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Exosomal Consignment in Renal Allograft Injury

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Abstract

Exosomes are small mobile endocytic vesicles (30-120nm), shredded by every cell to conduct trafficking of cell generated cargo. They are found in almost all body fluids (blood, csf, saliva, urine). These include proteins, lipids, DNA, mi(cro)RNAs etc. In multicellular organisms, they are packaged into numerous vesicles mainly in exosomes to conduct their transport for various cellular activities which can be exploited clinically. Presently the survival of renal allograft is monitored by mostly invasive methods (tissue biopsy, Creatinine, GFR) where curving the injury is quite difficult. Hence potency of molecular markers like proteins and then circulating miRNAs came to picture for early detection of renal injury (Acute Kidney Injury-AKI and Chronic Kidney Disease-CKD). However, due to lack of specificity of circulating miRNAs lose their feasibility and the discovery of these exosomal cargos in cellular communication has become an efficient tool for treatment of various complicated clinical condition including renal allograft injury.

Keywords: *micro RNAs,exosome, Renal Allograft Injury*

Introduction

Exosomal world: a prologue

Exosomes are membrane bound mobile vehicles that are found in almost all circulating body fluids like- blood, CSF, saliva, urine, etc. These are responsible for transport of respective cellular cargo to extracellular target sites **[1]**. Recent studies with exosomes have revealed that exosomal cargo delivery has many important biological, physiological and pathological significance thus, can be an effective diagnostic tool for various diseases **[2]**. Exosomes are small circulating units of 30-120 nm in diameter, generating from late endosomal compartments of cells by its cell membrane invagination or budding or released as shedding vesicles. Cellular cargos include proteins, lipids, DNAs, mRNAs, miRNAs, etc **[1]**. The exosomal cell membrane mainly constitute a limiting lipid bilayer, transmembrane proteins and a hydrophilic core containing proteins, mRNAs and microRNAs (miRNAs).

Exsosomes were first discovered by Pan and Johnstone in 1983 **[3]** when they found that the release of transferrin receptors into extracellular space during sheep reticulocyte maturation was released inside a type of small vesicles. In 1989 Johnstone regarded these mammalian cargo delivering vesicles as exosomes **[1-5]**. Valadi et al. in 2007 first described about the composition of exosomes that apart from proteins and lipids these also contains DNAs and RNAs **[6]** which are recorded in ExoCarta database **[7,8]**. The exosomal cargo delivery requires stimulation of target cell which may be direct by receptor mediated interactions or may aid in transport from cell of origin to various bioactive molecules e.g. membrane receptors, proteins, lipids, mRNAs, miRNAs, etc **[7]**. When exosomes deliver its contents into the respective target sites the property and behavior of these cells changes to a great extent **[8]**. It is also understood from various studies done in last couple of years that miRNA composition of parent cell and exosomal components vary a lot **[8]** and of all the components, miRNAs have drawn the attention due to their regulatory role in gene expression as these are protected against RNAase-dependent degradation **[1-8]**. Thus exosomal cell-to-cell communication influence both physiological as well as pathological environment of the body. These play important roles in immune reactions, tumorigenesis and in neurodegenerative disorders **[1]**. e.g. in prostate cancer, ovarian cancers, lymphoma glioblastoma, etc **[1]**.

Biogenesis

Exosomes are formed from late endosomal compartments of cells through endosomal sorting complex required for transport (ESCRT-that recognizes ubiquitylated proteins) to deliver the cargo to target cell or to fuse with lysosomes to degrade the undesired contents **[1]**. Earlier these exosomes were only considered to be "garbage bags" as their diversified capabilities were unknown then. But now these are the most emerging field of research. The way of formation and secretion of these vesicles from mutlivesicular bodies (MVBs) are of two types **[9]**:

a) Microvesicles, which are directly shed from cell membrane.

b) Exosomes, which are released by exocytosis when MVBs fuse with plasma membrane.

Exosomes can be identified by transmission microscopy as a cup-shaped morphology with negative staining **[10-12]**. These can be concentrated in 1.10-1.21 g/ml section of a sucrose density gradient **[10-12]**. Exosomes can be identified by various protein markers e.g. tetraspanin proteins- CD63, CD9, CD81, HSP70 and HSP90, etc **[1, 8]**. ExoQuick (a one-step precipitation procedure for exosome extraction), Immuno affinity capture, Immunobead (EpCAM), combination of EpCAM and ultracentrifugation, size exclusion chromatography and EpCAM and followed by Quantitative PCR, Microarray techniques for extraction and quantification of exosomes **[1,8,13]**.

Exosomes formation and secretion requires enzymes and ATP. First the cell membrane is internalized to produce endosomes. Subsequently, many small vesicles are formed within endosomes by invagination of its cell membranes **[8, 14]**. Such endosomes are called MVBs. Finally, the MVBs fuse with endosomal cell membranes to release intraluminal vesicles into extracellular space which become exosomes **[14]**.

The secretion or cell-to-cell communication of exosomes requires certain regulatory factors which were first identified by Ostrowski et al. who observed that Rab27a and Rab27b were associated with exosomal secretion **[8]**. It was also found that effectors of Rab27- SYTL4 and EXPH5 could also inhibit exosomal secretion in HeLa cells **[15]**. Also Yu et al. discovered that tumor repressor protein p53 and its downstream effector TSAP6 were required for influencing exosome secretion **[16]**. Another working group, Baietti et al. observed the importance of syndecan-syntenin which directly interact with ALIX protein via Leu-Tyr-Pro-X(n)-Leu motif in secrection of exosomes by endosomal budding **[17]**. Koumangoye et al. found that disruption of lipid rafts in exosomal membranes could inhibit its internalization in breast cell carcinoma cell line **[18]**. Trafficking of exosomes to target sites occurs in following mechanisms:

1. The transmembrane proteins of exosomes directly interact with signaling receptors of target cell membranes **[19]**.
2. The exosomal fusion with plasma membrane of recipient cells to deliver the cargo into their cytosol **[20]**.
3. The exosomes internalization into recipient cells have two fates **[21]** -

3.1. in one, some exosomes are engulfed by the cell and may merge with the cell's endosome and undergo transcytosis

3.2. in other case, engulfed exosomes fuse with endosomes and mature into lysosomes for degradation.

As per ExoCarta database records, of all the components proteins and miRNAs have been exploited for various research to correlate some application with different diseased state that could render some remedy. Due to the regulatory role of miRNAs in gene expression these are used as recent area of research as diagnostic tool **[8,22]**. Goldie et al. demonstrated that among small RNAs, the percentage of miRNAs is higher in exosomes than in parent cells **[23]**. Studies done with exosomalmiRNAs shows there are specific sorting mechanisms for miRNAs into exosomes. These are:

a) The neural sphingomyelinase 2 (nSMase-2)-dependent pathway by Kosaka et al. **[24]**.

b) The miRNA motif and sumoylated heterogeneous nuclear ribonucleoproteins (hnRNPs)-dependent pathway by Villarroya- Beltri et al. **[25]**.

c) The 3' end of the miRNA sequence-dependent pathway by Koppers-Lalic et al. **[26]**.

d) The miRNA induced silencing complex (miRISC)-related pathway and human AGO2 protein **[27]**.

In short there are specific sequence in miRNAs as well as enzymes and proteins that guide them for their sorting into exosomes **[8]**. Exosomes are shed by cells during both normal as well as pathological conditions. Thus several studies have been made with exosomes in diseased states.

A brief sketch on therapeutic exosomal cargos:

Exosomal miRNA: miRNAs are the recent findings in the field of clinical research which are thought to be crucial in depicting human health and diseases. These biomarkers can also be an indicator for rejection onset of transplanted allograft. miRNAs are a class of small 18-25 nucleotide (nt) long endogenous, non-coding RNAs which play an important role in regulating gene expression **[28,29]**. A single miRNA has the ability to regulate expression (mostly silencing) of hundreds of mRNAs and have been known to play important role in many cellular functions that include induction of post-translational repression, mRNA degradation/silencing and transcriptional inhibition, cell development, differentiation, proliferation and functional

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regulation of immune response among others **[28-31]**.

The mystery behind the functional maturation of miRNAs has been solved by research in last couple of years. Similar to mRNAs, miRNAs are also initially transcribed in the nucleus **[32]**. miRNAs are at first transcribed in nucleus as primary transcript by RNA polymerase II called pri-miRNA **[32-35]**. This pri-miRNA has a hairpin stem-loop structure (~80nt length) that contains the mature miRNAs **[36]**. The pri-miRNA processing include recognition of the stem loop followed by its cleavage by DROSHA (a class 2 ribonuclease III) and DGCR8 (a miRNA-processing multiprotein complex) to release pre-miRNA **[32-35]**. Pre-miRNA is then recognized by Exportin-5 which allows its exports to cytosol for further maturation into 19-25 nucleotide strands by RNA endonuclease III called Dicer **[32-35, 37]**. Cleavage of this pre-miRNA by Dicer result in double stranded (ds) RNA molecule of which one of the single strand with more unstable 5' base pairing is selected and transferred to an Argonaute (AGO) protein and the other strand is degraded **[35,38,39]**. The selected strand induces silencing of mRNAs through RNA Induced Silencing Complex(RISC) thus affecting various cellular functions like cell differentiation, proliferation as well as development and functional regulation of immune system **[32-35,40].** In normal tissues, RISC remain as a low molecular weight entity with reduced regulatory activity while under stressed or replicating conditions these become high molecular weight units with intensified regulatory activity when bound to mRNA **[36]**. Thus mRNA silencing by miRNAs results in lower protein levels in the body **[36,41]**.

ExosomalProteins: Proteins are the building blocks of life in all living organisms. These are amino acid chains linked by peptide bonds. They are exquisite necessity in every cellular events, may it be the formation of new cells or cell repair. Thus, can be an important biomarker in depicting biological changes. Emerging research have exploited this idea and conducted various proteomic studies. A more burning concept is ofexosomal proteins. The work done and data obtained shows that besides miRNAs another important exosomal load isexosomal proteins. TrairakPisitkun et al had worked on urinary biomarkers and found that urinary exosomal proteins can also be an efficient protein biomarker in reporting renal tubulopathies and other renal disorders **[42]**. Exosomes normally found in urine accounts for around 3% of the total urinary protein contents and isolation of these exosomes can result in very large enrichment of urinary proteins derived from renal tubular epithelial cells **[42].** The exosomal packaging occurs when the apical membrane proteins undergo endocytosis and packaged into MVBs. These MVBs undergo encapsulation of cytosolic proteins into small vesicles. Finally outer membrane of MVBs fuse with apical plasma membrane releasing exosomes containing both membrane and cytosolic proteins **[42]**. The proteomics study with LC-MS/MS coupled with upstream one dimensional SDS-PAGE separation experiments had disclosed a number of proteins associated with exosome biogenesis like class E vacuolar protein sorting (VPS), ALIX, Aquaporin 1, Aquaporin 2, ESCRT, etc **[43].** A total of 295 proteins of urinary exosomeswere found to be associated with renal diseases and hypertension. These have been enlisted in Urinary Exosome Protein Database **[42]**. In another experiment where polypeptides were considered reflect that β_2-microglobulin could be an indicator of damage of renal proximal tubule cells **[42,44].** The techniques used to evaluate exosomal protein change is carried out by two dimensional difference in gel electrophoresis and change proteins are identified by mass spectroscopy and validated by Western Blotting **[45].** Zhou et al worked with Fetuin-A, a protein of liver as an important exosomal protein that can indicate occurrence of AKI(Acute Kidney Injury) **[45]**.

Early Molecular Biomarkers for Renal allograft status

Years of research with renal allograft injury for either Acute Kidney Injury (AKI) or Chronic Kidney Disease (CKD) suggest that instead of invasive detection of allograft status there are scopes for early and non-invasive detection of injury through molecular markers. The studies made at the molecular level have disclosed the fact that acute and chronic rejections to a transplanted graft at preliminary stage can be ascertained by alteration in levels as well as expressions of various molecular markers involved in signaling of graft injury. These can be measured from blood/urine samples of patients. In acute rejection the early pathological change is defined by Ischemia-Reperfusion Injury (IRI) where altered expression of various miRNAs **[46]** is observed 3-7 days post-injury **[47]**. At later stage when rejection is in progress changes in levels of miR-210,-10a and -10b as well as some proteins (like perforin, granzyme A andB mRNA, FAS Ligand, FOXP3, etc) are observed **[48]**. Chronic rejection in early graft injury is generally associated with Interstitial Fibrosis and Tubular Atrophy (IF/TA). Pathophysiology of IF/TA is the deposition of Extracellular matrix (ECM) proteins and Epithelial-Mesenchymal Transition (EMT) which can be stimulated by Transforming Growth Factor beta (TGF-β)/Smad signaling cascades. Ample of literature suggest that TGF-β/Smad signaling can cause up-regulation and down-regulation of various miRNAs (miR-21,-192 & miR-29 and -200 families under IF/TA conditions) **[49,50]**. Even though these biomarkers have provided fruitful information but they lack specificity and their cellular source is unknown since they circulate. So to get a much clearer picture of a particular injured cell research at molecular level have unrevealed the next generation biomarker –exosomalmiRNAs for early, specific and non-invasive detection. Moreover their cellular source is also defined so they can deliver exact status of a particular cell **[1,8]**.

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Urinary Exosomal proteins and miRNAs in renal allograft injury as Next Gen Molecular Biomarkers

Studies done with renal diseases is pretty less and still a burning area of research that reveals the fact that urinary exosomal proteins as well as miRNAs can be a potential therapeutic tool for kidney and associated diseases **[1,8]**.

The urinary exosomal proteins can be easily attainable by noninvasive means for diagnosis of ESRD as well as Urinary Tract Infection (UTI) **[1]**. In 2006 Zhou et al. reported that urinary exosomal protein- fetuin A was found to be increased in AKI (Acute Kidney Injury) patients in ICU than AKI patients in normal care **[1,41,45]**. In 2008, same group discovered that activating transcription factor-3 (ATF-3) was found in exosomes isolated from AKI patients than CKD patients or control **[41,45,51]**. Thus suggesting urinary exosomal proteins could be a diagnostic tool. Moreover, a reduced level of urinary exosomal aquaporin-1 has been observed in ischemia-reperfusion injury in rats **[7]**. ExosomalmiRNAs demonstrate potential diagnostic biomarker for renal fibrosis **[8]**. MiR-29c and CD2APmRNA **[52,53]** were observed in urinary exosomes of renal fibrosis patients. The findings by Stefano Gatti[1] et al. showed that bone marrow derived Mesenchymal Stem Cells (MSC) Microvesicles (MV) when administered immediately after IR injury can prevent AKI and CKD in rats **[8,54]** through their paracrine actions. Tara K Sigdel et al have described that in AKI patients with perturbation exosomal proteins like CLCA1, PROS1, KIAA0753 were observed. In addition to that exosomal ApoM is more than soluble ApoM **[55]**. M.W. Welker group found that in patients with chronic Hepatitis C serum soluble exosomal CD 81, a surface protein marker is elevated **[56].**

Future Prospective and limitations

Lots of work have been done with circulating miRNAs but due to their less specificity with the exact status of injured tissues and accuracy in determining role of a miRNA and its cellular source, still more feasible molecular markers have been searched and scientists have found that the circulating vehicles of cells-circulating exosomes that carry respective cellular cargo to the target sites to conduct cell-to-cell communication can be an option. These can be more proficient in delivering the most specific information on the status of any cell, may it is normal or injured cells. The molecular composition of exosomes that has been found till date is being recorded in the ExoCarta database. By exploiting these data in different pathological diseases scientists have done lots of research with carcinomas. In renal diseases also these exosomal miRNAs are being used to find out a means for noninvasive early detection of graft rejection. The conclusion drawn from these studies that proteins like fetuin-A and activating transcription factor-3 (ATF-3) can be used as marker in acute kidney disease and miR-29c and CD2AP mRNA are identified from urinary exosomes in renal fibrosis patients.

Thus, the various convergent studies made in the field of transplantation have led to the discovery of potential therapeutic targets- non-invasive urinary exosomal miRNAs and proteins which can be used to investigate and confirm the injury of transplanted allograft at an early stage. Though the data obtained define exosomes as an appropriate marker when compared with mRNAs, still it has few limitations:

a) Diverse isolation procedures that can affect exosomal contents,

b) Exosomes containing large number of miRNAs that affect the signaling of the cell together but not itself alone and

c) Difficultly in measuring the exact quantity of a particular miRNAs in a exosome when miRNA is in low concentration.

Conclusion

The exosome cell-to-cell communication mechanisms' experiments are still at its infant stage. There is the need for development of more sophisticated techniques to detect the exact amount of specific functional exosomal proteins and miRNAs and their proper signaling pathways. Thus more investigation are still required to exploit exosomes in clinical fields as therapeutic targets.

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