Involvement of Dendritic Cells in Allograft Rejection New implications of Dendritic Cell-Endothelial Cell Interactions

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Abstract: For almost half a century immunologists have tried to tear down the MHC barrier, which separates two unrelated individuals during transplantation. Latest experimental data suggest that a breakthrough *in vitro* is imminent. Dendritic cells (DCs),which activate naïve allo-reactive T-cells (TCs), play a central role in the establishment of allo-antigen-specific immunity. Allograft solid organ rejection is initiated at the foreign endothelial cell (EC) layer, which forms an immunogenic barrier for migrating DCs. Thus, DC/EC interactions might play a crucial role in antigen-specific allograft rejection. Organ rejection is mediated by host allo-reactive TCs, which are activated by donor DCs (direct activation) or host DCs (indirect activation). Direct allo-antigen presentation by regulatory dendritic cells (DCreg) can play an instructive role towards tolerance induction. Several groups established that, DCregs, if transplanted beforehand, enter host thymus, spleen, or bone marrow where they might eventually establish allo-antigen-specific tolerance. A fundamental aspect of DC function is migration throughout the entire organism. After solid organ transplantation, host DCs bind to ECs, invade allograft tissues, and finally transmigrate into lymphoid vessels and secondary lymphoid organs, where they present allo-antigens to naïve host TCs. Recent data suggest that *in vitro* manipulated DCregs may mediate allo-transplantation tolerance induction. However, the fundamental mechanisms on how such DCregs cause host TCs in the periphery towards tolerance remain unclear. One very promising experimental concept is the simultaneous manipulation of DC direct and indirect TC activation/suppression, towards donor antigen-specific allo-transplantation tolerance. The allo-antigen-specific long-term tolerance induction mediated by DCreg pre-transplantation (with simultaneous short-term immunosuppression) has become reproducible in the laboratory animal setting. Despite the shortcomings of laboratory animal studies, strong promises are deriving from these studies for clinical kidney, heart, and liver transplantation.

Key Words: Immune response, inflammation, rejection, arteriosclerosis.

INTRODUCTION

For a long time it was believed, that allogeneic T-cell (TC) responses differ from classical immune responses, mainly by the extraordinary strength of the TC mediated response to allo-MHC antigens *in vitro* without *in vivo* priming. It appears that, this is not an inherent feature of allo-MHC antigens but rather two different modes of TC activation, namely by direct and indirect allo-recognition pathways [1]. Direct recognition occurs if donor dendritic cells (DCs) prime recipient TCs and indirect recognition occurs if recipient DCs migrate into the allograft *via* endothelial cells (ECs), to take up foreign antigens. The latter are presented to host TCs in secondary lymphoid organs. Current understanding of transplantation immunology suggests that direct recognition initiates acute rejection and indirect recognition mediates long-term allograft rejection. During the course of vascularized solid organ transplantation, the first immune reactions are detectable at the interface between vasculature and adjacent tissue. Human ECs injured by ischemia and reperfusion are particularly vulnerable to neutrophil and DC adhesion and migration [2,3]. Early in the rejection process, grafts show a nonspecific peri-endothelial inflammation with early DC migration. Latest concepts in the field of DC immunobiology to induce donor-specific hypo-responsiveness and subsequent long-term allograft tolerance include donor-specific, pre-transplant DC transfusion, manipulation of DC/TC costimulation, manipulation of DCreg and TCreg, and finally the hindrance of vascular injury. Researchers have evolved several methods, which simultaneously target direct and indirect allograft recognition toward donor-specific tolerance induction. The most promising scheme for long-term allograft acceptance in the experimental animal setting includes donor-specific pre-transplantation transfusion of DCreg with peri-transplant short-term immunosuppression.

DC AND EC INTERACTIONS

Allograft ECs (AECs) form an immunogenic barrier between recipient circulating immunoactive cells and the transplanted organ, serving as antigen-presenting cells, as well as targets of lymphocyte reactivity. Activation of arterial endothelium predicts development of chronic transplant vasculopathy and increases risk of graft failure [4]. Repetitive alterations of the endothelial barrier result in response to injury mechanisms leading to endothelial dysfunction and intimal hyperplasia [5]. Important insults contributing to AEC-injury after transplantation may include preservation-injury, ischemia/reperfusion, innate and adaptive immune-system response, vascular denervation, viral infection (e.g. cytomega-

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lovirus), immunosuppressive therapy, and the occurrence of classical arteriosclerosis risk factors. Independent of the cause leading to AEC injury, EC activation/dysfunction occurs in association with modification in EC-dependent molecule expression. As a result of the continuing functional alterations of the endothelium, lymphocytes, monocytes and macrophages, migrate through the endothelium, inducing further activation of cytokines and growth factors, and in turn, initiating smooth muscle cell promotion [6-9]. The role of DC in induction of vascular inflammation and dysfunction is not well defined. However, cytokine release is a major component of DC activation. Release of cytokines and chemokines by DC may attract adaptive immune effectors within the vasculature [10,11].

Initially, researchers thought that there are crucial distinctions between rodents and humans, with regards, to vascular endothelium. The different amount of MHC class II expression seemed particularly important during transplantation [12]. Recent evidence suggests that MHC class II on rodent vascular endothelium is easily up regulated [13]. In contrast, human vascular ECs are constitutively expressing MHC class I and class II antigens [14]. The onset of alloreactivity, which takes place at the EC interface and includes DCs and TCs, might be significantly different between mouse and man. Nevertheless, the initial onset of allograft rejection correlates with a perivascular inflammation in both rodents and man. Liu et.al. showed the importance of the EC, DC, and TC network in a rat model of heart allo-transplantation. They demonstrated that tolerance induction by CD8+ FOXP3+ TCs correlated with the up-regulation of the inhibitory receptor, PIR-B an ILT4 orthologue , in DCs and heart ECs. Importantly, the tolerance induced was adoptively transferable, because long-term surviving heart allografts with PIR-B+ ECs were transplanted from a primary to a secondary recipient, without rejection [15]. In conclusion, we support the idea that ECs play a central role in the rejection process and that immunosuppressive agents acting directly on graft DCs or ECs might eventually induce tolerance.

DC MIGRATION

The specificity and efficiency of leukocyte binding to ECs depends on information transfer from the tissue to endothelium and from there to the DC. The objective of DC-endothelial interactions is to direct circulating cells into their appropriate tissue sites. There is a high degree of specificity in the interaction of ECs with circulating cells. Recirculation is the process whereby lymphocytes undergo repetitive cycles of migration from the circulatory system into tissue and back into the vasculature. Superimposed onto this is recruitment of immune cells to activated sites. The anatomic location and the nature of the inflammatory stimulus determine which leukocytes migrate to an inflammatory site. Usually, recruitment includes cells that do not re-circulate, such as neutrophils, eosinophils, and macrophages. Rainger and colleagues described the prototypic adhesion cascade when neutrophils were binding to ischemia-injured endothelium [16]. The adhesion cascade has at least three different steps: 1) P-selectin/PSGL-1 (EC/MC) mediated tethering; 2) IL-8 mediated triggering; and 3) ICAM-1 and ICAM-2 mediated adhesion [17]. To post a signal for passing leukocytes, EC produce chemokines and adhesion molecules. Regulation of expression of chemokines and adhesion molecules on endothelium has been frequently reviewed [18]. It is important to mention that among the strongest stimuli for expression of chemokine and adhesion molecules on endothelium *in vitro* are TNF-α, IL-1, IFN-γ, LPS and ischemia [18-22]. An essential feature of DC biology is their capacity to bind and transmigrate through activated ECs. With regards to transplantation immunology, there are at least three different mechanisms underlying DC motility from the blood stream through the endothelium into the underlying tissue and to their place of demise in the peripheral lymphoid tissues: a) DC:EC migration; b) lymphatic vessel reverse migration; and c) lymphoid tissue traffic. Blood monocytes (MCs) develop through a maturation process into DCs and become the most effective activators of naïve TCs. In order to fulfill such a prominent role in the adaptive arm of the immune system, MCs physiologically develop after endothelium migration either into motile mature DCs or resident macrophages (MPs) [23].

VASCULAR ADHESION MOLECULES REGULATE EFFECTOR CELL TRAFFICKING

DCs initiate an antigen uptake and -processing machinery once they leave the blood stream through the EC lining. Subsequently, DCs mature and enter lymphatic vessels through reverse migration to become resident in lymph nodes. Finally, DCs travel to TC dependent areas to present foreign antigen and to activate naïve TCs. The regulation of lymphoid traffic by adhesion molecules is one of the fundamental features of DC-EC interaction during the course of allotransplantation. A key issue is the regulation of TC and DC migration from the blood stream into grafted organs to lymphatic tissues and their subsequent recirculation. DCs first tether to ECs by binding to P-selectin/PSGL-1. Robert and coworkers showed that DCs express both HECA-452-reactive and non-reactive isoforms of P-selectin glycoprotein ligand 1 (PSGL-1) and can tether and roll efficiently on E- and P-selectin under flow conditions *in vitro*. They hypothesized that DCs in blood are constitutively poised at the interface of blood and skin, ready to extravasate upon induction of inflammation, and a rapid recruitment of DCs from the blood to tissues [24]. DCs finally adhere to ECs by binding to various ligands like PECAM (CD31), VCAM (CD106), and ICAM-1 (CD54). PECAM is expressed by DCs and on ECs. PECAM interacts homotypically in cell adhesion assays [25]. VCAM is expressed predominantly on vascular endothelium; it binds to VLA-4 and contributes to the extravasations of leucocytes [26]. ICAM-1 is expressed on endothelium, binding to LFA-1 (CD11a/CD18) and also the related integrins [27]. LFA-1 is expressed on DCs and has three ligands -ICAM-1, ICAM-2 and ICAM-3 - and was found to mediate lymphocyte adhesion to many cells, including endothelium [28]. In adhesion assays a considerable proportion of DCs binds to resting EC monolayers and this adhesion is inhibited by anti-CD11a and CD11b [29]. Additionally, it was shown that DC-SIGN, a DC-specific C-type lectin, supports tethering and rolling of DC-SIGN-positive cells on the vascular ligand ICAM-2 and ICAM-3 under shear flow, a prerequisite for emigration from blood. The DC-SIGN-ICAM-2 interaction regulates chemokine-induced transmigration of DCs across both resting and activated endothelium. Thus, DC-SIGN is central to the unusual trafficking

capacity of DCs, further supported by the expression of DC-SIGN on precursors in blood and on immature and mature DCs in both peripheral and lymphoid tissues [30,31]. Inflammation alters the trafficking patterns through LFA-1, ICAM-1 and ICAM-2, VCAM-1, PCAM-1, DC-SIGN, and other adhesion molecules on vascular endothelial and lymphatic vessels [32]. The cellular infiltrate associated with graft rejection is a special case of inflammation and a unique feature associated with allo-reactivity compared to syngeneic graft. Interestingly, allografts can be distinguished from syngeneic grafts by the upregulated expression of VCAM-1 and ICAM-1 and the appearance of IL-2, IL-4 and IFN-γ [33,34]. Pennfield *et al*. showed that syngeneic allograft transplantation leads to increased DC invasion during syngeneic allograft transplantation likely due to vascular injury [35]. Thus, the onset of organ rejection is likely to start at the EC interface between host and recipient. We hypothesized that modulating DC-EC interactions will be of significant importance for long-term survival after solid organ transplantation. Therefore, we explored new endothelial determinants of DC and EC adhesion and migration that might lead to increased vascular DC invasion. We identified that the impairment of the endothelial nitric oxide pathway, the induction of oxidative stress and pro-inflammatory cytokines induce DC adhesion on allogeneic ECs, and thereby might contribute to allograft long-term organ rejection and transplant vasculopathy [3].

TRAFFICKING OF APC DURING ALLO-TRANSPLANTATION

Donor DCs begin to migrate from the graft to the recipient lymphoid compartments, finding their way to both draining lymph nodes and the spleen of the recipient, finally initiating direct recognition. Over time, the migration of donor DCs to the recipient presumably diminishes. The final replacement of donor DCs by recipient DCs is well documented [36-38]. The reduction of donor DCs over time is obviously shifting immune reactions towards the indirect activation pathways of alloreactivity. These migration patterns seem to be mediated through CCR7 and CCL19 or CCL20, respectively [39-41]. We investigated *in vitro* how EC physiology changes heterologous DC migration patterns, eventually leading to all-graft long-term rejection. We have demonstrated that: i) high concentrations of calcineurin-inhibitors increase DC binding on allogeneic ECs; ii) high concentrations of calcineurin inhibitors increase DC migration through ECs; and iii) different adhesion molecule patterns on ECs are responsible for enhanced DC invasion under cyclosporine and tacrolimus exposure [42]. We speculate that the massive migration of DCs in the sub-endothelial space during allo-transplantation may change downstream events, potentially leading to allograft rejection.

THE ROLE OF DCS AND T-CELLS FOR ALLO-TRANSPLANTATION

The critical role of DCs for allograft destruction has been shown conceptually by the prolonged survival of donor DC-depleted grafts [43]. The importance of TCs as effectors has been confirmed experimentally by the demonstration that athymic mice accept allografts [44]. The importance of DC-TC interactions in the case of allo-transplantation was best exemplified by interruption of co-stimulatory receptors interactions like CD80:CD28 and CD86:CD29 by CTLA-4-Ig or CD40 and OX40 blockade, that reportedly prolongs allograft survival [45,46]. Additionally, Lambolez *et al*. showed that self-antigen presentation exclusively by peripheral DCs results in a very efficient clonal deletion of the majority of antigen-specific TCs. The surviving TCs remain in an anergic state [47]. Therefore, it has been emphasized that, DCs may mediate antigen-specific peripheral tolerance. Thus, it was important to know if tolerogenic DCs are naturally occurring. Lately, it has been shown consistently that immature DCs (iDCs) sample self-antigen in peripheral tissues constitutively. Such iDCs transport self-antigens to local lymphoid tissue to present processed self-antigens in a tolerogenic fashion. Huang *et al*. showed that iDCs carried apoptotic bodies from intestinal epithelial origin to draining mesenteric lymph nodes [48]. Additionally, Hemmi *et al*. confirmed that steady state migrating iDCs were loaded with skin antigens and were trafficking to regional lymph nodes [49]. Hawiger *et al*. wrote that, in the steady state, peptide-loaded DCs induce antigen-specific peripheral tolerance [50]. Suss *et al*. wrote that *in vitro* migratory iDCs deliver self-antigens towards regulatory, which finally mediate TC tolerance *via* the Fas/Fas-L pathway resulting in CD4+ TC apoptosis [51]. It is now widely accepted that migratory DCs travel to regional lymph nodes in the steady state with an inherent capacity to induce TCregs, which might induce peripheral antigen-specific tolerance. Jiang and coworkers identified such allopeptide-specific human regulatory CD4+ CD25+ TC (TCreg) [52,53]. Interestingly, Levings and colleagues showed that human non-proliferating CD4+CD25+ TCs that up-regulate CLTA-4 and secrete IL-10 upon stimulation, decrease the proliferative responses of CD4+ TCs to allo-antigens *in vitro* [54]. The function of IL-10 to limit and ultimately terminate inflammatory responses is now well established [55]. Finally, Min *et al*. described a feedback loop between tolerogenic DCs and allo-specific TCregs. They induced donor-specific tolerance in a fully MHC-mismatched murine model of cardiac transplantation. In this model, tolerogenic DCs induce the generation of TCregs from naïve TCs. Moreover, TCregs induce DC progenitors to mature into tolerogenic DCs [56]. In summary, we believe that naturally occurring tolerogenic DCs and TCs play a critical role in the maintenance of self-tolerance in the periphery. We hypothesize, that targeting DCregs and TCs *in vivo* might be the key for antigen specific allograft tolerance induction *in vivo*. We speculate, that stabilizing EC physiology during transplantation might decrease DC-EC interaction prolonging allograft survival rates.

PHARMACOLOGICALLY INDUCED REGULATORY DCS

It appears that the DC maturational stage affects TC function. In contrast to mature DCs (mDC) that are extraordinarily good stimulators of TC alloreactivity, immature DCs (iDC) are poor TC activators. When DCs are produced from human blood monocytes by culture in IL-4 and GM-CSF, they are weak initiators of immunity. Ex vivo DCs need to mature through toll-like receptor stimuli [57], CD40L [58], or inflammatory cytokines [59], or trans-endothelial migration to become potent stimulators of TC effector cell devel-

opment [60]. Surprisingly, allogenic TCs can become refractory to antigenic stimulation when cultured with immature DCs. This DC regulatory function requires DC/TC cell contact and is partially blocked by anti IL-10 antibodies. Thus, it has been proposed that tolerogenic TCs can be induced by immature DCs [61].

Recently naturally occurring immature and high IL-10 secreting DC were identified in mice and rat [62,63]. Several groups reported methods to convert iDCs into tolerogenic DCregs (DCreg) which are suppressing TC alloreactivity *in vitro* and vivo. IDCs have been alternatively matured into DCregs by modification of culture conditions, administration of maturation inhibitors, or genetic modification. DCregs become suppressive as a result of low expression of MHC-II molecules, costimulatory receptors and inflammatory cytokines (TNF-α and IL-12) and vascular adhesion receptors (ICAM-1) [64-68]. Other mechanisms of tolerance induction by DCs in the steady state may include the targeting of antigen *via* the inhibitory FCγRIIb, and the expression of IDO by human DCs which inhibit TC proliferation [69,70]. Another inhibitory receptor expressed by DCregs is TRAIL. TRAIL is up-regulated on DCs after stimulation with IFN-γ or TNF-α and induces apoptosis in activated TCs [71]. Growing evidence suggests that DCregs have a distinct phenotype by up-regulation of specific tolerogenic receptors such as FCγRIIb, TRAIL, ILT3, ILT4 and PD-L1 [72,73]. When considering the effect of IL-10 on DCs, it is important to note that IL-10 inhibited the production of IL-12 and expression of costimulatory molecules by various DC types, which correlates with its ability to inhibit primary allo-antigen-specific TC responses and eventually contribute to a state of anergy in allo-antigen or peptide-antigen activated TC. In general the effect of IL-10 producing DCs directly affects the function of TCs and inhibits IL-2, TNF, and IL-5 production depending on activation conditions [74-76]. In summary, latest experimental data suggest that IL-10 expression by DCs *in vivo* is associated with differentiation of a population of TCregs which suppress antigen specific responses.

FROM BENCH TO BEDSIDE?

For at least 30 years it has been noticed that pre-transplant blood or bone marrow transfusion could induce donor-specific hypo-responsiveness towards subsequent transplants [77,78]. The idea of donor-specific transfusion has now seen a revival because some immune regulatory features of DCs have been elucidated. It became evident that DCs can directly kill TCs [79] or induce anergy [80]. It appears that, depending on their maturation state, DCs can play a significant role in stimulation or inhibition of TC responses due to their expression of co-stimulatory or -inhibitory molecules (see above).

Latest tolerance induction schemes in the laboratory animal setting include pre-transplant inoculation of DCregs, followed by solid organ transplantation under initial short-term immunosuppression. Thus, direct and indirect allo-activation can be targeted [81-83]. DePaz *et al*. adoptively transferred rat DCregs combined with transient immunosuppression on day –7, resulting in donor-specific permanent graft survival in 50% of recipients. Rat iDCs were prepared from bone marrow in low dose GM-CSF and IL-4, for the generation of iDCs. DCreg injection of $1x10^6$ cells combined with transient immunosuppression resulted in donor-specific permanent cardiac allograft survival (>200days) in 50% of recipients. Analysis of intra-cytoplasmic cytokine production of CD4+ TCs from spleen of unresponsive cardiac allograft recipients showed up-regulation of IL-10 but down-regulation of IL-4 and IFN-γ [84]. Additionally, Garrovillo *et al*. demonstrated that tolerance can be induced in a rat cardiac allograft model by adoptive transfer of allopeptide pulsed host DCs [85]. Lutz showed that immature DCs are maturation resistant and prolong allograft survival *in vivo*, when they were administered 7 days before transplantation [86]. Finally, Bonham published that a marked prolongation of cardiac allograft survival was detected by DC maturation blockade *via* NF-kappa B and CTLA4 to generate stably immature murine DCs. The administration of such immature donor DCs before transplantation induced donor-specific tolerance [87]. In summary, pioneering work demonstrating increased allograft survival after pre-transplant infusion of DCs has prompted the evaluation of several approaches for the generation of DC with tolerogenic properties. These include identification of culture conditions for the propagation of DCregs, pharmacological manipulation of DCs to stabilize their tolerogenic phenotype, and genetic modification of DCs to impair their stimulating ability. These approaches have rendered DCs capable of prolonging experimental allograft survival and antigen-specific hypo-responsiveness in rodents.

CONCLUDING REMARKS

Achieving donor antigen-specific transplantation tolerance without chronic systemic immunosuppression remains the ultimate goal in the field of transplantation immunology.

Short term survival rates of allografts are high but long term allograft acceptance remains an obstacle with severe side effects such as increased cancer incidence [88-90]. The fundamental mechanisms, of tolerance induction remain elusive. Latest insights into transplantation immunology suggest that direct and indirect allograft recognition plays a significant role in the rejection process. Current concepts for increased allograft survival in rodent animal models of solid organ transplantation now include simultaneously targeting direct and indirect allo-recognition through DC manipulations. Further studies, which take both direct and indirect allo-recognition into consideration, are needed.

It appears that the rejection process starts at the endothelial allograft interface. ECs, DCs, and TCs play key roles in the initiation and maintenance of immune responses to organ allografts. Latest experimental data suggest that ECs, DCs, and TCs form a regulatory network. It is a major challenge to better characterize this regulatory network.

Recent data regarding tolerogenic DCs has driven the assessment of DC-based therapy of allograft rejection. Nevertheless, the basic principles on how to manipulate DCs towards antigen-specific tolerance induction *in vitro* and vivo still remain elusive.

From latest laboratory animal studies in rodents strong promises are deriving for clinical kidney, heart, and liver

transplantation. A major step is to translate the knowledge of rodent in-vitro and in-vivo studies into safe and effective therapies for primates. However many approaches in animal studies have been promising but have never made it into clinic. The central role of heterologous immunity as a barrier to transplantation tolerance should be kept in mind [91].

Undisputed proof for the clinical efficiency of DC-based tolerance induction vaccinations is missing. Eventually, DCs might even act towards autoimmunity [92]. However, there is now increasing experimental evidence demonstrating that DCregs migrate in response to allografts, subsequently inducing antigen-specific TC hypo-responsiveness. The pharmacological manipulation of DCs may facilitate the induction of transplant tolerance. We therefore suggest that *in vitro* and vivo pharmacologically manipulated DCs may represent the equivalent of regulatory migrating DC *in vivo*. With many immunosuppressive agents to choose from, we might witness the use of DCs as clinical reality in allotransplantation immunotherapy in the future [93].

ABBREVIATIONS

AEC	=	Allograft endothelial cells
CMV	=	Cytomegalovirus
C C	=	Chemokines
DC	=	Dendritic Cell
MC	=	Monocyte
MP	=	Macrophage
MD-DC	=	Monocyte derived DC
BM-DC	=	Bone marrow derived DC
TC	=	T cell
BC	=	B cell
APC	=	Antigen presenting cell
TCR	=	T cell receptor
MHC	=	Major histocompatibility complex
IL	=	Interleukin
CD	=	Cluster of differentiation
EC	=	Endothelial Cell

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