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Multi-faceted role of exosomes in organ transplantation

Abstract

The development of allograft rejections is a major setback in the field of organ transplantation. New insights gained from studies on exosomes have facilitated in better understanding of allorecognition, alloreactivity and allo-rejection. Exosomes are nano-sized (40-100 nm in diameter) membrane vesicles of endosomal origin that harbor different cargos depending on the cells from which they originate. The functional outcomes on immune regulation are stated to differ with regards to the distinct constituent of exosomes' cargo, which culminates in either activation or suppression of immune response. Based on the immune response mediated by exosomes, rejection or immune tolerance mechanisms are explained. Taken together, in this review, we have attempted to cover diverse role of exosomes in the field of transplantation, which includes rejection, diagnosis and immune tolerance.

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Swetha Thirukannamangai Krishnan,[1] Sunjay Kaushal,[1] Muthukumar Gunasekaran[1]

[1]Departments of Surgery and Pediatrics, Northwestern University, Chicago, USA

Correspondence: Muthukumar Gunasekaran, Ph.D., Departments of Surgery and Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, Simpson Querrey Biomedical Research Center, Room #4-406 303 E Superior St, Chicago, Illinois, 60611, Tel 314.677.7477, Email mgunasekaran@luriechildrens.org

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Abbreviations: OT, organ transplantation; GONT, global observatory on donation and transplantation; WHO-ONT, world health organization-the Spanish transplant organization; HLA, human leukocyte antigen; AR, acute rejection; DCs, dentritic cells; ICAM-I, intercellular adhesion molecule I; MHC, major histocompatibility complex; LT, lung transplant; BOS, bronchiolitis obliterans syndrome; KT, kidney transplant; TCMR, T cell mediated rejection; AMR, antibody mediated rejection; CMR, cell mediated rejection; HT, heart transplant; ACR, acute cellular rejection; ImDCExos, immature DCs derived exosomes; T-regs, regulatory T cells; BMMSC-exos, bone marrow mesenchymal derived exosomes; DANCR, differentiation antagonizing non-protein coding RNA.

Introduction

Remarkable scientific advancements since 20th century have led to the deployment of organ transplantation (OT) as a lifesaving option for patients with end-stage organ dysfunction. According to the latest Global Observatory on Donation and Transplantation (GONT) data generated by the World Health Organization-the Spanish Transplant Organization (WHO-ONT) collaboration, a total number of 144,302 OTs has occurred in the year 2021 with an average count of 16 OTs/hour and an overall increase of 11.3% OTs over the year 2020.[1] These facts exemplify the significance of OTs in improving the quality and expectancy of patients' life with end-stage organ dysfunction. Regardless of the continual progression in OT techniques such as immunosuppressive therapies, usage of anti-lymphocytic serum, human leukocyte antigen (HLA) typing, antibody screening and organ preservation, allograft rejections are recounted to be one of the major setbacks, which highly impact the success rate of OTs.[2,3] For instance, the incidence of acute rejection (AR) of liver transplantation has been stated to be 15-25%,[4] which potentially increase the jeopardy of chronic rejection, augment the demand of re-transplantation and create organ shortage for transplantation. Though AR rates have been cut down with the advent of immunosuppressive therapies, the imbalance formed between under and over-immunosuppression during therapy has been reported to culminate in death censored graft failure as a consequence of post-transplantation infections, malignancies and cardiovascular diseases.[3,5,6] Thus, there is an inevitable need to identify potential ways in prolonging the graft survival with minimal risk of post-transplantation complications.

Evolving knowledge of transplant immunology has facilitated the understanding of intricate process of allograft rejection. Both innate (including monocytes, natural killer cells and dendritic cells) and adaptive (including T cells and B cells) immunity of the host system are stated to influence graft rejection.[7,8,9] Besides host immunity, multiple evidences suggest that donor derived exosomes play pivotal role in allorecognition and allo-rejection.[10,11,12] Exosomes are homogenous nano-sized (40-100 nm in diameter) membrane vesicles of endosomal origin, which are secreted by almost all cells and present in a wide array of biological fluids (including blood, breast milk, saliva, urine, amniotic fluid, synovial fluid, cerebrospinal fluid, seminal fluid). It harbors mRNAs, long non-coding RNAs, microRNAs, lipids and non-specific proteins exhibiting multitude of functions. In addition to the alloreactivity, exosomes have garnered vast attention in the field of transplantation medicine owing to their multifaceted role as potential prognostic/diagnostic biomarkers and therapeutic agents.[13] In this review, a comprehensive overview of exosomes in rejection, diagnosis and tolerance has been provided in an attempt to gain better insights into the progress of exosomes research and their potential clinical applicability in transplantation medicine.

Exosomes in allorecognition and allo-rejection of transplants

At the outset, exosomes were once considered to be a cellular waste expelled as a consequence of cell maturation, damage and or homeostasis without any implications on neighboring cells.[14,15] This conception has changed with the course of extensive research on exosomes revealing their diverse roles in various biological processes such as immune response, inflammation, signal transduction, intercellular communication, lactation and cell proliferation. Additionally, numerous studies have divulged their role in pathogenesis and or progression of many diseases such as diabetes, thrombosis, lipid metabolic diseases, renal diseases, arthrosclerosis, neurological disorders, autoimmune diseases, cardiovascular diseases, and cancer.[16,17] Of note, the immunoregulatory potential of exosomes such as elicitation/ suppression of immune response, antigen presentation and immune tolerance have offered significant

insights into the immunology of graft rejection/ tolerance. Particularly, these immunoregulatory effects are implemented by the exosomes' cargo (including proteins, lipids and nucleic acids) whose functional outcomes and composition differ based on the cells from which exosomes originate. For instance, quantitative variation in the protein composition of exosomes derived from immature and mature dendritic cells (DCs; antigen presenting cell) has been evidenced to be accountable for different functional T cell responses. Among differential expression of several proteins, up regulation of intercellular adhesion molecule I (ICAM-I) has been identified to be crucial for strong immunogenicity of mature DC derived exosomes, which induce effector T cells leading to fast skin graft rejection. However, immature DC derived exosomes with less ICAM-I were less efficient in inducing T cell activation and skin graft rejection.[18]

Allorecognition is described to be the activation of recipient T cells following the recognition of donor antigens which results in the elicitation of inflammatory immune response that act as the initiator of graft rejection. This proposition was initially described by Snell in 1957 and later termed as 'passenger leukocyte' concept by Elkins and Guttman in 1968.[19,20] According to this concept, leukocytes or hematolymphoid cells residing temporarily in the allografts (called as passenger leukocytes) present allo-antigens to host lymphoid organs and up regulate cellular and humoral adaptive immunity. In 2016, Marino et al., have revisited the passenger leukocyte concept by studying it in mice transplanted with heart, islets and skin grafts using flow cytometry combined with microscopy. Unlike passenger leukocyte concept, they did not find any donor leukocytes in recipient lymphoid organs till 15 days post-transplantation of skin graft. Nevertheless, they observed large number of recipient leukocytes overlaid with donor exosomes harboring major histocompatibility complex (MHC) molecules in non-vascularized skin-grafted mice after 12 hours of transplantation. At 7 days post-transplantation of skin allograft, they found allo-MHC cross-dressing of recipient cells wherein, recipient DCs (60-70%) and B cells (10-15%) expressed donor MHC together with their own MHC. In mice transplanted with heart and islets allograft, they noticed similar phenomenon in addition to the presence of considerable number of passenger leukocytes in recipient lymphoid organs that declined gradually in 7 days post-transplantation. To validate exosome mediated allo-specific T cell response, they injected mice with purified allogenic exosomes and observed potent induction of T cell alloreactivity.[21] In another study, Liu et al., investigated whether the insubstantial population of donor DCs from cardiac allograft was suffice to induce alloreactivity and identified that the allo-antigen presentation to recipient DCs was carried out by exosomes released from donor DCs which mobilized to lymphoid tissues from graft to activate T cell allo-response in a murine cardiac transplant model.[10] Similarly, Gunasekaran et al., have compared the constituents of exosomes isolated from sera of stable lung transplant (LT) recipients and LT recipients presented with bronchiolitis obliterans syndrome (BOS; chronic lung allograft rejection) wherein, they divulged the expression of donor HLA, co-stimulatory molecules, MHC class-II, lung self antigens, diverse transcription factors and adhesion molecules on the surface of serum derived exosomes of LT recipients diagnosed with BOS. Further, they corroborated the immunogenic potential of exosomes derived from LT recipients diagnosed with BOS by using a murine immunization model.[22] Altogether, these observations shed light on the significance of donor derived exosomes in allorecognition, alloreactivity and allo-rejection, which was also accredited in several other studies.[23,24,25]

Mechanisms of allo-rejection and exosomes

Based on the onset time, graft rejections are predominantly classified as hyperacute, acute and chronic rejection. Hyperacute rejection happens within initial few minutes to hours of transplantation in response to immune elicitation caused by the presence of anti-donor antibodies in recipient before transplantation of vascularized graft. These preformed antibodies trigger endothelial cells via complement activation and stimulation to secrete von Willebrand factor (a large procoagulant adhesive glycoprotein) that results in ischemia and thrombosis ultimately leading to graft necrosis. Nowadays, the occurrence of hyperacute rejections is mostly curtailed by ABO compatibility testing and cross-matching. Secondly, AR is said to happen anytime between a week and few months after transplantation and generally characterized by inflammation and cell damage. In this type of rejection, immune reaction is mainly mediated by either cellular (T cell) or humoral (antibody) pathway. Immunosuppressive therapies have been reported to facilitate in reducing the occurrence of ARs. Finally, chronic rejection is stated to be a late graft failure that develops between several months and years of transplantation with regards to the immune response mediated by memory cells and antibodies via cellular or humoral pathway. The characteristic features of this rejection mainly include vasculopathy, fibrosis and atrophy of grafts ultimately leading to graft failure with progressive functional loss.[26,27]

There are multiple pathways described for allo-rejection which includes direct, indirect and semi-direct pathway of allorecognition resulting in T cell mediated graft rejection. Direct pathway of allorecognition attributes to the passenger leukocyte concept wherein, the graft-residing donor DCs mobilize to the recipient lymphoid tissue to present intact allo-antigens (MHC molecules) and induce T cell alloreactivity. This pathway majorly accounts for acute graft rejection in MHC-incompatible transplants by activating adaptive immunity. As donor leukocytes are short lived, the indirect pathway of allorecognition was recognized, which trails the normal mechanism of antigen presentation to T lymphocytes following an infection. Herein, the recipient leukocytes engulf and process the donor derived allo-antigens by infiltrating the graft and present them as allo-peptides that leads to alloreactivity of T cells and graft rejection. This pathway is stated to be a long-term allorecognition mode that is liable for the production of allo-antibodies and chronic rejection.[26,28] In addition, the semi-direct pathway is the third described mode of allorecognition, which relies on cell-to-cell communication concepts such as trogocytosis (cell nibbling) and intercellular communication via exosomes.[28,29] Notably, exosomes have gained much attention with numerous studies reporting their implication in allo-rejection.[21–25] In this pathway, the intact allo-MHC molecules are transferred to recipient leukocytes by a process called cross-dressing/cross-decoration that is facilitated by donor derived exosomes. Then, the recipient DCs cross-dressed with clusters of donor derived exosomes present allo-MHC molecules to host immune system and thereby leading to allo-rejection.[28]

Exosomes as rejection biomarkers in organ transplantation

As exosomes carry a portion of molecular content such as proteins and nucleic acids from the cell it originates, the feasibility of utilizing exosomes as non-invasive biomarkers to monitor the status of allograft post-transplantation has been largely investigated. Besides, disparities

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in cargo and surface markers of exosomes have been observed between recipients with graft rejection and recipients with stable allograft, which offers an added detail to the potential deployment of exosomes as liquid biopsy to predict and diagnose allograft rejection. [13,30] Many studies have highlighted the use of exosomes as rejection biomarkers for various OTs. Some candidate exosome-based biomarkers reported in several studies for lung, kidney, heart and liver transplantations are described below.

Lung transplantation

Gunasekaran et al, have studied the exosomes of sera and bronchoalveolar lavage (BAL) fluid collected from 10 recipients with stable LT, 10 LT recipients diagnosed with BOS and 10 LT recipients with AR. They identified the expression of donor HLA and self antigens in exosomes collected from LT recipients with AR and BOS, but not in exosomes of recipients with stable LT. Besides, they demonstrated that exosomes with collagen type V expression can be detected in sera prior to AR or BOS diagnosis, thereby suggesting the potential use of exosomes as rejection biomarkers.[11] Sharma et al., have conducted a retrospective analysis that included plasma exosomes collected from 71 LT recipients (40 LT recipients diagnosed with BOS and 30 recipients with stable LT). They identified increased expression of lung self antigens (collagen type V and Kα1 tubulin) in exosomes of LT recipients with BOS up to a year before clinical diagnosis of BOS and suggested the use of circulating exosomes harboring lung self antigens as potential non-invasive biomarker for chronic rejection of LT.[31] Sharma and group conducted another retrospective study in circulating exosomes isolated from plasma samples of 19 pediatric LT recipients (13 recipients with stable LT and 6 LT recipients with BOS diagnosis). Unlike recipients with stable LT, higher expression of donor MHC class II, HLA class I, lung self antigens, costimulatory molecules, various transcription factors and 20S proteosome was detected in exosomes of LT recipients with BOS diagnosis. Similar to their other retrospective study, they reported the detection of lung self antigens in circulating exosomes of LT recipients with BOS diagnosis up to one year prior to clinical diagnosis of BOS, which further dictates the potential of exosomes as biomarkers.[32]

Kidney transplantation

In a cross-sectional study, Liu et al., have conducted proteomic profiling of urinary exosomes from 22 recipients with stable kidney transplant (KT) and 25 KT recipients with diagnosis of T cell mediated rejection (TCMR). They detected significantly higher expression of two proteins namely tetraspanin-1 and hemopexin in KT recipients with biopsy proven TCMR, which were stated by the authors of this study to be potent candidate biomarkers to diagnose TCMR in KT recipients.[33] Zhang et al., have analyzed the expression of several candidate genes in plasma exosomes from 38 no rejection KT recipients, 18 KT recipients with antibody mediated rejection (AMR) and 8 KT recipients with cell mediated rejection (CMR). Among the tested candidate genes, the expression of CCL4, gp130, DARC, TNFα, CAV1 and SH2D1B were relatively higher in KT recipients with AMR than CMR and control group, which were posited to be potential candidate biomarkers for identifying AMR in KT recipients.[34] Further, mRNA signature in exosomes of urinary samples from 175 KT recipients with no rejection and pathologic diagnosis of CMR and AMR was analyzed by El Fekih and group wherein, they noticed a difference in mRNA signature of urinary exosomes that potentially discriminated AMR from CMR.[35]

Heart transplantation

Kennel et al., have investigated the protein profile of serum exosomes from patients presented with various cardiac pathologies. In this study, the authors have included five groups encompassing 10 healthy controls, 10 heart failure patients without graft, 10 heart transplant (HT) recipients with no rejection, 10 HT recipients with acute cellular rejection (ACR) and 10 HT recipients with AMR. From proteomic profiling, they identified 15 differentially regulated proteins in no rejection and AMR/ACR rejection groups. Of these 15 proteins, 8 proteins were identified to be involved in adaptive immunity and complement activation, which could act as plausible biomarkers to diagnose AR in heart transplantation.[36] In a pilot study, circulating exosomes were isolated from plasma of 4 HT patients (3 patients without ACR/AMR and 1 patient developed AMR). Circulating exosomes isolated during 26 days of peri-operative follow-up demonstrated the expression of mRNA and troponin protein. Additionally, cd4 protein was detected in exosomes on post operative day 7 in one patient with AMR (resolved after treatment) and undetected in other 3 patients. From this study, the authors concluded that the analysis of cargo of circulating donor heart derived exosomes could act as a non-invasive option to diagnose AMR.[37]

Liver transplantation

Number of studies focusing on the deployment of exosomes as diagnostic rejection biomarkers in liver transplantation is relatively scarce than other OTs. In 2019, Zhang et al., have analyzed the protein profile of circulating exosomes isolated from patients with and without ACR. They demonstrated significantly higher expression of galectin-9 protein in exosomes of patients with ACR, which could be used to predict graft rejection in liver transplantation.[38] Though numerous studies divulged a plethora of potential exosome-based rejection biomarkers for various OTs, validation of these reported results using large cohort study with many patients is undeniable before extrapolating these exosome-based biomarkers to clinical application.

Exosomes in induction of allograft tolerance

The dual role played by exosomes in immunomodulation i.e., activation or suppression of immune response has opened the door for utilizing exosomes to induce immune tolerance. Many studies have explored the feasibility of using exosomes in inducing tolerogenicity and prolonging graft survival. For instance, Yang et al., have reported the tolerogenic potential of immature DCs derived exosomes (ImDCExos) by *in vitro* experiments and wistar rats' intestinal transplantation model.[39] Similarly, Pang et al., investigated the tolerogenic potential of ImDCExos in mice model of renal transplantation. They reported the crucial role of highly expressed miR-682 in ImDCExos which increases the graft survival rate and decreases inflammatory response. ImDCExos secreted miR-682 negatively regulated the mRNA level of its downstream target ROCK2 and increased the differentiation of regulatory T cells (T-regs), thereby conferring immune tolerance in the mice model.[40] In a recent study by Cui and group, next-generation sequencing assisted microRNA profiling of exosomes isolated from plasma of 58 liver transplant patients and 9 donors revealed the increased expression of miR-193-3p in exosomes of liver transplant patients with no rejection. DCs derived mi-193-3p down regulated the expression of its downstream target NLRP3 and promoted T-regs, which could confer immune tolerance and alleviate liver transplant rejection.[41] Furthermore, T-regs derived exosomes have also been explored recently for their tolerogenic potential. Tung et al., have reported that T-regs derived exosomes inhibited effector T cell proliferation, decreased proinflammatory cytokines (IL-2, IL-6, INF- γ) and increased anti-inflammatory cytokines (IL-4 and IL-10). They also used skin graft mice model and attested the ability of T-regs derived exosomes to limit skin allograft damage by reducing immune cell infiltration.[42] In addition to DCs derived exosomes and T-regs

derived exosomes, exosomes derived from mesenchymal stem cells were also investigated for inducing immune tolerance. For example, Wu et al., have demonstrated the tolerogenic potential of bone marrow mesenchymal derived exosomes (BMMSC-Exos) in mouse model of kidney transplantation wherein, differentiation antagonizing non-protein coding RNA (DANCR) in BMMSC-Exos promoted the differentiation of T-regs and conferred immune tolerance in the tested mice model by repressing the expression of SIRT1 in CD4+ T cells.[43] These findings elucidate the potential of using exosomes for promoting immune tolerance and increasing the survival rate of grafts.

Concluding remark

Extensive research on exosomes in recent decades has offered answers to several old long-standing conundrums in the field of transplantation. With growing number of evidence and progressive understanding of exosomes' role in transplant immunology, numerous studies directed towards the plausibility of deploying exosomes as non-invasive biomarkers and therapeutic tools to monitor transplant status and prolong graft survival rate, respectively have been recently reported. As non-invasive biomarkers, exosomes are expected to greatly support clinicians in tracking the status of allograft post-transplantation and diagnose allograft rejection. Furthermore, exosomes as immune tolerance inducing therapeutic agents are anticipated to lessen the life time dependency of patients on immunosuppressive drugs. Altogether, the current knowledge of exosomes provides new outlook in utilizing exosomes for improving the graft survival rate and quality of life of patients. Nonetheless, further in-depth investigations are warranted before taking exosomes to clinical applications.

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Conflicts of interest

Authors have no conflict of interest.

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