



The Application of Exosomes in the Diagnosis and Treatment of Renal Cell Carcinoma

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Abstract

Renal cell carcinoma (RCC) is an epithelial tumor originating from the proximal renal tubule of the urinary system. RCC is one of the most common and deadly tumors representing clear cell renal cell carcinoma (ccRCC) (about 75%) as major subtype characterized by high incidence and poor prognosis. There are no obvious clinical symptoms in the early stage ccRCC, but are readily visible in the late stage with >30% patients diagnosed with diffusion and metastasis. The incidence of RCC is higher in males than females and frequent in developed countries than in developing ones. The current treatment for rRCC mainly focuses on surgical excision and chemotherapy, however, it still suffers from high recurrence and poor survival, due to metastatic growth and insensitivity to radiotherapy and chemotherapy. Early diagnosis of RCC is very important and remains a top priority for its treatment. Exosomes are small vesicles with a lipid bilayer membrane structure that are actively secreted by normal and cancer cells in the body, containing bioactive substances such as proteins, nucleic acids, and lipids. The detection of extracellular vesicles in body fluids can play an important role in the early diagnosis of RCC. This article reviews the role of exosomes in the diagnosis and treatment of RCC.

Key words renal cell carcinoma, renal tumors, exosomes, diagnosis

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Introduction

Renal cell carcinoma (RCC) is one of the most common malignant tumors in the urinary system [1]. The global incidence rate is on the rise as each year, there are about 403000 new cases, 175000 deaths, occur due to renal cancer, ranking first in the mortality of urinary tumors. Several renal cancer patients develop advancedstage disease without visible symptoms, with approximately 20% of patients experiencing the three classic symptoms such as hematuria, abdominal mass, and pain. More than 50% of patients are accidentally detected through imaging during physical examination, and about 16% of RCC has already metastasized at the time of diagnosis. Most patients can only adopt palliative treatment, with poor prognosis and a 5-year survival rate of less than 10%. Therefore, there is a rapid requirement for sensitive and specific biomarkers of renal cell carcinoma that plays an important role in the diagnosis of early disease onset. Studies have shown that the blood level of exosomes in tumor patients is higher than that in normal individuals, as tumor cells secrete more exosomes. Exosomes play an important role in the occurrence, development, diagnosis, and treatment of various solid tumors including prostate, bladder, pancreatic and breast cancer. In recent years, a series of breakthrough achievements have been made in the application and in the basic research on exosomes. A large amount of evidence shows that exosomes promote the occurrence and development of tumors, and most of the research on exosomes in the field of urologic malignancies focus on the cellular level or small-scale clinical trials. The application of exosomes in the treatment of urinary cancers is an important direction of biomarker research. It is of great significance to modify the contents or surface markers of exosomes and select appropriate sources for exosomes therapy, which provides a new idea and solution for the diagnosis and treatment of RCC [2-7].

Overview of exosomes

Exosomes are a type of cup shaped vesicles with a lipid bilayer membrane structure that are autonomously produced and secreted by cells, with an average diameter of 40-100nm. They are the smallest extracellular vesicles. In the early stage, lysosomal particles collapse to form a multivesicular body (MVB). Some of the multivesicles fuse with the plasma membrane under the mediation of Rab protein, and then are transported out of the cell through exocytosis. These released vesicles are termed as 'exosomes'. Currently, it is known that exosomes originate from various cells, including hematopoietic and non hematopoietic sources. It was previously thought that exosomes are non-functional substances. It was found that exosomes may transfer genetic materials like "messengers" to exchange information between cells and play a role in receptor cells until 2007, which indicates that exosomes can participate in information exchange between cells. Now more and more studies show that exosomes play an important role in tumors [8], cardiovascular diseases [9], neurodegenerative diseases [10], and rheumatic immune diseases [11]. Exosomes can be isolated from cell culture medium and body fluids such as plasma, serum, urine, saliva, emulsion, etc. The extracellular membrane structure is with the ability to resist exogenous proteases and RNA enzymes, making intracellular functional proteins, mRNA, and miRNA more stable. Therefore, exosomes can be used as sensitive biomarkers for disease diagnosis.

Exosomes and renal cell carcinoma

Figure 1 shows the category of exosome on diagnosis and treatment of RCC.

Participate in the construction of tumor microenvironment

Tumor microenvironment is closely related to the biological function of tumor cells, similar to the relationship between seed and soil. Changes in tumor microenvironment can affect proliferation, apoptosis and invasion of tumor cells. With the advancement in studies on cancers, the tumor microenvironment has attracted the attention of researchers and scientists. The effects of tumor microenvironment on malignant cells can be divided into cellular components and non-cellular components [12,13]. In addition to immune cells, some related molecules of the tumor microenvironment also affect the biological behavior of tumor cells [14-16]. Primary tumors can release some biological factors to the areas of preferential metastasis and participate in the formation of metastatic microenvironment. Some studies have shown that exosomes can build a bridge between cells and the microenvironment and can transfer relevant information from the microenvironment to the cell through exosomes. Besides, exosomes can also transmit the genetic signals from the cell to the surrounding microenvironment, maintaining signal communication between cells and the surrounding microenvironment [17]. Fu et al. found that exosomes derived from renal tumor cells can promote cell proliferation and inhibit apoptosis through ERK5 signaling pathway in anoxic environment [17-19]. Exosomes also show certain organ and histiocyte tropism, and this tendency is related to the expression of integrin on the exocrine body surface. The initiation process of ecological niche formation before metastasis is very complex, involving the combination of exosomes secreted by cancer cells and stromal cells, leading to the reprogramming of target cells and the activation of important signal transduction pathways. Finally, the target cells develops the microenvironment before tumor spread, providing a prerequisite for tumor metastasis.

Advantage angiogenesis

Cancer stem cells promote angiogenesis by differentiating endothelial cells. MiRNAs derived from exosomes secreted by tumor cells, such as miR-23a, miR-210, miR-135b, miR-494, miR-1246, and miR-9, can be transferred to endothelial cells to promote the expression of vascular endothelial growth factor, fibroblast growth factor, angiopoietin-1, and accelerate the reconstruction of tumor tissue vascular network. The effect of exosomes on mesenchymal stem cells can promote tumor vascularization and proliferation by increasing the expression levels of MMP1, MMP2, MMP3, CXCR4 and CXCR7 [20]. In addition, exosomes with high expression of carbonic anhydrase IX (CAIX) are associated with vascular remodeling in renal cell carcinoma. Carbonic anhydrase 9 (CA9), a hypoxic response induced by hypoxic-inducible factor (HIF1), is overexpressed in RCCs, and CA9 exosomes released by anoxic RCCs may promote angiogenesis in the tumor microenvironment [21]. The formation of a vascular network is not only crucial for the normal growth of tumor tissue, but also provides important means for tumor invasion.

Advantage immune escape

The exosomes secreted by RCC cells can not only induce immune response of T cells, but also induce apoptosis of activated T lymphocytes by activating caspase pathway, weakening cytotoxicity of natural killer cell, and reducing the production of IL-2, IFN- γ , IL-6 and IL-10 contributing to the immune escape. Exosomes derived from tumors contain FasL and PDL-1, which can activate the Fas/FasL and PD-1/PDL-1 pathways. They induce apoptosis of CD8⁺T cells, inhibit the immune system, and

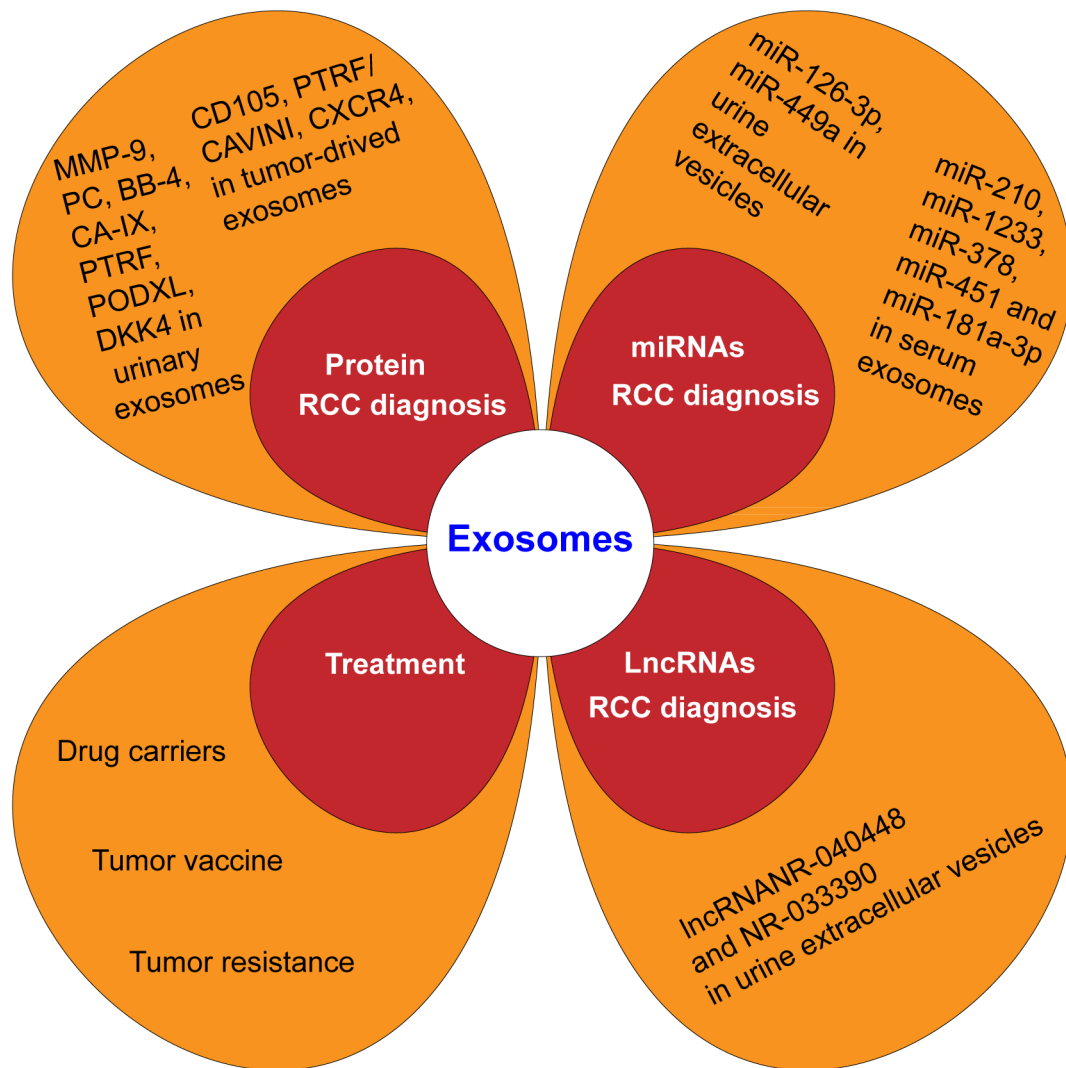


Figure 1. Exosome on diagnosis and treatment of renal cell carcinoma (RCC).

ultimately help cancer cells achieve immune escape [13]. ccRCC derives TGF- β -rich exosomes, which impair the function of TINK cells by activating the TGF- β /SMAD pathway and evade natural immune surveillance, leading to dysfunction of NK cells [22]. The aggregation of myeloid derived suppressor cells (MDSCs) in the tumor microenvironment is one of the most important factors for immune escape. It has been found that Hsp70 is abundant in RCC exosomes, which can aggregate tumor growth factors and proinflammatory cytokines, inducing the expression of MDSCs through the p-STAT3 pathway promoting tumor growth [14].

Participation in cancer cell invasion and metastasis

The exosomes can change the function of target cells through the transport substance. The tumor-derived exosomes affect urothelium cells and lead to epithelial mesenchymal transformation, which is an important step of tumor metastasis. Renal cancer stem cell exosomes promote EMT migration and invasion, accelerate the proliferation of ccRCC cells in vivo and lung metastasis [23], and the released exosomes promote

the formation of lung metastasis through the up-regulation of MMP2, MMP9 and VEGF receptors by lung endothelial cells. Study further show that miR-19a, miR-19b, miR-650 and miR-151 were associated with tumor invasion and metastasis [20]. In addition, miR-25-3p released by exosomes transfers to vascular endothelial cells, leading to increase of the vascular permeability and promoting tumor metastasis.

The role of exosomes in the diagnosis of renal cell carcinoma

Exosomes are a substance anomously secreted by cells, and these substances represent a pathological and physiological state of the secretion site. Therefore, the separation and detection of exosomes has great application prospects in the diagnosis, treatment, and monitoring the prognosis of renal cancer. **Table 1** shows a summary on these exosome-derived tumor markers in RCC.

Long chain non coding RNAs (lncRNAs)

LncRNAs, are RNAs with a length greater than 200 nucleotides

Table 1. Exosome tumor markers in renal cell carcinoma.

Exosome contents	Tumor biomarkers	Expression levels	Exosome source	Reference
miRNA	miR-135b	Increased	tissue	[20]
	miR-494	Increased	tissue	[20]
	miR-1246	Increased	tissue	[20]
	miR-9	Increased	tissue	[20]
	miR-19a	Increased	tissue	[20]
	miR-19b	Increased	tissue	[20]
	miR-650	Increased	tissue	[20]
	miR-151	Increased	tissue	[20]
	miR-25-3p	Increased	tissue	[20]
	miR-126-3p	Increased	urine	[25]
	miR-449a	Increased	urine	[25]
	miR-1233	Increased	blood	[25]
	miR-378	Increased	blood	[25]
	miR-451	Increased	blood	[25]
	miR-181a-3p	Increased	blood	[25]
	miR-199a-3p	Decreased	urine	[28, 29]
	miR-486-5p	Increased	urine	[30]
miR-30c-5p	Increased	urine	[31, 32]	
LncRNA	lncRNANR-040448	Increased	urine	[24]
	NR-033390	Increased	urine	[24]
	CAIX	Increased	plasma	[32, 34]
Protein	MMP1	Increased	plasma	[20]
	MMP2	Increased	plasma	[20]
	MMP3	Increased	plasma	[20]
	CXCR4	Increased	plasma	[20]
	CXCR7	Increased	plasma	[20]
	FasL	Increased	plasma	[13]
	PDL-1	Increased	plasma	[13]
	Hsp70	Increased	plasma	[14]
	MMP9	Increased	plasma	[20]
	CD105	Increased	urine	[20]
	black body 4	Increased	urine	[20]
	podocycalyprotein	Increased	urine	[20]
matrix metalloproteinase 9	Increased	urine	[20]	
PTRF/CAVINI	Increased	urine	[33]	
PODXL	Increased	urine	[32, 34]	
DKK4	Increased	urine	[32, 34]	

that lack protein encoding ability. Malignant cells can express specific lncRNA markers, indicating that lncRNA can serve as a specific marker for diseases, which is of great significance for the diagnosis of cancer. The presence of lncRNAs in exosomes is particularly abundant, and exosomes can protect the nucleic acids from enzymatic decomposition; Similar to miRNA, lncRNA also plays an important role in the growth, proliferation, invasion, and metastasis of cancer cells. The differential expression of lncRNANR-040448 and NR-033390 in urine extracellular vesicles is most significant, with sensitivity and specificity exceeding 70%, indicating that lncRNA can serve as a potential diagnostic marker for renal cell carcinoma [24].

MicroRNAs (miRNAs)

MiRNAs are small endogenous noncoding RNAs (18-24 nucleotides) in the process of gene post transcriptional protein translation, which are involved in the tumorigenesis and development processes. The miRNA in urine can be produced from various tissues and organs of the urinary system, including tumor tissue, normal urothelium tissue, renal parenchyma, etc. Exosome can be transferred between cells that contains a variety of bioactive components such as miRNA, mRNA, and protein, and is an important intercellular communication molecule. Exosome transport-specific miRNA may play an important role in the pathogenesis of tumors. It has great application foreground in the pathogenesis, diagnosis and treatment of RCC and other malignant tumors of urinary system. The detection through combining urine miR-126-3p with miR-449a can distinguish healthy individuals from RCC patients and can serve as a marker for highly sensitive ccRCC patients. Redova et al. found that the levels of exosomes miR-210, miR-1233, miR-378, and miR-451 in the blood were significantly increased in patients with ccRCC. The increase of miR-181a-3p in serum exosomes of patients with kidney cancer is extremely significant in the early stage, which can be used as a marker for its early diagnosis [25-27]. However, Fan et al. found that the level of exosomes miR-199a-3p, miR-145 were decreased in some patients with ccRCC [28, 29]. Other studies have shown a significant decrease in the expression of miR-210 and miR-1233 in the blood exosomes of renal cancer patients after surgery. Compared with healthy individuals, the expression of miR-183 is increased in kidney cancer patients, and miR-183 levels are positively correlated with poor prognosis in renal cancer patients, playing a role in promoting tumor invasion and metastasis. Combined diagnosis of miR-126-3p and miR-486-5p in exosomes can distinguish benign lesions from ccRCC [30]. miR-19a is overexpressed in renal cancer tissues and up-regulated in metastatic renal cancer and is considered as a possible prognostic marker [20]. Song et al. found significant differences in the expression of miR-30c-5p between ccRCC patients and healthy control individuals, indicating its specificity for ccRCC and potential diagnostic biomarkers for early ccRCC. The intracellular level of miR-224 in primary renal cancer cell lines is significantly up-regulated, and miR-224 in exosomes affects the prognosis of patients, may mediate cell-cell interactions and cancer invasion and metastasis, and is a potential prognostic biomarker in ccRCC patients [31, 32].

Protein

Herreros-Villanueva and Bujanda obtained 261 and 186 types of proteins by isolating the urine exosomes of normal people and renal cancer patients. However, there were not many similarities of these two groups of protein types. Among them, the expression of matrix metalloproteinase 9, podocycalyprotein, black body 4 and CA IX in urinary exosomes of patients with renal cancer is

higher than that of normal individuals. Among a group of proteins detected in urinary exosomes of patients with renal cancer, 10 of them may be potential markers of renal cancer. CD105 expression is associated with poor prognosis of renal carcinoma. The high expression of CXCR4 is considered to be a novel marker of CSC, which is associated with the more aggressive and metastatic RCC [20]. The expression of PTRF/CAVINI (transcription releasing factor) is regulated by SHC1 (polymerase), which is significantly overexpressed in high-grade ccRCCs, and abnormally increased PTRF can be detected in urinary exosomes, suggesting that PTRF could be a potential marker for the diagnosis of ccRCC [33]. MMP9, PODXL, DKK4 and CAIX are highly expressed in urinary exosomes of patients with renal cancer and are not lost due to individual differences in patients with renal cancer, which can provide valuable clinical information for the diagnosis and treatment of renal cancer [32, 34].

The role of extracellular vesicles in the treatment of renal cell carcinoma

Drug carriers

According to the characteristics of exosomes, they can serve as drug carriers for therapeutic purposes. The lipid bilayer membrane structure of exosomes can protect RNA from being degraded by RNA enzymes, and their size and deformability make it easier to penetrate the biofilm, for accurate delivery of therapeutic genes to the target cells. In addition, the size of exosomes is at the nanoscale, and changing the substances in exosomes can make them a tool for delivering drugs, antigens and genes, with significant advantages such as long half-life, targeting ability, biocompatibility and low toxicity [35]. The anti-tumor substances carried by the exosomes can not only hinder the development of bladder cancer, but also have no obvious damage to the normal urothelium, which indicates that the exosomes are ideal carriers for the treatment of urinary cancer.

Tumor vaccine

Compared with traditional vaccines, exosomes secreted by tumor cells have incomparable effects and higher affinity. Exosomes can express immunosuppressive molecules in the body, thereby reducing their immunogenicity. Zhang Yao et al. found that extracellular vesicles derived from RCC anchored interleukin-12 have more significant anti-tumor effects than that derived from normal cells. In vitro experiments, it was found that this new vaccine has stronger cytotoxic reactions, providing cogent evidence for the treatment of rRCC through extracellular vesicles. These cells can highly express RCC-associated antigen G250 and can effectively induce the body's specific immune response and CTL. This group prepared EXO/IL-12 vaccine. Exosomes produced by antigen-sensitized dendritic cells can activate tumor-specific CTL and produce strong anticyclidal activity, thus exerting anti-renal cancer effect [36]. The tumor suppressor genes loaded and transported by exosomes can inhibit tumor cell growth, providing necessary conditions for exosome-mediated targeted therapy.

Tumor resistance

Tumor resistance is one of the main reasons for clinical treatment failure. Tumor cells that do not develop drug resistance until they receive genetic information related to multidrug-resistant proteins secreted by other tumor cells in exosomes, leading to their acquisition of drug resistance. Qu et al. found that nephrotic drug-resistant cells transmit lncARSR to other cells through exosomes,

inducing them to develop drug resistance; LncARSR promotes the expression of AXL/c-MET through competitive combination with miR-34/miR-449, and AXL/c-MET promotes the expression of LncARSR in the form of positive feedback, further promoting drug resistance to RCC cells. In addition, the exosomes miR-210 can mediate drug resistance in gemcitabine sensitive tumor cells. Liu et al. found that overexpression of miR-145 in hUCMSCs can be transferred to RCC cells by exosomes, improving tumor sensitivity to Sunitinib [37-44]. The above research indicates that extracellular vesicles can mediate the development of drug resistance in tumor cells, which not only provides new therapeutic targets for cancer patients, but also predicts the patient's response to anti-tumor drugs through the detection of extracellular vesicle markers, providing important reference for personalized treatment of renal cell carcinoma.

Summary and Outlook

Early diagnosis of RCC is one of the key factors in improving patient survival, and the discovery of exosomes provides a huge possibility. Exosomes can be isolated from the blood, urine, and tumor tissue of RCC patients. There are several methods to separate and purify exosomes, and currently the most widely recognized separation method is ultracentrifugation. However, it is time-consuming and requires a number of raw materials, and there is still no reliable and simple separation method that can be applied to the clinical practice. Exosomes derived from tumor carry a large amount of substances, including proteins, nucleic acids, lipids, etc., which can change the biological behavior of target cells and promote cell growth and development. Due to the advantage of simple and fast extraction of exosomes from urine and blood, tumor derived exosomes have incomparable potential in the early diagnosis of RCC. However, the main focus of research is on renal clear cell carcinoma currently, and most of them are retrospective studies. If promoted and applied to clinical practice, it is necessary to combine more extensive research with clinical trials.

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Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

ZX designed the study and was responsible for the writing of the original draft. GX edited and approved the final manuscript.

Competing interests

All authors declare no competing interests.

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