve deeper into understanding these molecular mechanisms, we edge closer to unlocking new realms of possibilities in CKD management. The promise of exosomal miR-126 as a beacon of hope for patients with CKD is a testament to the power of molecular medicine, heralding a new era in the battle against CKD.

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إكسوزوم مير-١٢٦: الكشف عن إمكاناته التشخيصية والعلاجية في مرض الكلى المزمن

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المستخلص. تمثل أمراض الكلى المزمنة تحديًا صحيًا عالميًا كبيرًا، حيث يقدر انتشارها بما يتراوح بين ٨-١٩٪ من سكان العالم. تتضمن آلية نشوء أمراض الكلى المزمنة تفاعلات معقدة بين آليات خلوية وجزيئية متنوعة، حيث تلعب الحويصلات خارج الخلوية دورًا محوريًا. تُعد الحويصلات خارج الخلوية جزيئات صغيرة تسهل التواصل بين الخلايا عبر نقل الجزيئات الحيوية، بما في ذلك ميكرو ر.ن.أ (مير)، بين الخلايا. تستعرض هذه المراجعة الدور الحاسم للحويصلات خارج الخلوية في أمراض الكلى المزمنة، مع تركيز خاص على دور مير-١٢٦، وهو ميكرو ر.ن.أ يتم نقله داخل هذه الحويصلات، وقد أظهر إمكانيات واعدة كعلامة تشخيصية وهدف علاجي لـ أمراض الكلى المزمنة. نناقش هنا في طبيعة ووظيفة وأنماط التعبير المتغيرة للحويصلات خارج الخلوية في أمراض الكلى المزمنة، مؤكدين على الأهمية التشخيصية والتنبؤية للحويصلات البولية خارج الخلوية. بالإضافة إلى ذلك، نستكشف الدور التنظيمي لـ مير-١٢٦ في سلامة الأوعية الدموية وتكوُّن الأوعية، وارتباطه بتطور أمراض الكلى المزمنة، وإمكانياته العلاجية المحتملة. يهدف تحليلنا الشامل إلى إيضاح الآليات المعقدة التي تسهم من خلالها الحويصلات خارج الخلوية ومير-١٢٦ في فيسيولوجيا أمراض الكلى المزمنة، مقدِّمين رؤى حول فائدتها في تطوير أدوات تشخيصية جديدة واستراتيجيات علاجية. تؤكد هذه المراجعة على أهمية المزيد من البحث في مير-١٢٦ الموجودة في الحويصلات خارج الخلوية، مما يمهد الطريق لنهج مبتكرة لمعالجة أمراض الكلى المزمنة.

الكلمات المفتاحية: مرض الكلى المزمن، الحويصلات الخارجية، ميكرو ر.ن.أ-١٢٦(مير-١٢٦)، المؤشرات الحيوية التشخيصية، الأهداف العلاجية.