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Dendritic cells and Chemokine-Directed Migration in Transplantation: Where are we Headed?

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Summary

The role of dendritic cells (DC) in transplantation is often overshadowed by the more prominent roles of T and B cells, which directly interact with, and in the absence of immunosuppressive therapy, destroy the allograft. It has become increasingly recognized, however, that these potent antigen (Ag)-presenting cells exert control over the immune response, and regulate the balance between tolerance and immunity to transplanted organs and tissues. The role that chemokines play in influencing DC function with impact on regulation of immune responses against the graft is only beginning to be understood. Herein we consider how the manipulation of DC trafficking during an alloimmune response can affect graft outcome.

Keywords

dendritic cells; chemokines; transplantation; T cells

As the sole antigen (Ag)-presenting cells (APC) capable of transporting Ag from the periphery to secondary lymphoid tissues for the activation of naïve T cells, dendritic cells (DC) are essential regulators of the balance between allograft tolerance and immunity. Although rare, these ubiquitous cells are transferred as donor “passenger leukocytes” in virtually every transplanted organ or tissue. They thus are believed to have a significant impact on the initiation of acute graft rejection by what is termed the “direct pathway” of allorecognition. Further, the uptake of Ag shed from the graft by recipient immature DC is believed to lead to long-term (chronic) rejection of the transplant mediated by “indirect” allorecognition. It is generally understood that immature DC are recruited to sites of inflammation by inducible chemokines. Thereafter, they are directed to draining secondary lymphoid tissues by constitutive chemokines (i.e., CCL19 and CCL21) via upregulation of CCR7, concomitant with their acquisition of other maturation hallmarks (e.g., loss of Ag endocytic ability, upregulation of Ag-presenting and co-signaling molecules, and acquisition of potent naive T cell stimulatory

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ability) (1). However, little is known about the specifics of chemokine-directed trafficking of Ag-presenting host vs donor DC in relation to activation of naive T cells and the initiation of immune responses to allografts, despite the fact that Ag-specific immune tolerance is the principal goal in transplant-related immunological research.

DC trafficking pathways

Numerous studies have shown that immature human and mouse blood- and bone marrow-derived DC subsets express a panel of inflammatory chemokine receptors (CCR1-6,8,9, CXCR3,4, CX_3CR1) [Table 1 and reviewed in (1-5)]. Few studies (6,7) have been performed, however, to evaluate the migratory response(s) of immature DC isolated from peripheral tissues to inflammatory chemokine ligands. Yet it is these chemokines that are most likely to have a significant impact on DC recruitment and graft survival in a transplant setting. In the few studies that have been performed, it was determined that immature, tissue-isolated (e.g., liver) DC do not respond to inducible chemokine exposure *in vitro* (6) and that they migrate poorly to secondary lymphoid tissues *in vivo* (7). A recent study also has shown that the method (e.g., propagation from $CD34^+$ hematopoietic progenitors vs blood monocytes) by which human DC are generated can affect their migratory response to specific chemokines *in vitro* (8). Thus, it is still unknown which chemokine(s) and receptors are important in directing immature recipient DC to the allograft, and even whether immature DC are recruited to the graft at all.

Monocytes can differentiate into DC during reverse transmigration (9-11). Thus, immature DC, that express low levels of major histocompatibility complex (MHC) and B7 molecules and that are poor stimulators of naïve T cell activity, may play only a limited role in the uptake of donor Ag during inflammation, possibly explaining why tissue-resident/isolated DC exhibit refractory chemotactic responses *in vitro*. It may be that some of the monocytes (that also respond to inducible chemokines) that are recruited during the early response to a graft transform into DC as they exit the graft and enter afferent lymphatics [or, in some cases, the blood (12,13)], and transport Ag to alloAg-specific T cells in secondary lymphoid tissues. Further, it also may prove important to consider whether the Ag-bearing DC are the same DC that initiate the immune response, or whether migratory, peripheral DC pass on their antigenic message to their sedentary, secondary lymphoid tissue-resident DC counterparts (14).

Mature DC, on the other hand, regardless of tissue of origin or method of generation, respond to the constitutive CC chemokines CCL19 and CC21 *in vitro* (Table 1), expressing on their surface the constitutive CC chemokine receptor, CCR7 (1). It is important to note, however, that, DC of varying degrees of maturity (as determined by cell surface phenotype and/or function) have been shown either to express CCR7 or to migrate in response to its chemokine ligands (3,6,7,15-20). Thus, use of this chemokine receptor as a maturation marker may be fallible. Further study is necessary to determine, for example, the role that CCR7 plays in maintenance of peripheral tolerance (16,18,21,22).

CCL19, CCL21, and CCR7

We (23) and others (24) have investigated the impact that interruption of the constitutive chemokine pathway has on prolongation of murine allograft survival utilizing paucity of *l*ymph node *T* cell (*plt/plt*) mice that lack expression of CCL19 and have impaired CCL21 expression. In *plt* allograft recipients, prolongation of normal heart graft survival is minimal (24) to modest (23), and skin allografts are rejected rapidly (23,24), whereas islet allografts (engrafted under the kidney capsule) are permanently accepted (24). Thus, it appears that the requirement for CCL19- and CCL21-directed leukocyte migration may be strain combination- and/or transplant tissue-specific. At least a partial explanation for the delayed but eventual rejection of murine heart allografts and the rapid rejection of skin allografts is likely the presence of a small amount of functional CCL21 in *plt* recipients [two genes exist for CCL21 protein,-

CCL21-leu and CCL21-ser. CCL21-leu, that is expressed in the lymphatics, remains intact in *plt* recipients, while CCL21-ser, that is expressed in T cell stroma, as well as within lymphatics, is deleted (25,26)]. However, that CCR7 knock-out mice also do not exhibit a protective phenotype for skin or heart allografts (27,28) further underscores the importance of this pathway in immune regulation. Clearly, a 'back-up' mechanism exists to insure that essential DC:T cell interactions can still occur [e.g., it has been shown that "tertiary lymphoid tissues" form in some virally-infected *plt* mice (26)] in the case of a breakdown in constitutive chemokine receptor or ligand function.

When the CCR7/CCL19/CCL21 pathway is disrupted via administration of fusion protein (CCL19-Ig) to murine heart allograft recipients, the effect on graft survival also is modest (29). However, kidney transplant recipients that received CCL19-Ig exhibited >100 day (~22 weeks) survival of their allografts (28). Strikingly, the significant prolongation of islet allografts in *plt* recipients only occurred in recipients with kidney-encapsulated islets; when islets were transplanted intrahepatically, the allografts were rejected rapidly. Using lymph node (*aly/aly*)- or spleen ($Hox11^{-/-}$)- deficient mice as recipients, it has been determined that skin transplants rely mainly on draining lymph nodes (DLN) for T cell interaction, escaping immunologic detection in the presence of splenic T cells alone (30), while heart transplants are rejected by either spleen-resident or DLN T cells (27,30). In the islet allograft studies, the authors linked a deficiency in donor DC migration to DLN in *plt* recipients to the indefinite islet graft survival (24). In corneal transplantation also, it recently has been shown that $CCR7^{+}$ DC transport Ag from the graft to draining lymph tissue, and that this transport can be reduced through the administration of an αCCL21 antagonist (31). Collectively, these studies call into question whether each transplanted organ or tissue is regulated by specific immunologic tissues and migratory pathways, and whether therapies that aim to alter leukocyte trafficking may have to be tailored to the specific tissue being transplanted. That hearts are robustly rejected, while kidneys persist beyond the acute rejection phase when CCR7 reception of its ligands is blocked, warrants deeper investigation into the degree to which the CCR7 chemokine pathway is involved in specific allograft models.

Donor vs recipient DC trafficking

In addition to the need for a better understanding of the specifics of chemokine-directed trafficking of APC to and from the graft and into T cell areas of secondary lymphoid tissues, the role(s) and kinetics of donor vs recipient DC trafficking in anti-allograft immune responses is another understudied area in transplantation immunobiology (4). Early studies of donor APC trafficking revealed that donor leukocytes traffic from murine skin (32) or heart (33) allografts into recipient draining lymph nodes or spleen, respectively. However, in the heart allograft studies (33), the donor cells were identified by their expression of MHC II alone, leaving the migratory pathway of DC specifically still in question. Unlike T cells, that can be depleted successfully with toxins directed against the CD3 Ag (34,35), the explicit targeting of DC for removal from donor tissue and/or recipient animals can be difficult, as murine CD11c expression is not exclusive to DC (36,37). Recently, the generation of the diphtheria toxin receptor (DTR)-GFP-DC mouse (discussed further below) has yielded some interesting data in DC depletion studies (29,36); in humans, the advent of the monoclonal mouse IgM antibody reactive against human DC, CMRF-44, holds promise, at least for *in vitro* DC depletion investigations (38). Early investigations (39-41) utilizing MHC II-deficient donors and recipients found that murine allografts can be rejected by either donor or recipient MHC II-competent APC; depleting APC from only the donor or the recipient is not enough to protect the graft. These studies did not evaluate APC trafficking, nor was the role that DC alone played in the immune response to the graft in MHC-deficient donors or recipients determined.

Recently, an elegant study was performed to track DC migration during allograft rejection (29). The investigators observed donor DC in recipient lymphoid tissues within 3 hours of (islet) transplantation; with their numbers peaking around 24 h post-transplant. Interestingly, these donor DC remained in the spleen of recipients that had rejected their allografts up to two weeks after rejection. The authors determined that donor DC exhibited a more mature cell surface phenotype earlier after transplant than did recipient DC, and that donor DC displayed a distinct chemokine receptor pattern (e.g., higher levels of CXCR4, CCR5, and CCR7 compared to recipient DC). Of further interest, while DT-mediated depletion of donor DC in islets prior to transplantation induced only modest protection of the allografts (29), culture of islets with CCL21 for 24 hours before transplant, inducing robust efflux of donor passenger DC from the tissue, resulted in a doubling of the median islets survival time. In another recent study utilizing a rat liver transplant model, donor MHC class II^+ cells (which included DC, T cells and B cells) were observed to rapidly traffic via the blood from the allograft into the spleen, DLN, and intestinal Peyer's patches of recipients (13). The transmigrated APC upregulated co-stimulatory molecules (i.e., $CD86^+$) and induced vigorous $CD8^+$ T cell proliferation in response to alloAg within 24 hours of transplant.

Conversely, it has been suggested that it is recipient (plasmacytoid) DC that are responsible for tolerance,- at least in a specific tolerance-inducing (anti-CD2 plus anti-CD3 mAb,- or donor-specific transfusion [DST] + anti-CD154) murine heart allograft model (12,42). While both donor and recipient DC were observed interacting with recipient $CD4^+$ T cells in the spleen and DLN of graft recipients, soon after transplant only recipient YAe^+ (donor Ag) DC:$CD4^+$ T cell interactions persisted, and only in the LN of tolerized animals. The authors found that APC:T cell interactions that occurred in the spleens of the tolerized animals were short-lived compared to those that occurred in the LN and that they induced a vigorous Ag-specific immune response, while YAe^+ APC:T cell interactions in the LN were linked to $CD4^+CD25^+Foxp3^+$ T regulatory cell development and tolerance induction (12). Somewhat relatedly, it also has been shown that oral tolerance to ingested Ag cannot be achieved in either wild-type mice that have undergone "draining" mesenteric lymphadenectomy or in CCR7 KO mice, that exhibit deficient trafficking of intestinal DC to mesenteric DLN (43). In another rat liver allograft study, it was determined that donor DC subsets localized differentially (in the white or red pulp or recipient spleens) according to whether the recipients had been administered tolerizing DST treatment prior to transplant (44). Taken together, these studies further emphasize the need to understand the compartmentalization of DC subsets during the alloimmune response, particularly if DC-regulated tolerance-inducing mechanisms occur only in specific immune environs.

Manipulation of DC trafficking

A great deal of attention has been afforded to evaluation of the effects that specific, commonly-used immunosuppressive drugs have on immune effector cells, namely T and B cells (45,46). More recent studies have focused on how agents affect DC and their interactions with T cells [reviewed in (47-50)]. Our group (17), has reported that FTY720, a sphingosine analogue pro-drug that prevents T cell exodus from secondary lymphoid tissues resulting in their depletion in the blood, also affects DC trafficking pathways. We found that FTY720 reduced DC chemotactic responses to CCL19 and CCL21 *in vitro*, which correlated with reduced CCR7 expression. Moreover, contrary to its effects on T and B cells, FTY720 impaired DC entry into spleen and LN, resulting in DC accumulation in the blood. We also have observed (20) that when (bone marrow-derived) DC are generated in the presence of the immunosuppressive macrolide rapamycin, DC are resistant to maturation, expressing lower levels of co-stimulatory and Ag-presenting molecules than their normally cultured counterparts. Interestingly, Sordi et al (19) found that rapamycin also enhanced DC migration to constitutive chemokines (i.e. CCL19) and that this enhanced migration was linked to upregulation of CCR7 expression on

rapamycin-exposed DC. In the same study, the authors observed that dexamethasone exposure downregulated DC expression of CCR7 and the chemotactic response to its ligand, but that neither cyclosporine nor tacrolimus was able to modulate chemokine receptor expression or DC migratory ability (19). Two other recent studies have determined that other potent T cell inhibitors also affect DC activity,- (i) triptolide, which downregulates cyclooxygenase-2 expression in DC, thereby impairing DC CCR7 expression and migration to CCR7 ligands *in vitro* and *in vivo* (51) and (ii) mycophenolic acid (MPA), which *upregulates* DC CCR7 expression but also IL-10 secretion, resulting in an impaired ability of the DC to induce $CD4^+$ T cell proliferation in response to alloAg, via both the direct and indirect pathways (52).

As speculated by the investigators in the MPA study (52), enhancement of CCR7 expression on DC and therefore DC:T cell interactions in T cell areas of secondary lymphoid tissues may actually be beneficial to graft recipients, if the DC in question possess immunoregulatory abilities. Potentially, these tolerogenic DC could then "deactivate" alloAg-responding T cells, rendering the transplanted tissue/organ a non-threat to the immune system. Building on our own early studies (53) utilizing retrovirus to overexpress CCR7 on bone marrow-derived, viral (v) IL-10-expressing DC, Garrod *et el* (54) used a novel gene transduction technique (retroviral gene transfer to bone marrow precursors prior to their differentiation into DC) to deliver CCR7 and vIL-10 to bone marrow DC. This technique greatly enhanced the transduction efficiency (the authors found >95% of cells expressed the transgene) without affecting their maturation state. These DC exhibited increased migration to T cell areas after their systemic administration and a reduced ability to stimulate naïve allogeneic T cell proliferation and IL-2 production. Moreover, they inhibited graft rejection for over 100 days in ~80% of heart allograft recipients when administered one week prior to transplant compared to control-transduced DC. Thus, while targeting CCR7 to impair "immunostimulatory" DC trafficking to T cell areas for abrogation of graft rejection may not be sufficient for long-term protection of allografts, optimization of "tolerogenic"/"regulatory" DC CCR7 expression for induction of alloAg-specific tolerance may be an avenue that warrants further exploration.

Concluding remarks

The study of DC immunobiology in the field of transplantation is gaining momentum. It has become apparent that in order to achieve the "holy grail" of alloAg-specific immune tolerance, it is necessary to look not just at how T and B cells carry out their immune functions against the graft, but also at how they are initially instructed to do so by DC (50,55). Just as the role of the DC as powerful induces and regulators of the immune response is not to be underestimated in any disease/inflammatory model, neither is the role of cytokines, chemokines, adhesion molecules and other proteins that direct DC migration and function.

Herein we have briefly surveyed the foremost studies on donor and recipient DC migration to and from experimental allografts. We also have discussed DC interactions with T cells in secondary lymphoid tissues and investigations of the role(s) that chemokines and their receptors may play in directing these activities. We are only beginning to understand the intricate instructions that chemokines provide for leukocytes in order to direct immune interactions. As we develop further understanding of the trafficking behavior of DC subsets (donor vs recipient, myeloid vs plasmacytoid), of how it is regulated and of how it relates to their important immunoregulatory functions, we will be better equipped to target/manipulate these important APC to achieve the desired therapeutic effect.

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References

1. Lukacs-Kornek V, Engel D, Tacke F, Kurts C. The role of chemokines and their receptors in dendritic cell biology. Front Biosci 2008;13:2238–2252. [PubMed: 17981706]
2. Sozzani S, Allavena P, Vecchi A, Mantovani A. The role of chemokines in the regulation of dendritic cell trafficking. J Leukoc Biol 1999;66:1–9. [PubMed: 10410984]
3. Vecchi A, Massimiliano L, Ramponi S, Luini W, Bernasconi S, Bonecchi R, Allavena P, Parmentier M, Mantovani A, Sozzani S. Differential responsiveness to constitutive vs. inducible chemokines of immature and mature mouse dendritic cells. J Leukoc Biol 1999;66:489–494. [PubMed: 10496320]
4. Colvin BL, Thomson AW. Location, location, location: dendritic cell trafficking and transplant tolerance. Curr Opin Organ Transplant 2007;12:1–4.
5. Colvin BL, Thomson AW. Chemokines, their receptors, and transplant outcome. Transplantation 2002;74:149–155. [PubMed: 12151723]
6. Abe M, Zahorchak AF, Colvin BL, Thomson AW. Migratory responses of murine hepatic myeloid, lymphoid-related, and plasmacytoid dendritic cells to CC chemokines. Transplantation 2004;78:762–765. [PubMed: 15371684]
7. Lau AH, Thomson AW, Colvin BL. Chronic ethanol exposure affects in vivo migration of hepatic dendritic cells to secondary lymphoid tissue. Hum Immunol 2007;68:577–585. [PubMed: 17584579]
8. Moldenhauer A, Moore MA, Schmidt K, Kiesewetter H, Salama A. Differences in the transmigration of different dendritic cells. Exp Hematol 2006;34:745–752. [PubMed: 16728279]
9. Muller WA, Randolph GJ. Migration of leukocytes across endothelium and beyond: molecules involved in the transmigration and fate of monocytes. J Leukoc Biol 1999;66:698–704. [PubMed: 10577496]
10. Randolph GJ, Sanchez-Schmitz G, Liebman RM, Schakel K. The CD16(+) (FcgammaRIII(+)) subset of human monocytes preferentially becomes migratory dendritic cells in a model tissue setting. J Exp Med 2002;196:517–527. [PubMed: 12186843]
11. Leon B, Martinez del Hoyo G, Parrillas V, Vargas HH, Sanchez-Mateos P, Longo N, Lopez-Bravo M, Ardavin C. Dendritic cell differentiation potential of mouse monocytes: monocytes represent immediate precursors of CD8- and CD8+ splenic dendritic cells. Blood 2004;103:2668–2676. [PubMed: 14630812]
12. Ochando JC, Homma C, Yang Y, Hidalgo A, Garin A, Tacke F, Angeli V, Li Y, Boros P, Ding Y, Jessberger R, Trinchieri G, Lira SA, Randolph GJ, Bromberg JS. Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. Nat Immunol 2006;7:652–662. [PubMed: 16633346]
13. Ueta H, Shi C, Miyanari N, Xu XD, Zhou S, Yamashita M, Ezaki T, Matsuno K. Systemic transmigration of allosensitizing donor dendritic cells to host secondary lymphoid organs after rat liver transplantation. Hepatology 2008;47:1352–1362. [PubMed: 18220273]
14. Allan RS, Waithman J, Bedoui S, Jones CM, Villadangos JA, Zhan Y, Lew AM, Shortman K, Heath WR, Carbone FR. Migratory dendritic cells transfer antigen to a lymph node-resident dendritic cell population for efficient CTL priming. Immunity 2006;25:153–162. [PubMed: 16860764]
15. Colvin BL, Morelli AE, Logar AJ, Lau AH, Thomson AW. Comparative evaluation of CC chemokine-induced migration of murine CD8alpha+ and CD8alpha- dendritic cells and their in vivo trafficking. J Leukoc Biol 2004;75:275–285. [PubMed: 14597730]
16. Jang MH, Sougawa N, Tanaka T, Hirata T, Hiroi T, Tohya K, Guo Z, Umemoto E, Ebisuno Y, Yang BG, Seoh JY, Lipp M, Kiyono H, Miyasaka M. CCR7 is critically important for migration of dendritic cells in intestinal lamina propria to mesenteric lymph nodes. J Immunol 2006;176:803–810. [PubMed: 16393963]
17. Lan YY, De Creus A, Colvin BL, Abe M, Brinkmann V, Coates PT, Thomson AW. The sphingosine-1-phosphate receptor agonist FTY720 modulates dendritic cell trafficking in vivo. Am J Transplant 2005;5:2649–2659. [PubMed: 16212624]

18. Ohl L, Mohaupt M, Czeloth N, Hintzen G, Kiafard Z, Zwirner J, Blankenstein T, Henning G, Forster R. CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions. Immunity 2004;21:279–288. [PubMed: 15308107]
19. Sordi V, Bianchi G, Buracchi C, Mercalli A, Marchesi F, D'Amico G, Yang CH, Luini W, Vecchi A, Mantovani A, Allavena P, Piemonti L. Differential effects of immunosuppressive drugs on chemokine receptor CCR7 in human monocyte-derived dendritic cells: selective upregulation by rapamycin. Transplantation 2006;82:826–834. [PubMed: 17006331]
20. Taner T, Hackstein H, Wang Z, Morelli AE, Thomson AW. Rapamycin-treated, alloantigen-pulsed host dendritic cells induce ag-specific T cell regulation and prolong graft survival. Am J Transplant 2005;5:228–236. [PubMed: 15643982]
21. Sille FC, Visser A, Boes M. T cell priming by tissue-derived dendritic cells: new insights from recent murine studies. Cell Immunol 2005;237:77–85. [PubMed: 16360134]
22. Worbs T, Forster R. A key role for CCR7 in establishing central and peripheral tolerance. Trends Immunol 2007;28:274–280. [PubMed: 17462953]
23. Colvin BL, Wang Z, Nakano H, Wu W, Kakiuchi T, Fairchild RL, Thomson AW. CXCL9 antagonism further extends prolonged cardiac allograft survival in CCL19/CCL21-deficient mice. Am J Transplant 2005;5:2104–2113. [PubMed: 16095489]
24. Wang L, Han R, Lee I, Hancock AS, Xiong G, Gunn MD, Hancock WW. Permanent survival of fully MHC-mismatched islet allografts by targeting a single chemokine receptor pathway. J Immunol 2005;175:6311–6318. [PubMed: 16272282]
25. Nakano H, Gunn MD. Gene duplications at the chemokine locus on mouse chromosome 4: multiple strain-specific haplotypes and the deletion of secondary lymphoid-organ chemokine and EBI-1 ligand chemokine genes in the plt mutation. J Immunol 2001;166:361–369. [PubMed: 11123313]
26. Mori S, Nakano H, Aritomi K, Wang CR, Gunn MD, Kakiuchi T. Mice lacking expression of the chemokines CCL21-ser and CCL19 (plt mice) demonstrate delayed but enhanced T cell immune responses. J Exp Med 2001;193:207–218. [PubMed: 11148224]
27. Beckmann JH, Yan S, Luhrs H, Heid B, Skubich S, Forster R, Hoffmann MW. Prolongation of allograft survival in ccr7-deficient mice. Transplantation 2004;77:1809–1814. [PubMed: 15223896]
28. Ziegler E, Gueler F, Rong S, Mengel M, Witzke O, Kribben A, Haller H, Kunzendorf U, Krautwald S. CCL19-IgG prevents allograft rejection by impairment of immune cell trafficking. J Am Soc Nephrol 2006;17:2521–2532. [PubMed: 16899521]
29. Fiorina P, Jurewicz M, Vergani A, Augello A, Paez J, Ricchiuti V, Tchipachvili V, Sayegh MH, Abdi R. Phenotypic and functional differences between wild-type and CCR2-/- dendritic cells: implications for islet transplantation. Transplantation 2008;85:1030–1038. [PubMed: 18408585]
30. Lakkis FG, Arakelov A, Konieczny BT, Inoue Y. Immunologic 'ignorance' of vascularized organ transplants in the absence of secondary lymphoid tissue. Nat Med 2000;6:686–688. [PubMed: 10835686]
31. Jin Y, Shen L, Chong EM, Hamrah P, Zhang Q, Chen L, Dana MR. The chemokine receptor CCR7 mediates corneal antigen-presenting cell trafficking. Mol Vis 2007;13:626–634. [PubMed: 17515886]
32. Larsen CP, Steinman RM, Witmer-Pack M, Hankins DF, Morris PJ, Austyn JM. Migration and maturation of Langerhans cells in skin transplants and explants. J Exp Med 1990;172:1483–1493. [PubMed: 2230654]
33. Larsen CP, Morris PJ, Austyn JM. Migration of dendritic leukocytes from cardiac allografts into host spleens. A novel pathway for initiation of rejection. J Exp Med 1990;171:307–314. [PubMed: 2404081]
34. Isaacs JD. T cell immunomodulation--the Holy Grail of therapeutic tolerance. Curr Opin Pharmacol 2007;7:418–425. [PubMed: 17611158]
35. Knechtle SJ. Treatment with immunotoxin. Philos Trans R Soc Lond B Biol Sci 2001;356:681–689. [PubMed: 11375071]
36. Probst HC, Tschannen K, Odermatt B, Schwendener R, Zinkernagel RM, Van Den Broek M. Histological analysis of CD11c-DTR/GFP mice after in vivo depletion of dendritic cells. Clin Exp Immunol 2005;141:398–404. [PubMed: 16045728]

37. Blasius AL, Barchet W, Cella M, Colonna M. Development and function of murine B220+CD11c +NK1.1+ cells identify them as a subset of NK cells. J Exp Med 2007;204:2561–2568. [PubMed: 17923504]
38. Collin MP, Munster D, Clark G, Wang XN, Dickinson AM, Hart DN. In vitro depletion of tissue-derived dendritic cells by CMRF-44 antibody and alemtuzumab: implications for the control of Graft-versus-host disease. Transplantation 2005;79:722–725. [PubMed: 15785380]
39. Auchincloss H Jr, Lee R, Shea S, Markowitz JS, Grusby MJ, Glimcher LH. The role of “indirect” recognition in initiating rejection of skin grafts from major histocompatibility complex class II-deficient mice. Proc Natl Acad Sci U S A 1993;90:3373–3377. [PubMed: 8475083]
40. Chitilian HV, Auchincloss H Jr. Studies of transplantation immunology with major histocompatibility complex knockout mice. J Heart Lung Transplant 1997;16:153–159. [PubMed: 9059926]
41. Grusby MJ, Auchincloss H Jr, Lee R, Johnson RS, Spencer JP, Zijlstra M, Jaenisch R, Papaioannou VE, Glimcher LH. Mice lacking major histocompatibility complex class I and class II molecules. Proc Natl Acad Sci U S A 1993;90:3913–3917. [PubMed: 8483910]
42. Ochando JC, Krieger NR, Bromberg JS. Direct versus indirect allorecognition: Visualization of dendritic cell distribution and interactions during rejection and tolerization. Am J Transplant 2006;6:2488–2496. [PubMed: 16889597]
43. Worbs T, Bode U, Yan S, Hoffmann MW, Hintzen G, Bernhardt G, Forster R, Pabst O. Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells. J Exp Med 2006;203:519–527. [PubMed: 16533884]
44. Furuhashi T, Yamaguchi Y, Wang FS, Uchino S, Okabe K, Ohshiro H, Kihara S, Yamada S, Mori K, Ogawa M. Hepatic CCR7lowCD62LlowCD45RClow allograft dendritic cells migrate to the splenic red pulp in immunologically unresponsive rats. J Surg Res 2005;124:29–37. [PubMed: 15734476]
45. Duncan MD, Wilkes DS. Transplant-related immunosuppression: a review of immunosuppression and pulmonary infections. Proc Am Thorac Soc 2005;2:449–455. [PubMed: 16322599]
46. Miao CH. Recent advances in immune modulation. Curr Gene Ther 2007;7:391–402. [PubMed: 17979685]
47. Abe M, Thomson AW. Influence of immunosuppressive drugs on dendritic cells. Transpl Immunol 2003;11:357–365. [PubMed: 12967788]
48. Coates PT, Colvin BL, Kaneko K, Taner T, Thomson AW. Pharmacologic, biologic, and genetic engineering approaches to potentiation of donor-derived dendritic cell tolerogenicity. Transplantation 2003;75:32S–36S. [PubMed: 12819488]
49. Hackstein H, Thomson AW. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. Nat Rev Immunol 2004;4:24–34. [PubMed: 14704765]
50. Paterson AM, Yates SF, Nolan KF, Waldmann H. The new immunosuppression: intervention at the dendritic cell-T-cell interface. Curr Drug Targets Immune Endocr Metabol Disord 2005;5:397–411. [PubMed: 16375693]
51. Liu Q, Chen T, Chen G, Shu X, Sun A, Ma P, Lu L, Cao X. Triptolide impairs dendritic cell migration by inhibiting CCR7 and COX-2 expression through PI3-K/Akt and NF-kappaB pathways. Mol Immunol 2007;44:2686–2696. [PubMed: 17223196]
52. Lagaraine C, Hoarau C, Chabot V, Velge-Roussel F, Lebranchu Y. Mycophenolic acid-treated human dendritic cells have a mature migratory phenotype and inhibit allogeneic responses via direct and indirect pathways. Int Immunol 2005;17:351–363. [PubMed: 15710908]
53. Takayama T, Morelli AE, Onai N, Hirao M, Matsushima K, Tahara H, Thomson AW. Mammalian and viral IL-10 enhance C-C chemokine receptor 5 but down-regulate C-C chemokine receptor 7 expression by myeloid dendritic cells: impact on chemotactic responses and in vivo homing ability. J Immunol 2001;166:7136–7143. [PubMed: 11390459]
54. Garrod KR, Chang CK, Liu FC, Brennan TV, Foster RD, Kang SM. Targeted lymphoid homing of dendritic cells is required for prolongation of allograft survival. J Immunol 2006;177:863–868. [PubMed: 16818740]
55. Schlichting CL, Schareck WD, Kofler S, Weis M. Involvement of dendritic cells in allograft rejection new implications of dendritic cell-endothelial cell interactions. Mini Rev Med Chem 2007;7:423–428. [PubMed: 17430227]

Table 1

Chemokine receptors expressed by DC and the functional outcome of receptor ligation

DC status	Chemokine Receptor	Ligand	Function
Immature DC	CCR1	CCL3 (MIP1α) CCL5 (RANTES) CCL7 (MCP-3) CCL8 (MCP-2) CCL9 (MRP-2) CCL14 (HCC1) CCL16 (HCC4)	Recruitment of DC/DC precursors to sites of Inflammation
	CCR2	CCL2 (MCP-1) CCL7 (MCP-3) CCL12 (MCP-5) CCL8 (MCP-2) CCL16 (HCC4)	Recruitment of DC/DC precursors to sites of inflammation
	CCR4	CCL17 (TARC) CCL19 (MIP-3β, ELC)	DC/DC precursor recruitment for skin homing
	CCR5	CCL3 (MIP1α) CCL4 (MIP1β) CCL5 (RANTES) CCL8 (MCP-2) CCL11 (eotaxin) CCL14 (HCC1) CCL16 (HCC4)	Recruitment of DC/DC precursors to sites of inflammation
	CCR6	CCL20 (MIP-3α)	Langerhans cell migration; DC migration into gut; DC localization in Peyer's patches
	CCR8	CCL1 (TCA3)	Monocyte-derived DC recruitment from skin to DLN
	CCR9	CCL25 (TECK)	pDC recruitment to inflamed gut
	CXCR3	CXCL9 (Mig) CXCL10 (IP10) CXCL11 (ITAC)	Murine pDC recruitment to LN; human pDC to sites of inflammation
	CX3CR	CX3Cl1 (fractalkine)	DC sentinel function
Immature and Mature DC[**]	CXCR4	CCL12 (SDF-1)	Enhances human pDC migration in response to CXCR3 ligands; DC recruitment
Mature DC[*]	CCR7	CCL19 (MIP-3β, ELC) CCL21 (6Ckine, SLC)	DC recruitment from periphery to T cell areas of secondary lymphoid tissue; Enhances DC endocytic ability

[*] During the process of maturation/in response to inflammatory stimuli, DC downregulate their cell surface expression of the chemokine receptors they expressed in their immature state and upregulate their cell surface expression of CCR7.

[**] Some immature DC express CXCR4, but do not respond chemotactically to its ligand; upon exposure to maturation stimuli, some DC acquire the ability to migrate to CCL12.

HCC - ; hemofiltrate CC chemokine; ELC – Epstein Bar Virus Ligand 1 chemokine; IP10 – interferon inducible protein-10; ITAC - interferonγ T cellα chemoattractant; MIP – macrophage inflammatory protein; MCP – monocyte chemoattractant protein; MRP – MIP-related; Mig – monokine induced by interferonγ; RANTES – regulated on activation normal T cell expressed and secreted; SDF – stromal cell-derived factor ; SLC – secondary lymphoid chemokine ; TARC – thymus and activation regulated chemokine ; TECK – thymus expressed chemokine