HHS Public Access

Author manuscript

Am J Transplant. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Am J Transplant. 2018 July ; 18(7): 1585–1586. doi:10.1111/ajt.14720.

Graft-derived exosomes. When small vesicles play a big role in transplant rejection

Gilles Benichou and **Aurore Prunevieille**

Center for Transplantation Sciences, Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Keywords

animal models: murine; autoantibody; autoantigen; basic (laboratory) research/science; heart failure/injury; heart transplantation/cardiology; immunobiology; rejection: T cell mediated (TCMR)

Recipient proinflammatory T cells recognizing donor major histocompatibility complex (MHC) molecules in a direct fashion trigger early acute rejection of cardiac allografts. In clinical settings, prevention of acute rejection is regularly achieved via continuous suppression of these T cells using immunosuppressive drugs, including calcineurin inhibitors. Nevertheless, within five years posttransplantation, up to 50% of patients suffer late cardiac allograft failure, the major pathological manifestation of which is chronic allograft vasculopathy (CAV). CAV is characterized by intimal thickening, smooth muscle cell proliferation, and accumulation of extracellular matrix, which result in arterial narrowing and eventually graft ischemia and fibrosis. There is a body of evidence showing that CAV is initiated via a process involving cells of both innate and adaptive systems. However, the immunological mechanisms underlying CAV are still largely unknown. Gaining insights into this question is critical to the design of strategies for the prevention and/or treatment of late cardiac allograft failure and CAV.

There is a clear association between indirect alloreactivity by $CD4^+$ T cells, the presence of donor-specific antibodies, and chronic allograft rejection. In addition, several studies have documented the presence of T cell autoimmunity and autoantibodies during chronic rejection. Original studies in our laboratory described de novo T and B cell responses to cardiac myosin (CM) in chronic rejection of cardiac allografts in mice and swine.[1] Subsequently, Kalache et al documented the relevance of anti-CM autoimmunity in patients with CAV.[2] Given that immunity to CM is known to cause autoimmune myocarditis, we hypothesized that CAV could be mediated through a process similar to that observed in chronic inflammatory autoimmune diseases. Subsequent reports from M. Rose and Mohanakumar's groups showed the presence of vimentin-specific autoimmunity in graft vasculopathy observed after heart transplantation in mice and patients.[3,4] Autoimmunity

Correspondence: Gilles Benichou, gbenichou@mgh.harvard.edu.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

against various self-antigens has now been documented during rejection of lung, kidney, and other organ transplants and therefore represents a general phenomenon in transplantation.[1] However, whether and how autoimmunity truly contributes to allograft rejection are still unclear.

In this issue of the *American Journal of Transplantation*, M. Sharma and colleagues revisited this issue using a model in which mice transplanted with a syngeneic heart were injected with rabbit anti-CM antibodies.[5] First, they observed that administration of anti-CM Abs at the time of transplantation (d0) was sufficient to induce graft rejection. This was associated with increased leukocyte infiltration of cardiac grafts, de novo production of mouse Abs against CM and vimentin (VIM) and expansion/activation of CM/VIM specific autoreactive $CD4^+$ T cells producing inflammatory cytokines (γIFN, TNFα and IL-17). Second, the serum of rejecting mice was shown to contain exosomes carrying CM, VIM and miRNAs involved in inflammation. Finally, administration of these exosomes to a mouse caused rejection of a syngeneic heart transplant. It is noteworthy that autoantibodies and rejectogenic exosomes were not detected in mice with stable graft functions. Another important observation was that administration of mice with anti-CM antibodies performed seven days posttransplantation (instead of d0) failed to induce autoimmunity and graft rejection. This suggests that anti-CM- mediated rejection occurs only in an inflammatory environment caused presumably by ischemia reperfusion injury associated with the surgical procedure.

Exosomes are microvesicles (50–100 nm) produced in the endosomes and secreted by a variety of cells during activation. Recent studies showed that exosomes released by allografts contribute to the host's immune response leading to their rejection. Apparently, recipient APCs displaying allogeneic MHC molecules acquired from donor exosomes (MHC cross-dressing) play a key role in the initiation of inflammatory direct alloresponses by T cells leading to acute allograft rejection.[6,7] In addition to direct alloreactivity, it is plausible that MHC and other proteins transported by graft-derived exosomes are regularly processed and presented as peptides by self-MHC molecules on recipient APCs thus eliciting indirect T cell alloresponses. Indirect T cell immunity drives alloantibody production and it is believed to be the driving force behind chronic allograft rejection. At the same time, there is accumulating evidence supporting the contribution of autoimmunity to selected graft tissue specific autoantigens in chronic rejection. Finally, recent studies have documented the contribution of exosomes carrying autoantigens in autoimmune diseases. Altogether, this raises the possibility that secondary indirect alloimmunity and autoimmune inflammatory responses may be elicited and perpetuated by graft-derived exosomes continuously released by the allograft. However, it is likely that such a cascade of events may only happen in an inflammatory environment caused by tissue injury or an infection. The results presented in the article by M. Sharma et al support this view. Indeed, in this study, mouse administration of anti-CM antibodies triggered an anti-CM inflammatory T cell response, which spread to VIM and caused the release of exosomes carrying both autoantigens outside the graft; a series of events presumably responsible for rejection of syngeneic heart transplants. Likewise, Dieudé et al described the ability of exosome-like vesicles from endothelial cells to induce anti-perlecan autoantibody production and accelerated rejection of aortic grafts in mice.[8] Further evaluation of the actual role of

exosomes carrying self-antigens in allograft rejection will require inhibition of graft exosome secretion in transplanted animals.

Autoantibodies are regularly found pretransplantation in patients and could contribute to rejection of allografts in a fashion similar to that described in this article.[9] In addition, graft injury caused by T and B cell inflammatory alloimmunity, including alloreactive antibodies, could promote the release of exosomes carrying pathogenic autoantigens by the allograft thus causing late acute or chronic rejection. These hypotheses must be investigated.

In conclusion, it is clear that presentation of graft tissue–specific antigens by recipient APCs in an inflammatory environment can trigger T and B cell autoimmune responses leading to chronic rejection. In clinical settings, auto-antibodies may be present in patients pretransplantation or produced as the result of B cell dysregulation due to T cell continuous suppression. At the same time, recent reports from A. Naji, T. Mohanakumar and other laboratories show the relevance of exosomes as biomarkers in chronic allograft rejection.[10,11] Together with Sharma's current study, this suggests that autoantibodies could initiate a local immune process, which spreads outside the graft via exosome release thus causing graft rejection.

References

1. Benichou G, Alessandrini A, Charrad RS, Wilkes DS. Induction of autoimmunity after allotransplantation. Front Biosci. 2007; 12:4362–4369. [PubMed: 17485380]
2. Kalache S, Dinavahi R, Pinney S, Mehrotra A, Cunningham MW, Heeger PS. Anticardiac myosin immunity and chronic allograft vasculopathy in heart transplant recipients. J Immunol. 2011; 187(2):1023–1030. [PubMed: 21677143]
3. Nath DS, Ilias Basha H, Tiriveedhi V, et al. Characterization of immune responses to cardiac self-antigens myosin and vimentin in human cardiac allograft recipients with antibody-mediated rejection and cardiac allograft vasculopathy. J Heart Lung Transplant. 2010; 29(11):1277–1285. [PubMed: 20615726]
4. Barber LD, Whitelegg A, Madrigal JA, Banner NR, Rose ML. Detection of vimentin-specific autoreactive CD8 + T cells in cardiac transplant patients. Transplantation. 2004; 77(10):1604–1609. [PubMed: 15239629]
5. Sharma M, Liu W, Perincheri S, Gunasekaran M, Mohanakumar T. Exosomes expressing the self-antigens myosin and vimentin play an important role in syngeneic cardiac transplant rejection induced by antibodies to cardiac myosin [published online ahead of print January 9, 2018]. Am J Transplant.
6. Liu Q, Rojas-Canales DM, Divito SJ, et al. Donor dendritic cell-derived exosomes promote allograft-targeting immune response. J Clin Invest. 2016; 126(8):2805–2820. [PubMed: 27348586]
7. Marino J, Babiker M, Crosby Bertorini P, et al. Donor exosomes rather than passenger leukocytes initiate alloreactive T cell responses after transplantation. Sci Immunol. 2016; 1(1):1–12.
8. Dieude M, Bell C, Turgeon J, et al. The 20S proteasome core, active within apoptotic exosome-like vesicles, induces autoantibody production and accelerates rejection. Sci Transl Med. 2015; 7(318): 318ra200.
9. Bharat A, Kuo E, Steward N, et al. Immunological link between primary graft dysfunction and chronic lung allograft rejection. Ann Thorac Surg. 2008; 86(1):189–195. discussion 196–187. [PubMed: 18573422]
10. Vallabhajosyula P, Korutla L, Habertheuer A, et al. Tissue-specific exosome biomarkers for noninvasively monitoring immunologic rejection of transplanted tissue. J Clin Invest. 2017; 127(4):1375–1391. [PubMed: 28319051]

11. Gunasekaran M, Xu Z, Nayak DK, et al. Donor-derived exosomes with lung self-antigens in human lung allograft rejection. Am J Transplant. 2017; 17(2):474–484. [PubMed: 27278097]