Review Article

Dendritic Cells in Transplant Tolerance

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ABSTRACT

Dendritic cells (DCs) are a heterogeneous family of professional APCs involved in priming adaptive immune responses. Donor DCs (direct pathway of allorecognition) and recipient DCs presenting processed donor major histocompatibility complex (MHC) as peptides (indirect pathway of allorecognition) participate actively in graft rejection by stimulating recipient T cell responses following organ transplantation. Recent studies have shown that DCs also play a central role in inducing and maintaining tolerance to self antigens (Ags) through deletion, anergy, and regulation mechanisms. It is easy to see how the remarkable functional plasticity of DCs renders them attractive therapeutic targets for immune modulation. Indeed, in the past few years, successful outcomes in rodent models have built the case that DC-based therapy may provide a novel approach to transplant tolerance. Ongoing research into our understanding of the mechanisms whereby DCs promote tolerance in the steady-state, together with development of biologically, pharmacologically and genetically manipulated *ex vivo* DCs to mimic/enhance their natural tolerogenicity, should warrant the success of these experimental DCs in establishing long-term allograft survival.

Keywords: Dendritic Cells, Graft Rejection, Tolerance

INTRODUCTION

Organ transplantation combined with the use of non-specific immunosuppressive drugs has become the routine treatment for therapy of renal, cardiac, hepatic and pulmonary failure. However, the complications associated with immunosuppressive drugs (1) and their limitations in controlling chronic rejection (2) have fuelled a growing number of studies by transplant immunologists in order to achieve a state of specific tolerance to the donor that lasts for the life of the recipient.

The use of *ex-vivo* manipulated DCs has become one of the viable strategies tested in experimental animal models for the induction of transplantation tolerance (3). Biologic, pharmacologic and genetic engineering approaches are currently being explored to potentiate the tolerogenicity of *ex vivo* generated donor- or recipient-derived DCs. These approaches are based on our current knowledge of the inherent regulatory properties of DCs to establish and maintain central and peripheral tolerance (4). Although there is now convincing evidence that transplantation tolerance can be achieved in rodents using DC-based approaches, the clinical efficacy of this approach remains to be determined and is being assessed in clinically-relevant non-human primates' models. This review highlights the role of DCs in immunity and tolerance and summarizes the latest developments in DC-based vaccines for prevention of allograft rejection.

DENDRITIC CELLS AND IMMUNITY

The induction of immunity depends on the recognition and capture of foreign antigens (Ags), the transport of foreign antigens from their site of initial exposure to the T cell areas of draining lymph nodes, and finally the instruction of both Ag-specific polarized T helper type 1 (Th1)-cells (responsible for cell-mediated immunity) and Th2-cells (that provide help to B cells and control humoral immunity) (5) (Figure 1). DCs constitute a family of antigen-presenting cells (APCs), with inherent abilities (i.e., antigen sampling and migratory capacities combined with sensing and translating environmental cues) to orchestrate both humoral and cell-mediated forms of immunity (6-8) (Figure 1A). In humans and mice, at least two distinct subsets of DCs, myeloid DC (mDC) and plasmacytoid DC (pDC), both with an impressive degree of flexibility or "plasticity" in response to different microbial and environmental stimuli have been described and reviewed (9, 10).

DCs residing in the interstitial space of most peripheral tissues including commonly transplanted organ/tissues, express various receptors such as calcium-type lectin receptors (mannose receptor, DEC [CD]-205, langerin, dectin), immunoglobulin receptors (FcRI/CD64, FcRII/CD32) and complement receptors (CD11b/CD18, CD11c/CD18), which allow these cells to recognize and internalize exogenous Ags efficiently through receptor-mediated endo- macro- or phagocytosis (11).

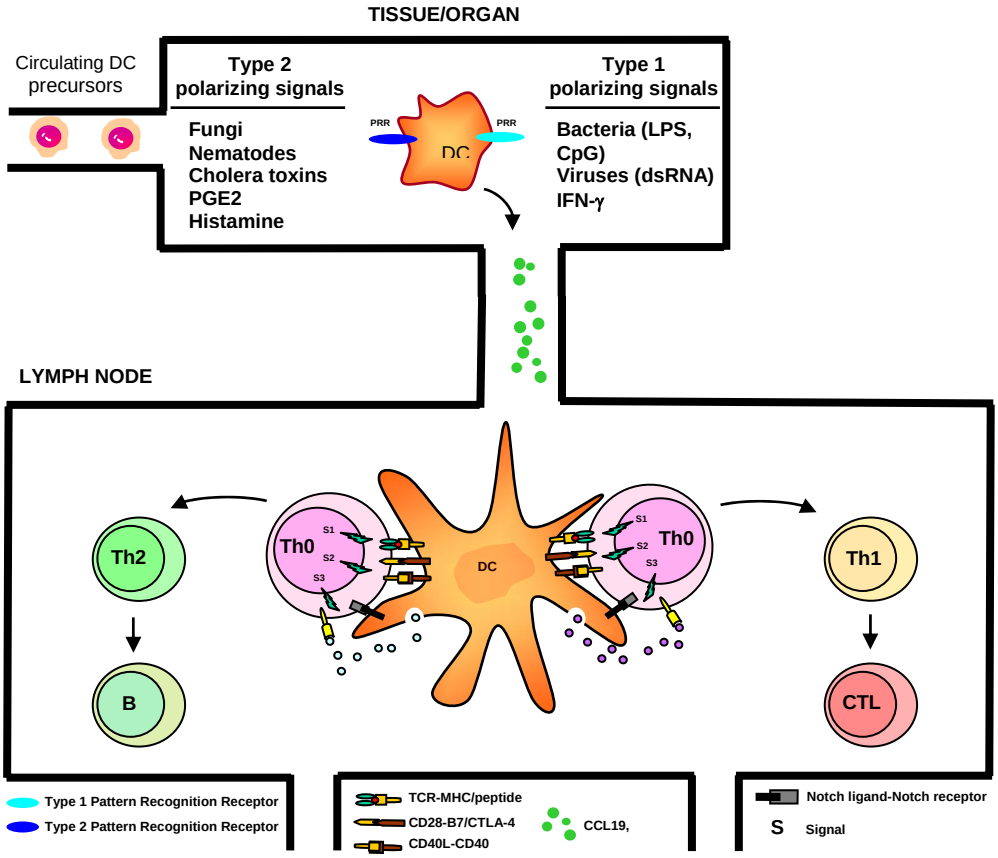

Figure 1. Schematic representation of an immune response following tissue damage or infection. Upon exposure to pathogens, and/or inflammatory mediators released by damaged tissue cells, tissue-resident DCs undergo maturation and migrate to the T cell area of draining lymph nodes (LNs) where they unravel collated information about the affected tissue to naïve T cells and promote different types of immune responses (Th1/Th2 effector cells).

Numerous maturational stimuli including endogenous factors released by necrotic cells (eg. heat-shock proteins), pro-inflammatory cytokines (e.g., TNF; GM-CSF; IL-1β; IFNα) secreted by bystander cells, exogenous microbial products (e.g., LPS; CpG rich DNA; ssRNA) that bind to Toll-like receptors (TLRs) or other pattern recognition receptors, and activated T cells that express ligands (e.g., CD40L [CD154]) for co-stimulatory molecules of the TNF receptor (TNFR) family (6) trigger the expression of the chemokine receptor CCR7 on Ag-bearing DCs and direct them towards afferent lymphatics and T cell areas of draining lymph nodes where the CCR7 ligands (CCL21, CCL19) are expressed (12, 13). During this migration, DCs process the Ags into immunogenic peptides and assemble surface MHC-peptide complexes that can be decoded by the T-cell receptor (TCR) on T lymphocytes (14, 15). These DCs also upregulate costimulatory molecules (CD40, CD80 and CD86) and intracellular adhesion molecules (CD54, CD58) that are essential for full activation of Ag-specific, naïve T lymphocytes of the adaptive immune response (16).

Maturing DCs are the most significant source of IL-12, the principal cytokine that drives Th1 polarization (17, 18). Several factors in the microenvironment at the time of DC maturation have been shown to dictate whether DCs will produce IL-12 and initiate

Th1 responses (19) or have their IL-12-producing capacity suppressed and initiate Th2 responses (7). For example, lipopolysaccharide (LPS) or bacteria (20, 21), poly (I:C) (22), and viruses (23) can all induce IL-12 production in DCs. Furthermore, environmental instruction in the form of IFN-γ secreted by NK cells during the course of viral infection, induces stable IL-12 production and instructs DCs for strong Th1-promoting capacity (19). Conversely, a variety of microbial stimuli, such as components of fungi (24), nematodes (25), and cholera toxins (26), can program DCs to induce Th2 responses. In addition, environments rich with mediators such as IL-10 (27), IL-4 (28), and agents with cAMP-elevating potential, such as PGE2 (29), β2 agonists (30), and histamine (31), all downregulate IL-12 production (7) and instigate the Th2-promoting capacity in DCs.

In response to certain microbial stimuli and tissue-derived factors, DCs can also instruct the distinct Th-cell fates by selectively expressing members of the Notch ligand families (32). For example, the microbial signal, LPS, induces DCs to express Delta, which is associated with conditions that stimulate Th1 responses. Conversely, environmental and microbial signals such as PGE2 and cholera toxin induce DCs to express Jagged, which is associated with conditions that stimulate Th2 responses.

DENDRITIC CELLS AND TOLERANCE

Tolerance is the specific inability of a host to respond to antigens and is generated both centrally and peripherally. Apart from their role in priming adaptive immune responses, DCs have a role in both central (33) and peripheral tolerance (4). During ontogeny in the thymus, thymic DCs contribute to negative selection, a process by which T cells that recognize MHC/self peptides with high avidity undergo apoptosis and are deleted (34-36). Several studies suggest that in the steady state, tissue-resident immature or semi-mature DCs (37, 38) that capture protein Ags, especially from cells dying through the normal process of cell turnover, may be critical in maintaining self-tolerance to the Ags not presented by thymic DCs within the neonatal period. Finkelman et al (39) showed that following intravenous administration of the rat IgG mAb 33D1 which recognizes a surface molecule expressed specifically by DCs, mice develop T-cell unresponsiveness to the rat IgG. Using hen egg lysozyme (HEL) 46-61 peptide fused to a DC-restricted endocytic receptor (DEC-205) monoclonal antibody, Hawiger et al (40) demonstrated that *in vivo* peptide-loaded DCs induce Ag-specific peripheral T-cell tolerance. Importantly, this peripheral tolerance can be converted to immunity if the anti-DEC-205/HEL is given together with the DC maturation stimulus, anti-CD40 (40). These findings were extended by Bonifaz et al (41) who used a similar approach of DEC-205-mediated targeting of ovalbumin (OVA) Ag to DC in situ and demonstrated that the cross-presentation of OVA by DC *in vivo* under steady state conditions induces OVA-specific TCR transgenic $CD8^+$ T cell tolerance.

T-cell death, T-cell anergy and active suppression by T regulatory (Treg) cells are all proposed models to describe the mechanisms by which immature or semi-mature DCs induce peripheral T-cell tolerance. The concept of deletional tolerance, i.e. rapid death of autoreactive T cells, derives from observations made by Suss et al (42) who showed that a subset of resident DCs within mouse lymph nodes express Fas ligand (CD95L) and are therefore able to mediate apoptosis in potentially self-reactive T cells after Ag encounter. There is also evidence for this subset of DCs to constitutively express trypto-

phan-catabolizing enzyme indoleamine 2,3 dioxygenase (IDO) (mouse ($CD11c^+CD8\alpha^+$) (43) and human ($CD123/IL\text{-}3R\alpha^+$, $CCR6^+$) (44)) which may subvert T-cell responses by promoting activation-induced cell death (44, 45).

Kuwana et al (46) reported that immature plasmacytoid DCs (pDCs), freshly-isolated from human peripheral blood, induce Ag-specific anergy (a state in which T cells recognize Ag in the absence of costimulation (47)) in $CD4^+$ T-cell lines. This model was further supported by Kawahata et al (48) who used transgenic mice expressing nuclear autoAg to demonstrate that continuous presentation of the self-peptide by immature DC in the steady-state induces anergy in $CD4^+$ autoreactive T cells and leads to peripheral tolerance.

The priming of Treg cells *in vivo* ($CD4^+CD25^+$ (49, 50) and NKT (51)) and *in vitro* (Tr1 (52), Th3 (53), $CD8^+CD28^-$ (54), $CD3^+CD4^-CD8^-$ (55)) by DCs that eventually inhibit the responses of other effector (helper and killer) lymphocytes has emerged from *in vitro* and *in vivo* studies of immature DCs. Jonuleit et al (56) showed that repetitive *in vitro* stimulation of naive allogeneic human T cells with immature, monocyte-derived DCs leads to the generation of non-proliferating, interleukin-10 (IL-10)-producing Treg cells. These cells inhibit the proliferation of Th1 cells in a contact-dependent, but Ag-nonspecific manner. The *in vivo* biological significance of these findings has been highlighted by Dhodapkar et al (57), who injected autologous monocyte-derived immature DCs pulsed with influenza matrix peptide subcutaneously in two human volunteers. They reported an Ag-specific inhibition of $CD8^+$ T cell killing and the appearance of peptide-specific IL-10-producing T cells, accompanied by a decrease in the number of interferon (IFN)-γ-producing T cells. This model is further supported by studies showing that DCs found either in the bronchial (58) or intestinal mucosa (59, 60) can induce Treg cell populations. In the respiratory tract, DCs produce large amounts of IL-10 following encounter with Ag, and induce the production of IL-10-producing Tr1 cells (61). In the gut, DCs preferentially induce Th2/Th3 cells that secrete IL-4, IL-10 and TGFβ (60) and play an important role in maintaining tolerance to oral Ags.

DONOR DENDRITIC CELLS AND TRANSPLANT REJECTION

Several observations have supported the idea that donor DCs are involved in allograft rejection. Following transplant surgery, graft-resident donor APCs migrate as 'passenger' leukocytes to the secondary lymphoid tissue of the recipient (62, 63), where they present allogeneic major histocompatibility complex (MHC) molecules to recipient T cells through a mechanism known as the *direct pathway of allorecognition* (donor MHC/peptide-recipient T cell) (64) (Figure 2). Original studies revealed that a period of *in vitro* culture of thyroid (65-67) or pancreatic islet (68) allografts or 'parking' the kidney in an intermediate recipient before retransplantation (69), could prolong graft survival, presumably due to the purging of donor passenger leukocytes. Lechler and Batchelor (69) further showed that injection of small numbers of donor DCs into the recipients of APC-depleted rat renal allografts provokes rapid graft rejection. The fast rejection of APC-depleted allografts in these experiments provided evidence that donor DCs are the key alloAg-presenting cells capable of priming naive T cells with direct allospecificity. Further credence to the role of the direct pathway emerged from studies showing that the reconstitution of MHC II-deficient/$Rag1^{-/-}$ mice with syngeneic $CD4^+$ T cells leads to rejection of MHC *class* II-expressing cardiac allografts (70). Given that

these mice had no $CD8^+$ T cells and lack self-MHC class II molecules, the results indicate that the direct pathway of allorecognition is sufficient to mediate allograft rejection in this particular model.

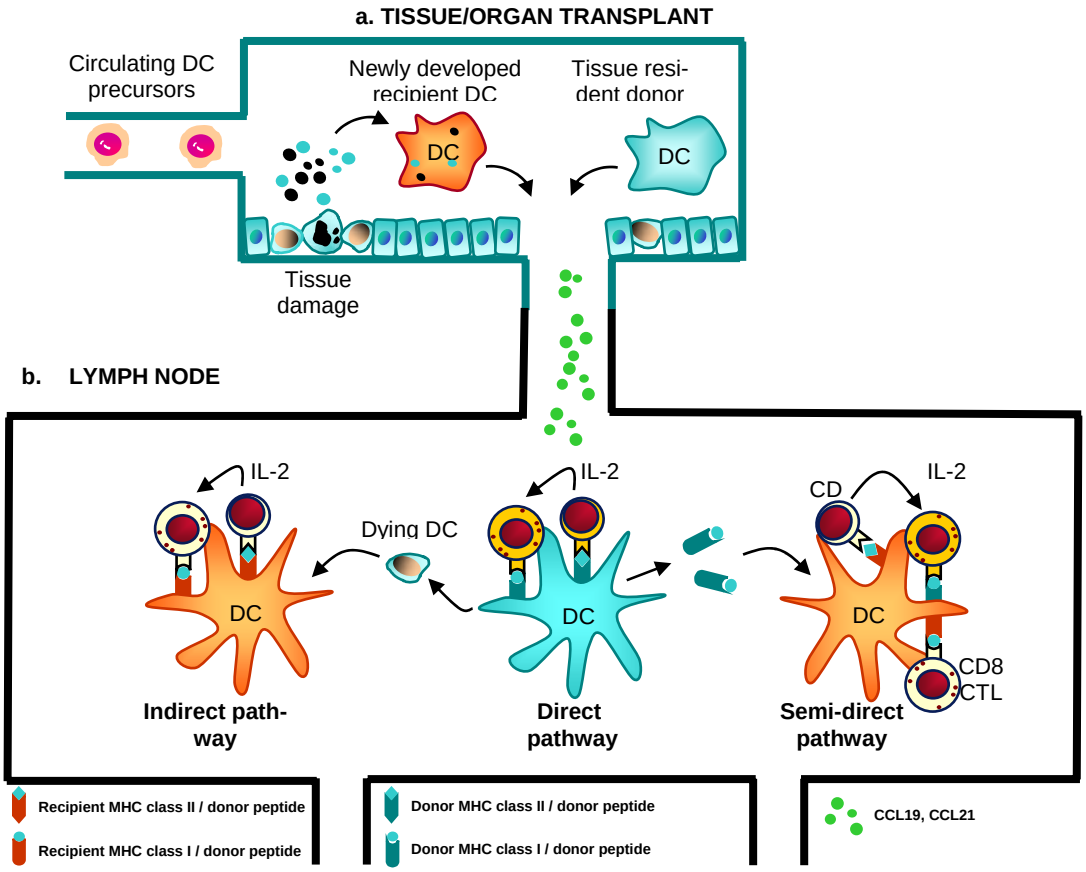

Figure 2. Schematic representation of pathways of allorecognition that mediate organ rejection. Donor-derived DCs trafficking through the draining LNs of the recipient prime recipient T cells via the direct pathway of allorecognition. Recipient DCs capture, process and present donor-derived antigenic materials (e.g. dying or apoptotic cells) and prime recipient T cells via the indirect pathway of allorecognition. Recipient DCs acquire intact donor-derived MHC molecules that are shed from the surface of donor cells (e.g. soluble MHC molecules) and prime simultaneously recipient T cells via both direct and indirect pathways of allorecognition.

The inflammatory response or tissue injury that follows transplantation surgery and the associated 'danger signals' (71, 72), combined with the well-recognized predominant role of donor passenger DCs in the instigation of acute allograft rejection provides a rational basis for their manipulation to modify transplant outcome.

THERAPEUTIC POTENTIAL OF DONOR TOLEROGENIC DENDRITIC CELLS

The development of techniques to generate large numbers of DCs *in vitro* with selective enhancement of their tolerogenic properties by use of various biological agents (i.e. GM-CSF alone (73-78) or with TGF-β(79), and/or IL-10 (27, 80-82)) has opened up the

possibility of evaluating DC potential as therapeutic vectors of transplant tolerance. The pioneering studies of Lu et al (73) and later others (77) showed that DCs propagated from normal mouse bone marrow (BM) in low concentrations of GM-CSF induce alloAg-specific T cell hyporesponsiveness. Intravenous administration of these immature donor-derived DCs before transplantation (day -7) prolonged the survival of pancreatic islet (74) or vascularized heart (75, 78) allografts in non-immunosuppressed recipients. In an effort to minimize a potential drawback of this approach (i.e. the maturation of the injected donor DCs within the recipients), some investigators have administered immature donor-derived DCs with a short course of anti-CD40L (anti-CD154) mAb (83-86), or have propagated the DCs with one or more biological agents to promote resistance to maturation before administration (78, 82, 87). Of particular interest, Sato et al (87) found that mouse BM-derived DCs generated with IL-10, TGF-β, and LPS in addition to GM-CSF, are not only resistant to further maturation, but can also induce Ag-specific $CD4^+CD25^+CD152^+$ Treg cells in the transplant recipients and can protect the mice from lethal, allogeneic BM-induced graft-versus-host disease.

Since then, a diverse variety of pharmacological agents including aspirin (88, 89), the vitamin D3 metabolite 1α,25-(OH)2D3 and its analogs (90-92), glucosamine (93), the antioxidant *N*-acetyl-*l*-cysteine (94-96) and immunosuppressive drugs (corticosteroids (97-99), cyclosporine A (100), rapamycin (101), deoxyspergualin (102), and mycophenolate mofetil (92, 103)) have been used in an attempt to obtain DCs with a stable, immature phenotype. In general, these agents affect DC activation/maturation by inhibiting nuclear translocation of specific members of the NF-kB family of transcription factors (104). One of the many examples of pharmalogical approaches *in vivo* (91, 92, 99, 102, 105, 106) is the administration of male donor-derived DCs generated in the presence of a vitamin D3 analog to female recipients that induces indefinite survival of syngeneic skin grafts expressing minor male Ags in 60% of recipients (91). Notably, Gregori et al (92) demonstrated that injection of donor-derived DCs generated in the presence of the active form of vitamin D3 [1α,25-(OH)2D3], in combination with mycophenolate mofetil, induces tolerance to fully mismatched mouse islet allografts, most likely due to the expansion of $CD4^+CD25^+CD152^+$ T cells. Targeting the NF-kB cell activation pathway specifically by antisense oligonucleotides has proved to be an alternate means when promoting a stably immature state in DCs (105, 106). Indeed, donor-derived DCs propagated in GM-CSF and NF-kB ODN exhibit selective suppression of costimulatory molecule expression without inhibiting MHC class I or II antigen expression. Administration of these DCs to fully allogeneic recipients as a single i.v. dose, 7 days before organ transplantation, significantly prolongs graft survival (105).

Using gene transfer technology, several investigators have modified donor-derived DCs to express 'immunosuppressive' molecules that can (1) inhibit or block cell-surface costimulatory molecule expression (e.g. IL-10 (107, 108), TGF-β(109), or CTLA4-Ig (110-113)), (2) prevent proliferation of allogeneic T cells (IDO) (114), and (3) promote the deletion (apoptosis) of Ag-specific T-cell clones (e.g. FasL (115)). Although, these modified DCs have been able to prolong the survival of kidney (109), vascularized heart (112, 115), pancreatic islet (113) and skin (108) grafts in MHC mismatched recipients, the success is limited in part by the potential of the gene delivery viral vectors (e.g. adenovirus [Ad]) to promote DC maturation. To overcome this limitation, Bonham et al (112) described the combined use of NF-kB ODNs and rAd vectors encoding CTLA4-Ig (Ad CTLA4-Ig) to generate stably immature murine myeloid DCs that secrete the potent costimulation blocking agent. Administration of Ad CTLA4-Ig ODN-treated

donor DCs before transplant promoted apoptosis of activated T cells and significantly prolonged MHC-mismatched vascularized heart allograft survival, with long-term (>100 days) donor-specific graft survival in 40% of recipients.

RECIPIENT DENDRITIC CELLS AND TRANSPLANT REJECTION

Lechler and Batchelor were first to recognize another pathway of allostimulation in graft rejection. Based on their original experiments with donor DC-depleted kidney grafts (69, 116), they proposed that when recipient APCs traffic into the graft as part of the initial inflammatory infiltrate, they capture, process and present fragments of donor alloAgs to recipient T cells through a mechanism called the *indirect pathway of allo-recognition* (self-MHC/donor MHC derived peptide-recipient T cell) (64, 117) (Figure 2). Their hypothesis has been supported by evidence from several experimental models (118-121). Notably, Auchincloss et al (120) showed that MHC class $I^{-/-}$ recipient mice (that lack $CD8^+$ T cells) rapidly reject MHC class II-deficient skin grafts lacking MHC class II Ags responsible for stimulating $CD4^+$ T cells. They concluded that graft rejection is mediated by $CD4^+$ T cells that recognize donor Ags presented in association with recipient class II molecules. Later on, Inaba et al (122) provided direct evidence for recipient DC involvement in indirect pathway allorecognition. They demonstrated that within two days of injection of H2-Eα-bearing DCs into H2-A^b recipients, most of the recipient DCs in the draining lymph node become reactive to Y-Ae, a monoclonal antibody specific for a peptide fragment from the H2-Eα chain presented on H2-A^b products. This observation implies that when migratory donor passenger leukocytes die upon reaching the lymph nodes, they are phagocytosed and processed by resident recipient DCs.

Lechler et al has recently proposed another mode of allorecognition termed the 'semi-direct pathway' (123, 124). They described that in this pathway, trafficking recipient DCs that have acquired intact MHC molecules shed from donor cells could contribute to allograft rejection by stimulating recipient T cells with both direct and indirect alloreactivity (Figure 2).

THERAPEUTIC POTENTIAL OF RECIPIENT TOLEROGENIC DENDRITIC CELLS

Given that the role of the direct pathway of allorecognition diminishes with time after transplantation, while that of the indirect pathway appears to be sustained and participates in chronic rejection, efforts have been made to utilize recipient DCs to promote tolerance. In an attempt to induce donor-specific tolerance, recipient BM- or thymic-derived DCs pulsed with immunodominant donor MHC I-derived allopeptides were injected intravenously or into the thymus of recipient rats, 7 days before transplant, in combination with antilymphocyte serum (ALS). This approach led to permanent survival (>200 days) of cardiac or islet allografts (125-128). Although limited by the necessity to identify donor MHC peptides, these approaches provided evidence for the therapeutic potential of recipient DCs in the induction of acquired thymic and systemic tolerance.

Few clinically applicable studies have been conducted so far on the manipulation of recipient DCs (129-131). These protocols illustrate that genetically or pharmacologically modified recipient DCs combined with additional treatment (in most cases) are able to promote systemic tolerance via a number of mechanisms that include deletion (129), anergy (131) as well as regulation (130). One example of such protocols showed that using donor DC-recipient DC hybrids engineered to express FasL delays the onset of alloAg-specific graft-versus-host disease (129). Another example (130) showed that the preoperative infusion of dexamethasone-treated F1 DC, followed by CTLA4-Ig, promotes the indefinite graft survival and immune regulation via the indirect pathway in a rat kidney transplant model. Recently, Beriou et al (132) reported that administration of non-pulsed recipient DCs and suboptimal treatment with LF 15-0195 (deoxyspergualin analog) induces the indefinite cardiac allograft survival in recipients, perhaps due to the development of regulatory mechanisms.

Several laboratories have explored the idea of inducing Ag-specific peripheral tolerance by targeting donor-derived dying or apoptotic cells to *ex vivo* modified recipient DCs (95, 133) or to *in vivo* recipient DCs in the normal steady-state (134-138). Xu et al (133) found that a single administration of *ex vivo*-generated recipient DCs, retained in an immature stage (NF-kB ODN decoy pretreatment) and loaded with donor-derived apoptotic cells, suppresses undesired immune reactivity and significantly prolongs cardiac allograft survival. More recently, Taner et al (131) demonstrated that multiple infusions of rapamycin-treated, alloAg-pulsed recipient-derived DCs prior to transplantation prolongs fully MHC-mismatched heart allograft survival (>100 days) in 40% of recipients. Lastly, Wang et al (138) reported that infusion of donor apoptotic cells combined with CD4-CD154-blockade inhibits the systemic anti-donor response and results in indefinite graft survival.

CONCLUSIONS

One of the major challenges of transplant immunologists has been to understand and mimic the tolerogenic potential of DCs in hopes of circumventing the complications of non-specific immunosuppression, as well as preventing chronic rejection. While there has been enormous progress in our understanding of tolerance mechanisms, optimism about a DC-based approach in clinical transplantation has to be tempered with the fact that our insight into the mechanism(s) employed by DCs to induce/maintain peripheral T cell tolerance in the normal steady state remains partial. Thus, it is important to establish reliable and quantitative assays for monitoring the efficacy of DC-based tolerance induction (deletion, anergy and regulation) in order to discover molecular signatures of tolerance and to elucidate the mechanisms whereby DCs induce/maintain peripheral tolerance.

Another challenge in this field is to identify and optimize the most successful DC-based strategies, applicable to both live and cadaveric organ donors (e.g., heart, lung), and to evaluate these in a clinically-relevant, non-human primate model of transplantation. Based on various DC-based approaches used in animal models of transplantation and cancer vaccines, we can envisage that intravenous injection of pharmacologically (e.g., Vitamin D3, Dexamethasone, Rapamycin) treated monocyte-derived DCs loaded with donor antigens (e.g., donor apoptotic cells, whole cell lysates), 7 days prior to organ transplant fits well with live organ donors and significantly prolongs graft survival. But,

it should be taken into account that the injection of cryopreserved recipient DCs loaded with donor antigens within one day prior to organ transplantation remains the only viable option for cadaveric organ donors. Thus, strategies that promote inactivation of the indirect pathway, pertinent to both live and cadaveric organ donors, clearly merit more extensive investigation into using recipient-derived tolerogenic DCs.
Worth mentioning is that exploiting the donor and/or recipient tolerogenic DCs in clinical settings requires a better understanding of the interplay between the three pathways of alloAg presentation because they may contribute in concert to mediate transplant rejection during the course of DC-based tolerance induction. Only when combined with additional regimens (e.g. immuosuppressive and costimulatory blocking agents), donor and recipient DCs have shown considerable promise as promoters of transplant tolerance in rodent models of organ transplantation (>100 days survival) (Table 1).

Table 1. Therapeutic effects of modified donor or recipient DCs in promotion of indefinite transplant survival

DC source	Species	DC Treatment	Additional treatment	Route of injection	Transplant model	MST (survival %)	Ref
Donor splenic DCs	mouse	None	Anti-CD40L mAb administration	i.v.	Heart	>100d (100%)	(85)
Donor BM-derived DCs	mouse	Low GM-CSF	Anti-CD54 mAb+CTLA4Ig administration	i.v.	Heart	>100d (100%)	(139)
Recipient BM-derived DCs	rat	Donor MHC class I peptide (RT1.Au)	Anti-lymphocyte serum administration	i.t.	Heart	>150d (100%)	(126)
Recipient BM-derived DCs	rat	Donor MHC class I peptide (RT1.Au)	Anti-lymphocyte serum administration	i.v.	Pancreatic islet	>200d (100%)	(127)
Recipient thymic and BM-derived DCs	rat	Donor MHC class I peptide (RT1.Au)	Anti-lymphocyte serum administration	i.t. or i.v.	Pancreatic islet	>200d (100%)	(128)
Recipient thymic DCs	rat	Donor MHC class I peptide (RT1.Au)	Anti-lymphocyte serum administration	i.v.	Heart	>200d (100%)	(125)
F1 BM-derived DCs	rat	Dexamethasone	CTLA4-Ig administration	i.v.	Kidney	>100d (100%)	(130)
Recipient BM-derived DCs	rat	None	LF 15-0195 administration	i.v.	Heart	>100d (100%)	(132)

GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor, CTLA4-Ig: Cytotoxic T-lymphocyte-associated Antigen 4-Ig, i.t: intrathymic, i.v: intravenous; MST: Median Survival Time, PBL: Peripheral Blood Leukocytes

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