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# Dendritic cells in liver transplantation immune response

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Dendritic cells (DCs) are the most powerful antigen presenting cells (APCs), they are considered one of the key regulatory factors in the liver immune system. There is currently much interest in modulating DC function to improve transplant immune response. In liver transplantation, DCs participate in both the promotion and inhibition of the alloresponse by adopting different phenotypes and function. Thus, in this review, we discussed the origin, maturation, migration and pathological effects of several DC subsets, including the conventional DC (cDC), plasmacytoid DC (pDC) and monocyte-derived DC (Mo-DC) in liver transplantation, and we summarized the roles of these DC subsets in liver transplant rejection and tolerance. In addition, we also outlined the latest progress in DC-based related treatment regimens. Overall, our discussion provides a beneficial resource for better understanding the biology of DCs and their manipulation to improve the immune adaptability of patients in transplant status.

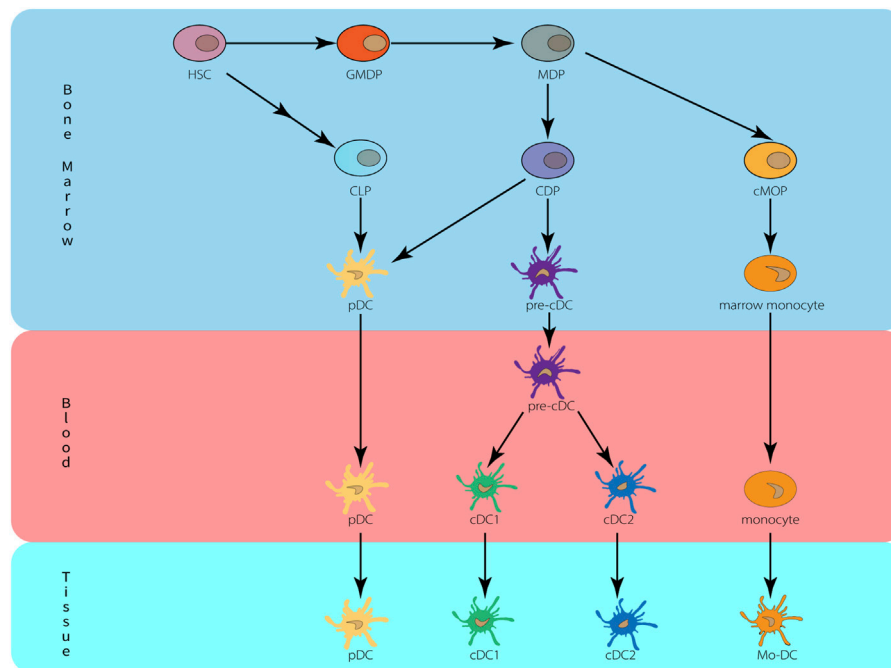
## KEYWORDS

liver transplantation, dendritic cells, immune rejection, immune tolerance, DC based treatment

## 1 Introduction

In the early 1970s, Ralph Steinman and others discovered a morphologically and functionally distinct, previously uncharacterized population of cells in their experiments. They called the cells “dendritic cell” (DC) due to their “stellate” or “dendritic” morphology (Steinman and Cohn, 1973). In the liver, DCs are preferentially found in the periportal and pericentral space (Rahman and Aloman, 2013; Eckert et al., 2015). They account for about 1% of non-parenchymal cells and are related to innate and adaptive immunity by promoting and regulating T cell immunity, which are considered to be one of the key regulators in liver immune system (Hsu et al., 2007; Thomson et al., 2020; Bošnjak et al., 2022). DCs continuously flow into the liver from the blood, and circulating DCs are recruited to the hepatic sinusoids by hepatic Kupffer cells in a c-type lectin-dependent manner (Kudo et al., 1997; Uwatoku et al., 2001). Liver normally contains more interstitial dendritic cells than other parenchymal organs (Steptoe et al., 2000), which may be the result of the pathogen associated molecular pattern (PAMP) in portal blood.

Liver transplantation is the most effective treatment for various end-stage liver diseases. The liver is an immune preferential organ (Demetris et al., 2016). In addition to patients undergoing transplantation for autoimmune liver diseases (such as primary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis), clinically more than 30% of patients can get rid of the use of immunosuppressant (IS) and achieve a state of immune tolerance (Clavien et al., 2017). In liver transplantation, DCs participate in both the



**FIGURE 1**

Origin and development of dendritic cells. HSC, hematopoietic stem cells; MDP, monocyte-macrophage DC progenitor; CDP, common dendritic cell progenitor; CLP, common lymphoid progenitor; cMoP, common monocyte progenitors; Mo-DC, monocyte-derived DC.

promotion and inhibition of the alloresponse by adopting different phenotypes and function. Here, we discussed the origin, maturation, migration and pathological effects of several DC subsets, including the conventional DC (cDC), plasmacytoid DC (pDC) and monocyte-derived DC (Mo-DC), and we summarized the roles of these DC subsets in liver transplant rejection and tolerance. In addition, we also outlined the latest progress in DC-based related treatment regimens.

## 2 The characteristics of DC

### 2.1 The subgroups of DC

According to the current novel, ontogenetic, and functionally relevant simplified classification system, DCs are classified into cDC, pDC, Mo-DC, and Langerhans cell (LC) (Satpathy et al., 2012). cDC can be further divided into two subsets: conventional DC type 1 (cDC1) and conventional DC type 2 (cDC2). cDC can maintain immune homeostasis, simultaneously rapidly respond to local damage, and initiate and guide innate and adaptive immunity (Cabeza-Cabrerizo et al., 2021). pDC act as both innate antiviral effectors and inducers and regulators of adaptive immunity (Fonteneau et al., 2003), regulating the induction and/or maintenance of tolerance to hematopoietic stem cells (HSCs) or allogeneic organ grafts (Rogers et al., 2013). Mo-DC is considered to be the main inflammatory cell type during infection (Geissmann et al., 2003; Serbina et al., 2003). Monocytes differentiate into Mo-DC during inflammation or infection, which cooperate with cDC to induce T cell-mediated immune responses (Bošnjak et al., 2022).

Traditionally, LC has been considered a DC population in the epidermis (Schuler and Steinman, 1985; Romani et al., 1989; Wilson and Villadangos, 2004). Therefore, this article will focus on cDC, pDC, and Mo-DC.

### 2.2 DC development

Human and mouse DC develop from progenitor cells in the bone marrow and then differentiate into distinct subpopulations that are spread across multiple tissues (Durai and Murphy, 2016; Guillems et al., 2016). HSCs in bone marrow can give rise to granulocytes, monocytes, and DC progenitor cell (GMDP), which in turn give rise to monocyte and macrophage DC progenitor cell (MDP). They give rise to a common DC progenitor (CDP) and a common monocyte progenitor (cMoP) (Fogg et al., 2006; Hettinger et al., 2013). CDP produces classical/conventional DC precursor cell (pre-cDC) and pDC, both cDC1 and cDC2 are derived from pre-cDC and can be found in blood and bone marrow. cMoP produces monocytes in the bone marrow, then enters the peripheral blood, enters the tissue during inflammation or infection and further differentiates into Mo-DC (Hettinger et al., 2013; Que et al., 2020). The development of DC is depicted in Figure 1.

### 2.3 Markers for DC identification

DC subsets differ in the expression of surface markers and transcription factors (Table 1). Mouse cDC could be divided into two subsets: cDC1 was identified as lineage (Lin)<sup>-</sup> major

TABLE 1 Human and mouse DC subsets with markers and transcription factors.

DC subset	Development, growth and transcription factors	Surface markers mouse	Surface markers human	References
Conventional DC1	FLT3L, GM-CSF, IRF8, ID2, NFIL3, BATF3	Lin <sup>-</sup> MHC-II <sup>+</sup> CD11c <sup>+</sup> CD103 <sup>+</sup> CD11b <sup>-</sup> XCR1 <sup>+</sup> CLEC9A <sup>+</sup>	Lin <sup>-</sup> HLA-DR <sup>+</sup> BDCA3/CD141 <sup>+</sup> XCR1 <sup>+</sup> CLEC9A <sup>+</sup> BTLA4 <sup>+</sup>	Bachem et al. (2010), Crozat et al. (2010), Edelson et al. (2010), Poulin et al. (2012), Merad et al. (2013), Williams et al. (2016), Anderson et al. (2018)
Conventional DC2	FLT3L, GM-CSF, IRF4, Notch2	Lin <sup>-</sup> MHC-II <sup>+</sup> CD11b <sup>+</sup> CD11c <sup>+</sup> CD103 <sup>-</sup> SIRPα <sup>+</sup>	Lin <sup>-</sup> HLA-DR <sup>+</sup> BDCA1/CD1c <sup>+</sup> SIRPα <sup>+</sup> XCR1 <sup>-</sup> CLEC9A <sup>-</sup>	Lewis et al. (2011), Merad et al. (2013), Satpathy et al. (2013), Yin et al. (2021)
Plasmacytoid DC	FLT3L, M-CSF, TCF4(E2-2), IRF8, BCL11A, ZEB2, Spi-B	MHC-II <sup>int</sup> CD11c <sup>int</sup> B220 <sup>+</sup> Ly6C <sup>+</sup> BST2 <sup>+</sup> SiglecH <sup>+</sup>	HLA-DR <sup>+</sup> CD11c <sup>-</sup> CD4 <sup>+</sup> BDCA2/CD303 <sup>+</sup> BDCA4CD304 <sup>+</sup> CD123 <sup>+</sup>	Colonna et al., 2004; Liu (2005), Cisse et al. (2008), Grajkowska et al. (2017), Reizis (2019)
Monocyte-derived DC	GM-CSF or IL-4 PU.1, IRF4, AHR, NR4A3, NCOR2	MHC-II <sup>+</sup> CD11c <sup>+</sup> CD11b <sup>+</sup> CD64 <sup>int</sup> Ly6C <sup>int</sup> CCR2 <sup>+</sup> CD209 <sup>+</sup>	HLA-DR <sup>+</sup> CD11c <sup>+</sup> CD14 <sup>int</sup> CD206 <sup>+</sup> CD1c <sup>+</sup>	Lehtonen et al. (2005), Segura et al. (2013), Schlitzer et al. (2015), Briseño et al. (2016), Menezes et al. (2016), Goudot et al. (2017), Sander et al. (2017), Boulet et al. (2019), Tang-Huau and Segura (2019)

histocompatibility complex Class II (MHC-II)<sup>+</sup> cluster of differentiation (CD)11c<sup>+</sup>CD103<sup>+</sup>CD11b<sup>-</sup>. cDC2 was identified as Lin<sup>-</sup>MHC-II<sup>+</sup>CD11c<sup>+</sup>CD103<sup>+</sup>CD11b<sup>+</sup>. Human cDC can be subdivided based on the expression of CD1c<sup>+</sup> [also known as blood dendritic cell antigen (BDCA)1] and CD141<sup>+</sup> (BDCA3) (Haniffa et al., 2012; Williams et al., 2014; Pulendran, 2015). CD141<sup>+</sup> cDC differentiate and mature under the influence of INF regulatory factor 8 (IRF8), express XC-chemokine receptor 1 (XCR1)<sup>+</sup>, C-type lectin domain containing 9A (CLEC9A)<sup>+</sup> and B- and T-lymphocyte attenuator 4 (BTLA4)<sup>+</sup>, secrete interleukin 12 (IL-12) to promote T helper 1 cell (T<sub>H</sub>1) differentiation, and also cross-present intracellular antigens (Murphy et al., 2016), these functions are similar to those of cDC1 in mice. CD1c<sup>+</sup> cDC differentiate and mature under the influence of IRF4, express high levels of CD1b<sup>+</sup>, CD14<sup>+</sup>, and signal-regulatory protein alpha (SIRPα)<sup>+</sup>, and may further differentiate through Krüppel-like factor 4 (KLF4) to promote T helper 2 cell (T<sub>H</sub>2) differentiation or Notch signaling pathway to promote IL-23, thereby contributing to T helper 17 cell (T<sub>H</sub>17) differentiation. These functions are similar to those of cDC2 in mice.

The phenotype of mouse pDC was identified as MHC-II<sup>int</sup>CD11c<sup>int</sup>B220<sup>+</sup>lymphocyte antigen 6 (Ly6)C<sup>+</sup> bone marrow stromal antigen (BST)2<sup>+</sup>Sialic acid-binding immunoglobulin-type lectin (Siglec)-H<sup>+</sup> (Colonna et al., 2004). The phenotype of human pDC was identified as human leukocyte antigen-DR isotype (HLA-DR)<sup>+</sup>CD11c<sup>-</sup>CD4<sup>+</sup> BDCA2<sup>+</sup>BDCA4<sup>+</sup>CD123<sup>+</sup> (Liu, 2005). Like pDC in mice, human pDC also can secrete type I interferon (IFN-I) and initiate antiviral immunity (Haniffa et al., 2012). The development of pDC depends on FMS-like tyrosine kinase 3 (FLT3) and its ligand FMS-like tyrosine kinase 3 ligand (FLT3L) (Schmid et al., 2010), and macrophage colony-stimulating factor (M-CSF) may also support the generation of pDC (Fancke et al., 2008). Transcription factor 4 (TCF4)(E2-2), IRF8, B-cell lymphoma/leukemia 11A (BCL11A), Zinc finger E-box-binding homeobox 2 (ZEB2), and Spi-B play important roles in the development and maintenance of the pDC phenotype (Reizis, 2019).

The phenotype of mouse Mo-DC was identified as MHC-II<sup>+</sup>CD11c<sup>+</sup>CD11b<sup>+</sup>CD64<sup>int</sup>Ly6C<sup>int</sup> C-C chemokine receptor 2 (CCR2)<sup>+</sup>CD209<sup>+</sup> (Schlitzer et al., 2015; Menezes et al., 2016). The phenotype of human Mo-DC was identified as HLA-

DR<sup>+</sup>CD11c<sup>+</sup>CD14<sup>int</sup>CD206<sup>+</sup>CD1c<sup>+</sup> (Segura et al., 2013; Tang-Huau and Segura, 2019). Monocyte differentiation into Mo-DC depends on some key regulators, such as PU.1, IRF4, aryl hydrocarbon receptor (AHR), nuclear receptor 4A3 (NR4A3), and nuclear receptor co-repressor 2 (NCOR2) (Lehtonen et al., 2005; Briseño et al., 2016; Menezes et al., 2016; Goudot et al., 2017; Sander et al., 2017; Boulet et al., 2019).

## 2.4 DC migration and activating T cells

### 2.4.1 DC migration

A study (Lämmermann et al., 2008) used live cell imaging devices to directly observe the movement of DC sensing and entering afferent lymphatic vessels through wide-field microscopy in a mouse ear skin explant model. DC migration mainly depends on two chemokines: C-C motif ligand 19 (CCL19) and CCL21 (Lämmermann et al., 2008). The chemokine CCL21 is constitutively expressed by lymphatic endothelial cells (LECs) (Saeki et al., 1999; Russo et al., 2016), while its corresponding chemokine receptor CCR7 is induced in mature DC (Sallusto et al., 1998). They are expressed in LECs and lymph node T cell regions and bind to CCR7, which is upregulated on DC after activation (Förster et al., 1999). After approaching the lymphatic vessel, DCs dock with the lymphatic endothelium and enter the lumen. The docking and transport process is mediated by the interaction between lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) on the LECs and the hyaluronan coating on the surface of the DC bound and organized by CD44 (Johnson et al., 2017; Johnson et al., 2021). Some researchers have used an intravital microscope (IVM) to prove that Rho-associated protein kinase (ROCK) is involved in the process of DC crawling and overall migration in lymph (Nitschké et al., 2012). After entering the initial lymphatic vessels, DCs use lamellipodia to crawl along the lymphatic endothelium and enter downstream by sensing lymphatic flow, and once DCs reach the collecting vessels, they begin to drift freely in lymphocytes (Tal et al., 2011). *In vivo* studies in mice, two-photon microscopy showed that after mature DC entered the lymph node parenchyma, there was a strong directional migration of DC to the T cell area, which was dependent on the expression of CCR7

(Braun et al., 2011), and possibly depend on the presence of CCL21 (Schumann et al., 2010). LECs, derived from the top of the subcapsular sinus (SCS) of lymph nodes, express atypical chemokine receptor 4 (ACKR4), which is a clearance receptor for CCR7 ligands and a few other chemokines. By scavenging CCR7 ligands in the SCS lumen, CCL21 gradients are actively created and drive DC exit from SCS into the lymph node parenchyma (Ulvmar et al., 2014). Imaging of these compartments revealed that ACKR4-expressing LECs create a chemokine gradient through local clearance of CCL19 and CCL21, which triggers directional DC migration (Ulvmar et al., 2014). Within lymph nodes, DCs process and present exogenous peptides in MHC I and II, and these MHC-peptide complexes are recognized by CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells through T cell receptors, respectively (Corse et al., 2011).

DCs migrate to the liver from the lymphatic or blood circulation. After entering the liver, Kupffer cells selectively capture DCs and transport them to the draining hepatic lymph nodes through the liver sinus-lymph pathway (Matsuno et al., 1996; Kudo et al., 1997; Matsuno and Ezaki, 2000). Blood-derived DCs are attracted by CCL3 on Kupffer cells and extravasate from the endothelial pores of liver sinus into the Disse space (Sato et al., 1998). The DCs then migrate to the portal vein area through the CCR7-CCL21 system and interact with T cells to create portal tract-associated lymphoid tissue (PALT) (Yoneyama et al., 2001). IL-1 receptor antagonist (IL-1RA), derived from hepatocytes, directly activates the IL-1 receptor (IL-1R)/toll-like receptor (TLR) signaling pathway of activated DCs to regulate this migration by inducing the expression of CCR7 (Iizasa et al., 2005).

#### 2.4.2 Activating T cells

DC carrying antigen in lymph node T cell area can be effectively scanned by naive T cells. When naive T cells encounter cognate antigens in MHC-peptide complexes on the surface of DCs, naive T cells are activated and begin to proliferate rapidly (Bošnjak et al., 2022). The priming of T cells generated in lymph nodes occurs in three distinct stages, which can be distinguished by contact time and migration speed (Mempel et al., 2004; Miller et al., 2004). The first stage occurs approximately 8 h after T cells enter the lymph nodes, and the contact time between T cells and DCs are very short, usually no more than 30 min, and this stage is characterized by short contact between T cells and many DCs, mainly around high endothelial blood vessels. Chemokine CCL21 and intercellular adhesion molecule 1 (ICAM-1) played an important role in their brief contact (Bromley and Dustin, 2002; Friedman et al., 2006). The second stage occurs between approximately 8 h and 24 h, and the binding formed by T cells and DCs is stable and lasts for more than 1 h, and this stage is characterized by the formation of mature synaptoid contact areas between T cells and DCs. Adhesion molecules such as CD2 (Binder et al., 2020), lymphocyte function associated 1 (LFA-1) and ICAM-1 (Bromley and Dustin, 2002), as well as cytokines (Mempel et al., 2004) such as CD40L, IL-2 and interferon gamma (IFN- $\gamma$ ) play a role in the formation of mature synaptoid contact areas. The third stage occurs 24 h after the T cells enter the lymph nodes, the T cells separate from the DC, and the T cells rapidly migrate and proliferate, while continuing to make short contact with the DC. Cytokines (Mempel et al., 2004) such as CD40L, IL-2 and IFN- $\gamma$  play a role in their short contact. The

scavenger molecule Clever-1 (also known as Stabilin-1 and FEEL-1) expressed by LECs was shown to affect the migration of DC from the skin to the draining lymph node (dLN), the maturation state of the migrating DC and its ability to induce T-cell proliferation (Tadayon et al., 2021). Moreover, DC contributes to creating a cytokine environment (such as IL-10, IL-12, IL-17, IL-22, IL-23, IFN-I, tumor necrosis factor [TNF]) that drives naive T cells to differentiate into different types of effector T cells (Satpathy et al., 2012).

## 2.5 DC subpopulations in liver homeostasis

In the liver under homeostasis, hepatic DCs account for approximately 1% of the non-parenchymal hepatic cells and are a diversified population of hepatic APCs linked to innate and adaptive immunity and considered as key modulator of hepatic immune system (Hsu et al., 2007). The conventional hepatic DCs located at the periportal region and central veins, whereas the plasmacytoid hepatic DCs are located within the liver parenchyma (Jomantaite et al., 2004). The cDCs primarily serve as APCs, aiding in the activation and regulation of hepatic immune responses. The pDCs can generate a large amount of IFN-I [IFN-alpha (IFN- $\alpha$ ) and IFN-beta (IFN- $\beta$ )], which are crucial in inhibiting viral replication and promoting antiviral immune responses (Villadangos and Young, 2008; Haniffa et al., 2012). Additionally, pDCs can modulate the functions of other immune cells by producing cytokines and chemical mediators, such as activating NK cells and T cells (Brewitz et al., 2017). What's more, Mo-DCs play important roles in immune regulation, anti-inflammatory effects, and immune surveillance in the liver homeostasis (León et al., 2007; Mildner et al., 2013; Plantinga et al., 2013). They also contribute to maintaining immune balance and protecting the liver from infection and damage (Boyette et al., 2017; Wolf et al., 2019).

## 3 cDC in the liver transplantation immune response

### 3.1 cDC in the liver transplant rejection

Acute cellular rejection (ACR) occurs in up to 30% of patients within the first year after liver transplantation, and the occurrence of ACR is associated with an increased risk of graft failure, graft failure-related death, and all-cause death (Levitsky et al., 2017). ACR is mainly a cellular immune response mediated by T cells after liver transplantation. DCs, as the most important APCs in priming T cells, they present allogeneic antigens to the cognate T-cell receptor (TCR) to activate them, thus initiating cellular immune responses (Yu et al., 2012; Ueta et al., 2021). Under homeostatic conditions, hepatic DCs exhibit an immature/anti-inflammatory phenotype, T cells are barely activated, and are less immunogenic (Bamboate et al., 2009). However, after liver transplantation, DC gradually matured under the stimulation of inflammatory factors such as TNF alpha (TNF- $\alpha$ ), IFN- $\beta$ , IFN- $\gamma$ , IL-6, and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). The mature DCs initiate immune responses by inducing T cell proliferation and activation (Reis e Sousa, 2006). Mature DCs are characterized by high expression of MHC-II molecules,



costimulatory molecules (such as CD80, CD86 and CD40), chemokine receptors (such as CCR7), adhesion molecules (such as CD62L), and enhanced producing proinflammatory cytokines (such as TNF- $\alpha$ , IL-12) (Penna et al., 2002; Steinman and Banchereau, 2007; Colvin et al., 2008). The production of proinflammatory cytokines due to ischemia-reperfusion injury (IRI) during transplantation is considered to be a key factor involved in the maturation of donor DCs and their migration to recipient secondary lymphoid tissues (Lechler et al., 2001). After transplantation, danger signals mediated by pattern recognition receptors (PRRs) immediately activate DCs, leading to maturation, upregulation of costimulatory molecules, secretion of proinflammatory cytokines, and cytotoxicity (LaRosa et al., 2007).

After liver transplantation, the MHC-peptide complex on donor DC is presented to the host T cells, inducing T cell activation to initiate the immune response, which is a key step leading a donor-direct alloresponse (Hughes et al., 2020; Ronca et al., 2020). It is currently believed that there are three ways of allorecognition (Duneton et al., 2022): the direct pathway is that the donor-derived DC presents the donor MHC-antigen complex to the recipient T cells, the indirect pathway is that the recipient DCs capture donor antigen and present it to the recipient T cells, the semi-direct pathway refers to the presentation of the intact donor MHC I-antigen complex to recipient CD8<sup>+</sup>T cells in secondary lymphoid organs by “cross-modifying” receptor-derived DCs (it means that recipient DCs have acquired MHC-antigen complexes).

Extracellular vesicles (EVs) with the characteristics of exosomes plays an important role in the semi-direct pathway (Liu et al., 2016; Marino et al., 2016). Exosomes are 70–120 nm EV originated in the endocytic compartment of living cells, which have been shown to transfer proteins and RNAs between cells (Colombo et al., 2014; Robbins and Morelli, 2014). The previous view was that acute graft rejection was related to the migration of immunogenic passenger DCs to recipient lymphoid tissues (Lechler et al., 2001), now the exosomes, as a new mode of intercellular communication, have been shown to participate in IRI and immune regulation early after organ transplantation (Liu et al., 2016; Zheng et al., 2018; Hughes et al., 2020).

### 3.2 cDC in the liver transplant tolerance

In addition to initiating immune responses, cDC also plays a role in inducing and preserving immune tolerance. Lutz et al. suggested that cDC that induces tolerance is in a semi-mature state, while the induction of T cell responses requires complete DC maturation (Lutz and Schuler, 2002). DCs have been shown to be essential for maintaining central and peripheral tolerance through immune bias, inducing T cell weakness, promoting T cell apoptosis, and inducing regulatory T cells (Tregs) (Baroja-Mazo et al., 2016). Allogeneic organ transplantation can produce high frequency of allogeneic T cells, and the loss of donor reactive T cells is the key to induce transplantation tolerance. DCs can eliminate donor reactive T cells by inhibiting signaling or producing apoptotic factors (Lu et al., 1994; Süß and Shortman, 1996; Lu et al., 1999).

In the liver microenvironment, the promotion of tolerance by cDCs may be associated with hepatic stellate cells, which activate multiple immunosuppressive circuits in cDCs by secreting cytokines and chemokines (such as IL-6, CCL2, and CCL3) and all trans

retinoic acid (ATRA) (Bhatt et al., 2014). These cytokines and chemokines activate the signal transducer and activator of transcription 3 (STAT3) signaling pathway in cDCs and promote apoptosis elimination and tolerance induction of effector T cells by upregulating indoleamine 2,3-dioxygenase (IDO) in a programmed death-ligand 1 (PD-L1)-independent manner (Sumpter et al., 2012). IDO inhibits effector T cells and supports Treg cells by decomposing tryptophan, leading to local tryptophan deficiency and secretion of kynurenine (Mellor et al., 2002; Favre et al., 2010; Higashitani et al., 2013). In addition, ATRA can induce arginase 1 (ARG1) and inducible nitric oxide synthase (iNOS) in cDCs, and both arginine catabolism and nitric oxide (NO) secretion can inhibit T cells (Bhatt et al., 2014).

Under homeostatic conditions, mouse and human hepatic DCs are tolerant (Rastellini et al., 1995; Thomson and Lu, 1999; Bamboat et al., 2009). Compared with DCs from extrahepatic tissues, hepatic DCs exhibit an immature phenotype with low expression of MHC-II and costimulatory molecules (Lu et al., 1994), and they exhibit lower endocytic capacity and are poor stimulators of T cells (Lukacs-Kornek and Schuppan, 2013). In addition, hepatic DCs also exert tolerance through the production of anti-inflammatory PGE<sub>2</sub>, which can upregulate IDO, enhance the secretion of IL-10 and induce the generation of Tregs (Raïch-Regué et al., 2014). Graft infiltrated host DCs expressed high levels of PD-L1, leading to depletion of CD8<sup>+</sup> T cells and induction of immune tolerance, suggesting that hepatic DCs have a tolerogenic function after liver transplantation, which was confirmed in a liver transplantation model (Ono et al., 2018). Hepatic cDCs are also less mature in phenotype and function than secondary lymphoid tissues DC. *In vivo* experiments in mice, cDCs from the liver showed reduced ability to activate allogeneic naive T cells (Pillarisetty et al., 2004; De Creus et al., 2005; Abe et al., 2006). In addition, hepatic cDCs can also induce immune tolerance by affecting the function of T cells. In mouse experiments, hepatic cDCs were injected into allogeneic recipients and found to induce IL-10 secretion of T cells (Khanna et al., 2000). Interestingly, exosomes can also exhibit immunosuppressive effects to affect the immunogenicity of allografts in liver transplantation (Mastoridis et al., 2021). In this study, the cross-dressed sEVs (exosomes) showed the ability to inhibit the proliferation of CD8<sup>+</sup> T cells in liver transplantation. In addition, DCs cocultured with exosomes from liver transplant patients can induce lower costimulatory molecule (CD40) expression, and produce less IL-6 and more IL-10, so they have higher ability to induce DC inhibitory phenotype. In a mouse liver transplantation model (Ono et al., 2018), graft infiltrating DCs cross-dressed by donor exosomes expressed high levels of PD-L1 and significantly inhibited the proliferation of donor reactive CD8<sup>+</sup> T cells by inducing an exhaustion phenotype. In another rat model of liver transplantation (Ma et al., 2016), exosomes derived from immature DCs have been shown to amplify Tregs and prevent acute rejection.

## 4 pDC in the liver transplantation immune response

### 4.1 pDC in the liver transplant rejection

It is well known that pDCs can rapidly secrete large amounts of IFN-I in response to viral infection. In addition to secreting IFN-I,

pDCs can express MHC-II molecules and costimulatory molecules CD40, CD80, and CD86, and can present antigens to CD4<sup>+</sup> T cells, although not as effective as cDCs (Villadangos and Young, 2008; Reizis et al., 2011). Furthermore, pDCs can also regulate the survival of natural killer (NK) cells, DCs and macrophages through IFN-I, and expand CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells (Cervantes-Barragan et al., 2012; Brewitz et al., 2017). pDCs are considered to be a key factor in allograft rejection, but the underlying mechanism is still unclear. Ruben *et al.* demonstrated that pDC is an effective APC that can coordinate alloimmune responses and may play a key role in inducing chronic rejection in kidney transplantation (Ruben et al., 2018). The role of pDCs in solid organ rejection remain elusive. Experimental transplantation models have demonstrated that pDCs have the ability to present alloantigen (Björck et al., 2005; Ochando et al., 2006; Koyama et al., 2009). Another study showed that there was a large influx of pDCs in the renal tubulointerstitium at the time of rejection compared with the renal biopsy at the time of transplantation (Zuidwijk et al., 2012). In mice liver transplantation, if the donor is injected with FLT3L before transplantation to stimulate the generation of hepatic DCs (Drakes et al., 1997; Kingham et al., 2007), acute allograft rejection will occur in mice receiving liver transplantation without immunosuppression (Steptoe et al., 1997). This may be due to the fact that both cDCs (Steptoe et al., 1997) and pDCs (Kingham et al., 2007) mobilized by FLT3L increased the expression of CD80, CD86 and MHC-II molecules and enhanced the stimulatory ability of allogeneic T cells compared with normal hepatic DCs.

## 4.2 pDC in the liver transplant tolerance

Like cDCs, pDCs exhibit dual functions of immunogenicity and tolerance based on receptor connectivity and activation status. pDCs act as both innate antiviral immune effectors and inducers and regulators of adaptive immunity (Fonteneau et al., 2003), including hepatic T cell responses (Swiecki and Colonna, 2010). They drive the development of natural Tregs (Martin-Gayo et al., 2010), induce and maintain antigen-specific Tregs (Moseman et al., 2004; Palomares et al., 2012). Compared with lymphoid tissue pDCs, donor derived hepatic pDCs express high levels of DNAX-activating protein of 12 kDa (DAP12), triggering receptor expressed on myeloid cells 2 (TREM2) and a high proportion of T cell coinhibitory molecule PD-L1: costimulatory molecule CD80/86, which can attenuate graft infiltrating T effector cell responses, enhance forkhead box P3 (FOXP3)+Treg, and promote spontaneous tolerance of liver allograft in mice (Nakano et al., 2021). Compared with spleen-derived pDCs, mouse liver-derived pDCs exhibit an immature phenotype and lower levels of IL-12p70 secretion, and therefore, they exhibit reduced ability to present antigens or activate T cells (Kingham et al., 2007; Tokita et al., 2008). In addition, compared with spleen pDCs, liver pDCs secrete lower levels of IFN-I after cytosine phosphate guanosine (CpG) stimulation (Castellaneta et al., 2009), which can be explained by their relatively high expression of nucleotide-binding oligomerization domain-containing protein 2 (NOD2), a member of the nucleotide-binding oligomerization domain-like receptor (NLR) family. NOD2 can inhibit DC maturation and its ability to induce the proliferation of allogeneic

T cells by inhibiting TLR signaling (Manicassamy and Pulendran, 2011). NOD2 can also interfere with TLR4 and TLR9 signaling pathways in pDCs through its ligands, but not in cDCs, resulting in decreased secretion of pro-inflammatory cytokines (IL-6, IL-12p70, TNF- $\alpha$ , and IFN- $\gamma$ ) (Castellaneta et al., 2009). What's more, NOD2 ligation upregulated the coinhibitory PD-L1 expression on pDCs, resulting in its reduced ability to stimulate T cell proliferation (Castellaneta et al., 2009). pDCs promote tolerance *in vivo* by inducing energy deficiency or deletion of circulating T cells (Thomson and Knolle, 2010). Studies have shown that pDCs can induce the expression of IL-10 in Tregs, as well as release IFN-I (IFN- $\alpha/\beta$ ) and IDO to attenuate the activation of allogeneic T cells (Cella et al., 1999; Munn et al., 2004; Ito et al., 2007). IDO has been shown to skew the development of naive CD4<sup>+</sup> T cells toward the Treg lineage (Fallarino et al., 2006), which relies on cell-cell contact mediated mechanisms (Sharma et al., 2007). The expression of highly inducible co-stimulator ligand (ICOS-L) endows mature pDC with the ability to suppress effector T cells and increase IL-10-producing Treg cells (Campana et al., 2015).

## 5 Mo-DC in the liver transplantation immune response

Monocytes can be divided into two main types in mice and humans (Auffray et al., 2007; Yona et al., 2013; Guilliams et al., 2018): classical or inflammatory monocytes (Ly6C<sup>hi</sup>CX3CR1<sup>int</sup> in mice and CD14<sup>hi</sup>CD16<sup>-</sup> in human), nonclassical or patrolling monocytes (Ly6C<sup>low</sup>CX3CR1<sup>hi</sup> in mice and CD14<sup>low</sup>CD16<sup>+</sup> in human). At steady state, classical monocytes are stored in the bone marrow and other extramedullary sites, such as the spleen (Wolf et al., 2019). They can maintain the stability of tissue-resident macrophages in multiple organs, as well as the conversion to nonclassical monocytes (Guilliams et al., 2018). During infection and inflammation, classical or inflammatory monocytes can immediately deploy to infected or injured tissues to control infection, limit inflammatory damage and initiate tissue repair by producing macrophages or Mo-DCs (Boyette et al., 2017; Wolf et al., 2019). Nonclassical or patrolling monocytes are characterized by patrolling the circulation, clearing cellular debris and repairing the endothelium in homeostasis (Hanna et al., 2011; Carlin et al., 2013).

Most of our knowledge about Mo-DC comes from infection models. Under inflammatory conditions, classical monocyte-derived DC can become a large population that complements the range of steady-state DCs (Serbina et al., 2003; Le Borgne et al., 2006; León et al., 2007). Mo-DCs upregulate CD11c and MHC-II, but generally retain expression of monocyte markers such as Ly6C, Ly6B, CD64 (León et al., 2007; Rosas et al., 2010; Plantinga et al., 2013). They mediate effector functions through the production of T<sub>H</sub>1 cytokines TNF- $\alpha$  and IL-12, as well as direct cytotoxicity through NO production (Serbina et al., 2003; León et al., 2007; Goldszmid et al., 2012; Plantinga et al., 2013). In addition, Mo-DCs have phagocytic activity and the ability to process antigens, participating in the initiation of naive T cells or the reactivation of antigen experienced T cells (Mildner et al., 2013). Furthermore, it has been found in some tumor studies that the presence of Mo-DC is associated with the activation of CD8<sup>+</sup> T cells and treatment success in some tumors (Rich et al., 2012; Kuhn et al., 2013;

Kuhn et al., 2015). Mo-DC based vaccination also plays a role in various malignant tumors (Frankenberger et al., 2005; Javed et al., 2016; Van den Bergh et al., 2017).

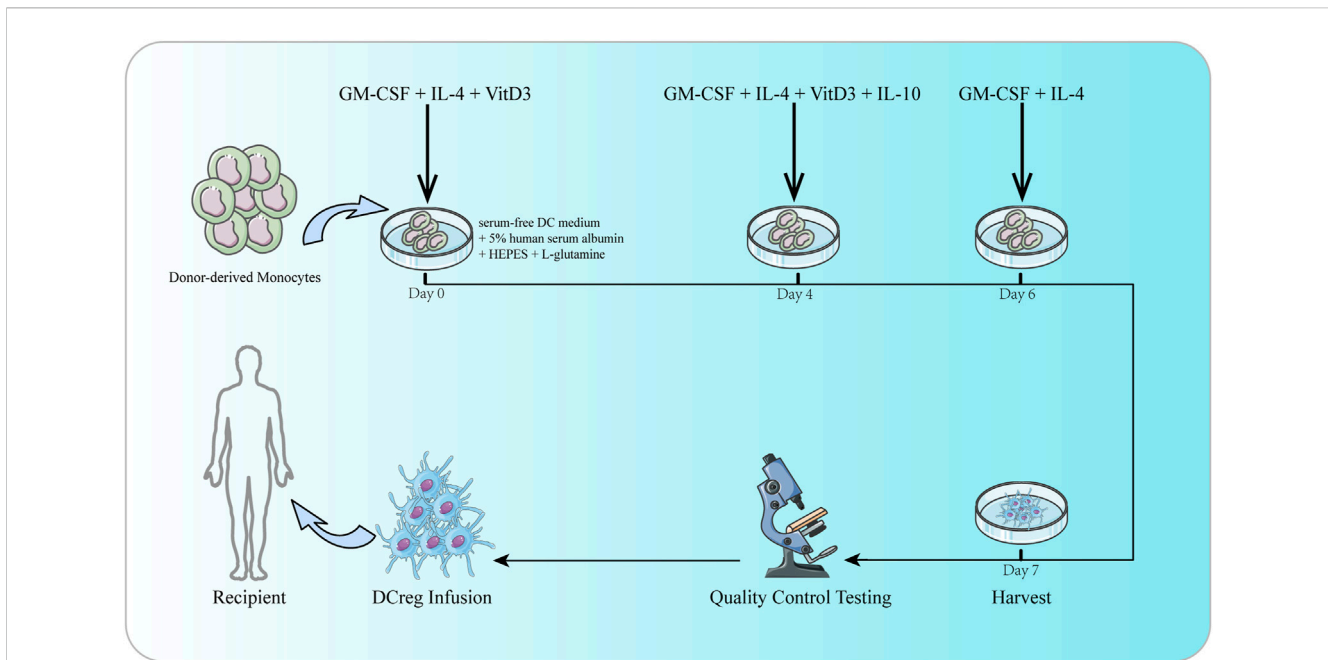
Unlike classical monocytes, which play a major role in the site of inflammation (Serbina et al., 2003), nonclassical monocytes play a major role in sterile inflammation (for instance, in atherosclerotic plaques (Tacke et al., 2007)). In organ transplantation, the synergistic effect of allogeneic non-self and sterile inflammation may trigger the differentiation of nonclassical monocytes into DCs (Zhuang et al., 2016), nonclassical monocyte-derived DCs may also arise in the context of transplanted organs and may be involved in inducing allograft rejection (Chow et al., 2016). In a study of heart and kidney transplantation in mice, it was found that donor DCs would be rapidly replaced by recipient DCs after transplantation. Recipient nonclassical monocyte derived DCs played an important role in rejection by promoting the proliferation and survival of effector T cells in the graft (Zhuang et al., 2016). In another experimental study in mice, Mo-DCs was rapidly recruited after experimental heart and kidney transplantation, allogeneic grafts elicited persistent differentiation of monocytes to mature DCs that express IL-12, stimulate T cell proliferation and IFN- $\gamma$  production, and precipitate graft rejection (Oberbarnscheidt et al., 2014). Similarly, Zecher et al. injected allogeneic splenocytes into the ear pinnae of recombination activating gene (RAG)<sup>-/-</sup> mice, resulting in significantly greater skin swelling and infiltration by host bone marrow cells compared with injection of syngeneic splenocytes. This response is mediated by Gr-1 (Ly6C)<sup>int</sup> monocytes, suggesting that they are able to discriminate between self and nonself tissue to initiate effector responses (Zecher et al., 2009). In another study, it was also observed that intravenous injection of allogeneic splenocytes in mice could stimulate the rapid (within 1 day) accumulation of splenic Mo-DCs more than syngeneic splenocytes or nothing injection. These findings suggest that (Chow et al., 2016) Mo-DCs have a potentially important role in responding to allogeneic stimuli, such as those occurring in the context of organ transplantation. In addition, in mouse pancreas transplantation, Mo-DCs can impair the early graft function after islet allograft transplantation, and the graft function of recipients with Mo-DC removed is improved as early as the first day after transplantation, which strongly suggests that Mo-DCs can participate in the early injury of islet allografts (Chow et al., 2017). In an experimental study of bone marrow transplantation (Asiedu et al., 2002), non-human primate (NHP) mature Mo-DCs can be genetically engineered as an alloantigen specific cellular immunosuppressant, which has the potential to promote the induction of allograft tolerance *in vivo*. What's more, In a recent study (Lee et al., 2021), due to the relatively simple culture process and more efficient Treg expansion capacity of stimulated mature Mo-DCs, they may be a viable alternative for producing alloreactive Tregs for clinical use. But until recently, experimental research on Mo-DC in liver transplantation was extremely rare. In a study of human liver transplantation (Shariat et al., 2014), researchers found that compared with healthy individuals, the gene expression of IL-12 and TLR2 secreted by Mo-DCs in liver transplant patients were significantly increased. Signaling through TLR2 can induce DCs to mature in a myeloid differentiation primary response 88 (MyD88) dependent or independent manner, ultimately leading to the release of proinflammatory cytokines (Chinen and Buckley, 2010). In

addition, the increase of TLR2 and TLR4 levels can also be used for the early prediction of acute rejection after liver transplantation (Deng et al., 2007). IL-12 can induce the development and inflammatory process of T<sub>H</sub>1 cells in transplanted patients (Goriely and Goldman, 2008), which may contribute to the occurrence of liver transplantation rejection. Overall, although the role of Mo-DC in infection and inflammation has been increasingly understood, their special role in organ transplantation, especially in the case of liver transplantation, still needs more research to explore.

## 6 The latest progress of DC based treatment

The use of donor or host-derived tolerogenic dendritic cell (Tol-DC) or *in situ* targeted DC for cell therapy to promote its tolerance is an emerging method to reduce the use of systemic IS in transplant patients and promote donor-specific tolerance (Ochando and Braza, 2017; Marín et al., 2018). Tol-DC refers to some DCs that can inhibit immune responses, including immature DC (imDC), regulatory DC (DCreg), maturation resistant or alternatively activated DC (Morelli and Thomson, 2007). Tol-DCs are characterized by low expression of MHC-II and co-stimulatory molecules CD80/CD86 and CD40, high expression of anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF- $\beta$ ), and low expression of pro-inflammatory cytokines such as IL-12p70 (Maldonado and von Andrian, 2010; Marín et al., 2018). In addition, Tol-DCs also have low antigen-presenting function and participate in immune tolerance by inducing reactive T cell weakness and apoptosis (Choo et al., 2017; Spiering et al., 2019). Tol-DC has been extensively studied in preclinical models and is very effective in limiting autoimmune diseases (Hilkens et al., 2010) or allograft rejection in transplantation (Ochando et al., 2020; Chen et al., 2023).

Extensive studies in rodent and NHP models have shown that adoptively transferred regulatory immune cells can promote transplant tolerance. DCreg is an important candidate for adoptive cell therapy in organ transplantation (Moreau et al., 2017; Thomson et al., 2019), which can suppress T cell responses by inducing T cell weakness or apoptosis (Lu et al., 1997; Lu and Thomson, 2002; Zahorchak et al., 2018). What's more, DCregs also have the potential to retain, expand or induce Treg (Morelli and Thomson, 2007; Huang et al., 2010; Raker et al., 2015). DCregs were generated in granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4 from rodent and human bone marrow precursor cells or human circulating blood monocytes *in vitro* (Zahorchak et al., 2023). In the culture of DCreg, one or more agents, cytokines or growth factors or genetic engineering (Bonham et al., 2002) methods are added to inhibit DC maturation and enhance its tolerance (Hackstein and Thomson, 2004). These agents include immunomodulatory drugs [such as vitamin D3 (VitD3), corticosteroids, rapamycin, cyclosporine, tacrolimus, and aspirin], cytokines or growth factors [such as hepatocyte growth factor (HGF), vasoactive intestinal peptide (VIP), thymic stromal lymphopoietin, PGE2, IL-10, and TGF- $\beta$ ] (Raker et al., 2015; Thomson et al., 2019). However, there is still no consensus on the best protocol for generating clinical-grade human DCreg (Navarro-Barruso et al., 2018;



**FIGURE 2**

The culture of DCreg. Donor-derived monocytes are resuspended in DC culture media consisting of serum-free DC medium, 5% human serum albumin, HEPES, and L-glutamine. GM-CSF, IL-4 and VitD3 are added on days 0 and 4. IL-10 is also added on day 4. On day 6, culture media is replenished with DC media supplemented with GM-CSF and IL-4. DCreg products are harvested on day 7. Before infusion, DCreg products are subjected to rigorous quality control testing to ensure purity, sterility, yield and viability.

**TABLE 2 Registered clinical trials targeting DC in liver or kidney transplantation.**

Cell type	Conditions	Intervention/treatment	Trial id	Status
Autologous tolerogenic dendritic cell	living donor renal transplantation	Autologous tol-DC treatment occurs the day before transplantation into recipients also recipients of a living donor renal transplantation	NCT02252055	Completed
Donor blood monocyte-derived regulatory dendritic cell	living donor renal transplantation	single infusion of donor-derived DCreg 1 week before living donor renal transplantation	NCT03726307	Recruiting
Donor blood monocyte-derived regulatory dendritic cell	living donor liver transplantation	single infusion of donor-derived DCreg 1 week prior to the initiation of immunosuppression weaning	NCT04208919	Active, not recruiting
Donor blood monocyte-derived regulatory dendritic cell	living donor liver transplantation	single infusion of donor-derived DCreg 1 week before living donor liver transplantation	NCT03164265	Active, not recruiting

Thomson et al., 2019). DCreg infusion improves the incidence of safe withdrawal of IS and operational tolerance in human liver transplantation (Thomson et al., 2019). The safety, feasibility and potential efficacy of autologous DCreg infusion has been confirmed in the treatment of various diseases, including type-1 diabetes, rheumatoid arthritis, Crohn’s colitis, multiple sclerosis (Giannoukakis et al., 2011; Jauregui-Amezaga et al., 2015; Bell et al., 2017; Zubizarreta et al., 2019). Studies have described the rationale for the first human trial of donor-derived DCreg injected before living donor liver transplantation (LDLT) in combination with triple IS (steroid hormones, mycophenolate mofetil and tacrolimus) to promote operational tolerance (Zahorchak et al., 2018). In another study (Macedo et al., 2021), infusion of donor monocyte-derived DCregs in the first 7 days of LDLT can induce changes in host APC, memory CD8+T cell and Treg, which may be beneficial to regulate immune reactivity during transplantation, thereby promoting operational tolerance. In the latest study of

manufacturing GMP grade DCreg for 27 liver transplant recipients (Zahorchak et al., 2023), under GMP conditions, circulating monocytes can easily produce high-purity DCreg that meets a series of quality standards to attain the target cell number injected into potential organ transplant recipients (Figure 2). Two clinical trials of DCreg in liver transplantation (NCT03164265 and NCT04208919) are ongoing to evaluate the safety and efficacy of donor derived DCreg in LDLT through a single infusion. The registered clinical trials targeting DC in transplantation are shown in Table 2.

What’s more, a recent study have used the optimization of physical and chemical properties of nanoparticles to design DC targeted nanomedicines for immune tolerance in organ transplantation and autoimmune diseases (Cifuentes-Rius et al., 2021). Targeting specific receptors on DC using nanomedicines not only helps to enhance absorption, but also has the ability of antigen cross presentation, thereby promoting peripheral tolerance.



Despite its great potential, this method is still in its infancy, and its persistence, safety, and complexity related to the immune system and multiple mechanisms may limit the development of this method.

## 7 Conclusion and future prospects

In this article, we described the subgroups, development, phenotype, migration and function of DC, and the roles of these DC subsets, including cDC, pDC, and Mo-DC in liver transplant rejection and tolerance. During rejection, cDC plays an important role in the initiation of immune rejection by presenting donor antigens. pDC, as a weaker APC, cannot be overlooked as they also enhance the stimulation ability of allogeneic T cells by expressing MHC-II molecules and costimulatory molecules. Now, increasingly evidence suggested the Mo-DC is the major mediator to activate alloreactive T cell in the graft, but their role in liver transplantation is not fully revealed. In the future, more effort is needed to explore the role of Mo-DC in alloresponse in the liver allograft.

By adopting an immature phenotype, both cDC and pDC can promote T cell apoptosis and generate Tregs to promote immune tolerance. Adoptive transfer of the DCreg or Tol-DC exhibiting immature phenotype induces tolerance, but the best clinical grade DCreg or Tol-DC production scheme is still needed.

In conclusion, these discussions provide useful resources for better understanding the biology of DC and improving the immune adaptability of transplant patients by manipulating DC.

## Author contributions

XD: Writing—original draft. ML: Writing—original draft, Writing—review and editing. CH: Writing—review and editing. GL: Writing—review and editing.

## References

- Abe, M., Tokita, D., Raimondi, G., and Thomson, A. W. (2006). Endotoxin modulates the capacity of CpG-activated liver myeloid DC to direct Th1-type responses. *Eur. J. Immunol.* 36 (9), 2483–2493. doi:10.1002/eji.200535767
- Anderson, D. A., Murphy, K. M., and Briseño, C. G. (2018). Development, Diversity, and Function of Dendritic Cells in Mouse and Human. *Cold Spring Harb. Perspect. Biol.* 10 (11), a028613. doi:10.1101/cshperspect.a028613
- Asiedu, C., Dong, S. S., Pereboev, A., Wang, W., Navarro, J., Curiel, D. T., et al. (2002). Rhesus monocyte-derived dendritic cells modified to over-express TGF-beta1 exhibit potent veto activity. *Transplantation* 74 (5), 629–637. doi:10.1097/00007890-200209150-00008
- Auffray, C., Fogg, D., Garfa, M., Elain, G., Join-Lambert, O., Kayal, S., et al. (2007). Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Sci. (New York, N.Y.)* 317 (5838), 666–670. doi:10.1126/science.1142883
- Bachem, A., Güttler, S., Hartung, E., Ebstein, F., Schaefer, M., Tannert, A., et al. (2010). Superior antigen cross-presentation and XCR1 expression define human CD11c+CD141+ cells as homologues of mouse CD8+ dendritic cells. *J. Exp. Med.* 207 (6), 1273–1281. doi:10.1084/jem.20100348
- Bamboas, Z. M., Stableford, J. A., Plitas, G., Burt, B. M., Nguyen, H. M., Welles, A. P., et al. (2009). Human liver dendritic cells promote T cell hyporesponsiveness. *J. Immunol.* 182 (4), 1901–1911. doi:10.4049/jimmunol.0803404
- Baroja-Mazo, A., Revilla-Nuin, B., Parrilla, P., Martínez-Alarcón, L., Ramírez, P., and Pons, J. A. (2016). Tolerance in liver transplantation: biomarkers and clinical relevance. *World J. Gastroenterology* 22 (34), 7676–7691. doi:10.3748/wjg.v22.i34.7676
- Bell, G. M., Anderson, A. E., Diboll, J., Reece, R., Eltherington, O., Harry, R. A., et al. (2017). Autologous tolerogenic dendritic cells for rheumatoid and inflammatory arthritis. *Ann. Rheumatic Dis.* 76 (1), 227–234. doi:10.1136/annrheumdis-2015-208456
- Bhatt, S., Qin, J., Bennett, C., Qian, S., Fung, J. J., Hamilton, T. A., et al. (2014). All-trans retinoic acid induces arginase-1 and inducible nitric oxide synthase-producing dendritic cells with T cell inhibitory function. *J. Immunol.* 192 (11), 5098–5108. doi:10.4049/jimmunol.1303073
- Binder, C., Cvetkovski, F., Sellberg, F., Berg, S., Paternina Visbal, H., Sachs, D. H., et al. (2020). CD2 Immunobiology. *Front. Immunol.* 11, 1090. doi:10.3389/fimmu.2020.101090
- Björck, P., Coates, P. T. H., Wang, Z., Duncan, F. J., and Thomson, A. W. (2005). Prolongation of long-term heart allograft survival by combination of mobilized donor plasmacytoid dendritic cells and anti-CD154 monoclonal antibody. *J. Heart Lung Transplant.* 24 (8), 1118–1120. doi:10.1016/j.healun.2004.10.007
- Bonham, C. A., Peng, L., Liang, X., Chen, Z., Wang, L., Ma, L., et al. (2002). Marked prolongation of cardiac allograft survival by dendritic cells genetically engineered with NF-kappa B oligodeoxynucleotide decoys and adenoviral vectors encoding CTLA4-Ig. *J. Immunol.* 169 (6), 3382–3391. doi:10.4049/jimmunol.169.6.3382
- Bošnjak, B., Do, K. T. H., Förster, R., and Hammerschmidt, S. I. (2022). Imaging dendritic cell functions. *Immunol. Rev.* 306 (1), 137–163. doi:10.1111/imr.13050
- Boulet, S., Daudelin, J.-F., Odagiu, L., Pelletier, A.-N., Yun, T. J., Lesage, S., et al. (2019). The orphan nuclear receptor NR4A3 controls the differentiation of monocyte-

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## Conflict of interest

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcell.2023.1277743/full#supplementary-material>

- derived dendritic cells following microbial stimulation. *Proc. Natl. Acad. Sci. U. S. A.* 116 (30), 15150–15159. doi:10.1073/pnas.1821296116
- Boyette, L. B., Macedo, C., Hadi, K., Elinoff, B. D., Walters, J. T., Ramaswami, B., et al. (2017). Phenotype, function, and differentiation potential of human monocyte subsets. *PLoS One* 12 (4), e0176460. doi:10.1371/journal.pone.0176460
- Braun, A., Worbs, T., Moschovakis, G. L., Halle, S., Hoffmann, K., Bölder, J., et al. (2011). Afferent lymph-derived T cells and DCs use different chemokine receptor CCR7-dependent routes for entry into the lymph node and intranodal migration. *Nat. Immunol.* 12 (9), 879–887. doi:10.1038/ni.2085
- Brewitz, A., Eickhoff, S., Dähling, S., Quast, T., Bedoui, S., Kroczeck, R. A., et al. (2017). CD8+ T Cells Orchestrate pDC-XCR1+ Dendritic Cell Spatial and Functional Cooperativity to Optimize Priming. *Immunity* 46 (2), 205–219. doi:10.1016/j.immuni.2017.01.003
- Briseño, C. G., Haldar, M., Kretzer, N. M., Wu, X., Theisen, D. J., Kc, W., et al. (2016). Distinct Transcriptional Programs Control Cross-Priming in Classical and Monocyte-Derived Dendritic Cells. *Cell Rep.* 15 (11), 2462–2474. doi:10.1016/j.celrep.2016.05.025
- Bromley, S. K., and Dustin, M. L. (2002). Stimulation of naïve T-cell adhesion and immunological synapse formation by chemokine-dependent and -independent mechanisms. *Immunology* 106 (3), 289–298. doi:10.1046/j.1365-2567.2002.01441.x
- Cabeza-Cabrerizo, M., Cardoso, A., Minutti, C. M., Pereira da Costa, M., and Reis e Sousa, C. (2021). Dendritic Cells Revisited. *Annu. Rev. Immunol.* 39, 131–166. doi:10.1146/annurev-immunol-061020-053707
- Campana, S., De Pasquale, C., Carrega, P., Ferlazzo, G., and Bonaccorsi, I. (2015). Cross-dressing: an alternative mechanism for antigen presentation. *Immunol. Lett.* 168 (2), 349–354. doi:10.1016/j.imlet.2015.11.002
- Carlin, L. M., Stamatiades, E. G., Auffray, C., Hanna, R. N., Glover, L., Vizcay-Barrena, G., et al. (2013). Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. *Cell* 153 (2), 362–375. doi:10.1016/j.cell.2013.03.010
- Castellaneta, A., Sumpter, T. L., Chen, L., Tokita, D., and Thomson, A. W. (2009). NOD2 ligation subverts IFN- $\alpha$  production by liver plasmacytoid dendritic cells and inhibits their T cell allostimulatory activity via B7-H1 up-regulation. *J. Immunol.* 183 (11), 6922–6932. doi:10.4049/jimmunol.0900582
- Cella, M., Jarrossay, D., Facchetti, F., Aleardi, O., Nakajima, H., Lanzavecchia, A., et al. (1999). Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nat. Med.* 5 (8), 919–923. doi:10.1038/11360
- Cervantes-Barragan, L., Lewis, K. L., Firner, S., Thiel, V., Hugues, S., Reith, W., et al. (2012). Plasmacytoid dendritic cells control T-cell response to chronic viral infection. *Proc. Natl. Acad. Sci. U. S. A.* 109 (8), 3012–3017. doi:10.1073/pnas.1117359109
- Chen, J., Cao, Y., Jia, O., Wang, X., Luo, Y., Cheuk, Y. C., et al. (2023). Monomethyl fumarate prevents alloimmune rejection in mouse heart transplantation by inducing tolerogenic dendritic cells. *Acta Biochimica Biophysica Sinica* 55 (5), 866–877. doi:10.3724/abbs.2023088
- Chinen, J., and Buckley, R. H. (2010). Transplantation immunology: solid organ and bone marrow. *J. Allergy Clin. Immunol.* 125 (2), S324–S335. doi:10.1016/j.jaci.2009.11.014
- Choo, E. H., Lee, J.-H., Park, E.-H., Park, H. E., Jung, N.-C., Kim, T.-H., et al. (2017). Infarcted Myocardium-Primed Dendritic Cells Improve Remodeling and Cardiac Function After Myocardial Infarction by Modulating the Regulatory T Cell and Macrophage Polarization. *Circulation* 135 (15), 1444–1457. doi:10.1161/CIRCULATIONAHA.116.023106
- Chow, K. V., Carrington, E. M., Zhan, Y., Lew, A. M., and Sutherland, R. M. (2017). Monocyte-Derived Dendritic Cells Impair Early Graft Function Following Allogeneic Islet Transplantation. *Cell Transplant.* 26 (2), 319–326. doi:10.3727/096368916X693482
- Chow, K. V., Delconte, R. B., Huntington, N. D., Tarlinton, D. M., Sutherland, R. M., Zhan, Y., et al. (2016). Innate Allorecognition Results in Rapid Accumulation of Monocyte-Derived Dendritic Cells. *J. Immunol.* 197 (5), 2000–2008. doi:10.4049/jimmunol.1600181
- Cifuentes-Rius, A., Desai, A., Yuen, D., Johnston, A. P. R., and Voelcker, N. H. (2021). Inducing immune tolerance with dendritic cell-targeting nanomedicines. *Nat. Nanotechnol.* 16 (1), 37–46. doi:10.1038/s41565-020-00810-2
- Cisse, B., Caton, M. L., Lehner, M., Maeda, T., Scheu, S., Locksley, R., et al. (2008). Transcription factor E2-2 is an essential and specific regulator of plasmacytoid dendritic cell development. *Cell* 135 (1), 37–48. doi:10.1016/j.cell.2008.09.016
- Clavien, P.-A., Muller, X., de Oliveira, M. L., Dutkowski, P., and Sanchez-Fueyo, A. (2017). Can immunosuppression be stopped after liver transplantation? *Lancet. Gastroenterology Hepatology* 2 (7), 531–537. doi:10.1016/S2468-1253(16)30208-4
- Colombo, M., Raposo, G., and Théry, C. (2014). Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu. Rev. Cell Dev. Biol.* 30, 255–289. doi:10.1146/annurev-cellbio-101512-122326
- Colonna, M., Trinchieri, G., and Liu, Y.-J. (2004). Plasmacytoid dendritic cells in immunity. *Nat. Immunol.* 5 (12), 1219–1226. doi:10.1038/ni1141
- Colvin, B. L., Matta, B. M., and Thomson, A. W. (2008). Dendritic cells and chemokine-directed migration in transplantation: where are we headed? *Clin. Laboratory Med.* 28 (3), 375–384. doi:10.1016/j.cl.2008.07.003
- Corse, E., Gottschalk, R. A., and Allison, J. P. (2011). Strength of TCR-peptide/MHC interactions and *in vivo* T cell responses. *J. Immunol.* 186 (9), 5039–5045. doi:10.4049/jimmunol.1003650
- Crozat, K., Guiton, R., Contreras, V., Feuillet, V., Dutertre, C.-A., Ventre, E., et al. (2010). The XC chemokine receptor 1 is a conserved selective marker of mammalian cells homologous to mouse CD8 $\alpha$ + dendritic cells. *J. Exp. Med.* 207 (6), 1283–1292. doi:10.1084/jem.20100223
- De Creus, A., Abe, M., Lau, A. H., Hackstein, H., Raimondi, G., and Thomson, A. W. (2005). Low TLR4 expression by liver dendritic cells correlates with reduced capacity to activate allogeneic T cells in response to endotoxin. *J. Immunol.* 174 (4), 2037–2045. doi:10.4049/jimmunol.174.4.2037
- Demetris, A. J., Bellamy, C. O. C., Gandhi, C. R., Prost, S., Nakanuma, Y., and Stolz, D. B. (2016). Functional Immune Anatomy of the Liver-As an Allograft. *Am. J. Transplant.* 16 (6), 1653–1680. doi:10.1111/ajt.13749
- Deng, J. F., Geng, L., Qian, Y. G., Li, H., Wang, Y., Xie, H. Y., et al. (2007). The role of toll-like receptors 2 and 4 in acute allograft rejection after liver transplantation. *Transplant. Proc.* 39 (10), 3222–3224. doi:10.1016/j.transproceed.2007.02.102
- Drakes, M. L., Lu, L., Subbotin, V. M., and Thomson, A. W. (1997). *In vivo* administration of flt3 ligand markedly stimulates generation of dendritic cell progenitors from mouse liver. *J. Immunol.* 159 (9), 4268–4278. doi:10.4049/jimmunol.159.9.4268
- Duneton, C., Winterberg, P. D., and Ford, M. L. (2022). Activation and regulation of alloreactive T cell immunity in solid organ transplantation. *Nat. Rev. Nephrol.* 18 (10), 663–676. doi:10.1038/s41581-022-00600-0
- Durai, V., and Murphy, K. M. (2016). Functions of Murine Dendritic Cells. *Immunity* 45 (4), 719–736. doi:10.1016/j.immuni.2016.10.010
- Eckert, C., Klein, N., Kornek, M., and Lukacs-Kornek, V. (2015). The complex myeloid network of the liver with diverse functional capacity at steady state and in inflammation. *Front. Immunol.* 6, 179. doi:10.3389/fimmu.2015.00179
- Edelson, B. T., Kc, W., Juang, R., Kohyama, M., Benoit, L. A., Klekotka, P. A., et al. (2010). Peripheral CD103+ dendritic cells form a unified subset developmentally related to CD8 $\alpha$ + conventional dendritic cells. *J. Exp. Med.* 207 (4), 823–836. doi:10.1084/jem.20091627
- Fallarino, F., Grohmann, U., You, S., McGrath, B. C., Cavener, D. R., Vacca, C., et al. (2006). The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naïve T cells. *J. Immunol.* 176 (11), 6752–6761. doi:10.4049/jimmunol.176.11.6752
- Fancke, B., Suter, M., Hochrein, H., and O’Keeffe, M. (2008). M-CSF: a novel plasmacytoid and conventional dendritic cell poietin. *Blood* 111 (1), 150–159. doi:10.1182/blood-2007-05-089292
- Favre, D., Mold, J., Hunt, P. W., Kanwar, B., Loke, P. n., Seu, L., et al. (2010). Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. *Sci. Transl. Med.* 2 (32), 32ra36. doi:10.1126/scitranslmed.3000632
- Fogg, D. K., Sibon, C., Miled, C., Jung, S., Aucouturier, P., Littman, D. R., et al. (2006). A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. *Sci. (New York, N.Y.)* 311 (5757), 83–87. doi:10.1126/science.1117729
- Fonteneau, J.-F., Gilliet, M., Larsson, M., Dasilva, I., Münz, C., Liu, Y.-J., et al. (2003). Activation of influenza virus-specific CD4+ and CD8+ T cells: a new role for plasmacytoid dendritic cells in adaptive immunity. *Blood* 101 (9), 3520–3526. doi:10.1182/blood-2002-10-3063
- Förster, R., Schubel, A., Breitfeld, D., Kremmer, E., Renner-Müller, I., Wolf, E., et al. (1999). CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. *Cell* 99 (1), 23–33. doi:10.1016/S0092-8674(00)80059-8
- Frankenberger, B., Regn, S., Geiger, C., Noessner, E., Falk, C. S., Pohla, H., et al. (2005). Cell-based vaccines for renal cell carcinoma: genetically-engineered tumor cells and monocyte-derived dendritic cells. *World J. Urology* 23 (3), 166–174. doi:10.1007/s00345-005-0505-5
- Friedman, R. S., Jacobelli, J., and Krummel, M. F. (2006). Surface-bound chemokines capture and prime T cells for synapse formation. *Nat. Immunol.* 7 (10), 1101–1108. doi:10.1038/ni1384
- Geissmann, F., Jung, S., and Littman, D. R. (2003). Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity* 19 (1), 71–82. doi:10.1016/S1074-7613(03)00174-2
- Giannoukakis, N., Phillips, B., Finegold, D., Harnaha, J., and Trucco, M. (2011). Phase I (safety) study of autologous tolerogenic dendritic cells in type 1 diabetic patients. *Diabetes Care* 34 (9), 2026–2032. doi:10.2337/dc11-0472
- Goldszmid, R. S., Caspar, P., Rivollier, A., White, S., Dzutsev, A., Hieny, S., et al. (2012). NK cell-derived interferon- $\gamma$  orchestrates cellular dynamics and the differentiation of monocytes into dendritic cells at the site of infection. *Immunity* 36 (6), 1047–1059. doi:10.1016/j.immuni.2012.03.026
- Goriely, S., and Goldman, M. (2008). Interleukin-12 family members and the balance between rejection and tolerance. *Curr. Opin. Organ Transplant.* 13 (1), 4–9. doi:10.1097/MOT.0b013e3282f406c4
- Goudot, C., Coillard, A., Villani, A.-C., Gueguen, P., Cros, A., Sarkizova, S., et al. (2017). Aryl Hydrocarbon Receptor Controls Monocyte Differentiation into Dendritic Cells versus Macrophages. *Immunity* 47 (3), 582–596. doi:10.1016/j.immuni.2017.08.016

- Grajkowska, L. T., Ceribelli, M., Lau, C. M., Warren, M. E., Tiniakou, I., Nakandakari Higa, S., et al. (2017). Isoform-Specific Expression and Feedback Regulation of E Protein TCF4 Control Dendritic Cell Lineage Specification. *Immunity* 46 (1), 65–77. doi:10.1016/j.immuni.2016.11.006
- Guilliams, M., Dutertre, C.-A., Scott, C. L., McGovern, N., Sichnen, D., Chakarov, S., et al. (2016). Unsupervised High-Dimensional Analysis Aligns Dendritic Cells across Tissues and Species. *Immunity* 45 (3), 669–684. doi:10.1016/j.immuni.2016.08.015
- Guilliams, M., Ginhoux, F., Jakubczick, C., Naik, S. H., Onai, N., Schraml, B. U., et al. (2014). Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. *Nat. Rev. Immunol.* 14 (8), 571–578. doi:10.1038/nri3712
- Guilliams, M., Mildner, A., and Yona, S. (2018). Developmental and Functional Heterogeneity of Monocytes. *Immunity* 49 (4), 595–613. doi:10.1016/j.immuni.2018.10.005
- Hackstein, H., and Thomson, A. W. (2004). Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. *Nat. Rev. Immunol.* 4 (1), 24–34. doi:10.1038/nri1256
- Haniffa, M., Shin, A., Bigley, V., McGovern, N., Teo, P., See, P., et al. (2012). Human tissues contain CD141hi cross-presenting dendritic cells with functional homology to mouse CD103+ nonlymphoid dendritic cells. *Immunity* 37 (1), 60–73. doi:10.1016/j.immuni.2012.04.012
- Hanna, R. N., Carlin, L. M., Hubbeling, H. G., Nackiewicz, D., Green, A. M., Punt, J. A., et al. (2011). The transcription factor NR4A1 (Nur77) controls bone marrow differentiation and the survival of Ly6C- monocytes. *Nat. Immunol.* 12 (8), 778–785. doi:10.1038/ni.2063
- Hettinger, J., Richards, D. M., Hansson, J., Barra, M. M., Joschko, A.-C., Krijgsvel, J., et al. (2013). Origin of monocytes and macrophages in a committed progenitor. *Nat. Immunol.* 14 (8), 821–830. doi:10.1038/ni.2638
- Higashitani, K., Kanto, T., Kuroda, S., Yoshio, S., Matsubara, T., Kakita, N., et al. (2013). Association of enhanced activity of indoleamine 2,3-dioxygenase in dendritic cells with the induction of regulatory T cells in chronic hepatitis C infection. *J. Gastroenterology* 48 (5), 660–670. doi:10.1007/s00535-012-0667-z
- Hilkens, C. M. U., Isaacs, J. D., and Thomson, A. W. (2010). Development of dendritic cell-based immunotherapy for autoimmunity. *Int. Rev. Immunol.* 29 (2), 156–183. doi:10.3109/08830180903281193
- Hsu, W., Shu, S.-A., Gershwin, E., and Lian, Z.-X. (2007). The current immune function of hepatic dendritic cells. *Cell. Mol. Immunol.* 4 (5), 321–328.
- Huang, H., Dawicki, W., Zhang, X., Town, J., and Gordon, J. R. (2010). Tolerogenic dendritic cells induce CD4+CD25hiFoxp3+ regulatory T cell differentiation from CD4+CD25-/loFoxp3-effector T cells. *J. Immunol.* 185 (9), 5003–5010. doi:10.4049/jimmunol.0903446
- Hughes, A. D., Zhao, D., Dai, H., Abou-Daya, K. I., Tieu, R., Rammal, R., et al. (2020). Cross-dressed dendritic cells sustain effector T cell responses in islet and kidney allografts. *J. Clin. Investigation* 130 (1), 287–294. doi:10.1172/JCI125773
- Iizasa, H., Yoneyama, H., Mukaida, N., Katakoka, Y., Naito, M., Yoshida, N., et al. (2005). Exacerbation of granuloma formation in IL-1 receptor antagonist-deficient mice with impaired dendritic cell maturation associated with Th2 cytokine production. *J. Immunol.* 174 (6), 3273–3280. doi:10.4049/jimmunol.174.6.3273
- Ito, T., Yang, M., Wang, Y.-H., Lande, R., Gregorio, J., Perng, O. A., et al. (2007). Plasmacytoid dendritic cells prime IL-10-producing T regulatory cells by inducible costimulator ligand. *J. Exp. Med.* 204 (1), 105–115. doi:10.1084/jem.20061660
- Jauregui-Amezaga, A., Cabezon, R., Ramirez-Morros, A., Espana, C., Rimola, J., Bru, C., et al. (2015). Intraperitoneal Administration of Autologous Tolerogenic Dendritic Cells for Refractory Crohn's Disease: A Phase I Study. *J. Crohn's Colitis* 9 (12), 1071–1078. doi:10.1093/ecco-jcc/jjv144
- Javed, A., Sato, S., and Sato, T. (2016). Autologous melanoma cell vaccine using monocyte-derived dendritic cells (NBS20/ultrapuldencl-T). *Future Oncol. Lond. Engl.* 12 (6), 751–762. doi:10.2217/fon.16.13
- Johnson, L. A., Banerji, S., Lagerholm, B. C., and Jackson, D. G. (2021). Dendritic cell entry to lymphatic capillaries is orchestrated by CD44 and the hyaluronan glycoalyx. *Life Sci. Alliance* 4 (5), e202000908. doi:10.26508/lsa.202000908
- Johnson, L. A., Banerji, S., Lawrance, W., Gileadi, U., Protá, G., Holder, K. A., et al. (2017). Dendritic cells enter lymph vessels by hyaluronan-mediated docking to the endothelial receptor LYVE-1. *Nat. Immunol.* 18 (7), 762–770. doi:10.1038/ni.3750
- Jomantaite, I., Dikopoulos, N., Kröger, A., Leithäuser, F., Hauser, H., Schirmbeck, R., et al. (2004). Hepatic dendritic cell subsets in the mouse. *Eur. J. Immunol.* 34 (2), 355–365. doi:10.1002/eji.200324336
- Khanna, A., Morelli, A. E., Zhong, C., Takayama, T., Lu, L., and Thomson, A. W. (2000). Effects of liver-derived dendritic cell progenitors on Th1- and Th2-like cytokine responses *in vitro* and *in vivo*. *J. Immunol.* 164 (3), 1346–1354. doi:10.4049/jimmunol.164.3.1346
- Kingham, T. P., Chaudhry, U. I., Plitas, G., Katz, S. C., Raab, J., and DeMatteo, R. P. (2007). Murine liver plasmacytoid dendritic cells become potent immunostimulatory cells after Flt-3 ligand expansion. *Hepatology* 45 (2), 445–454. doi:10.1002/hep.21457
- Koyama, M., Hashimoto, D., Aoyama, K., Matsuoka, K.-i., Karube, K., Niuro, H., et al. (2009). Plasmacytoid dendritic cells prime alloreactive T cells to mediate graft-versus-host disease as antigen-presenting cells. *Blood* 113 (9), 2088–2095. doi:10.1182/blood-2008-07-168609
- Kudo, S., Matsuno, K., Ezaki, T., and Ogawa, M. (1997). A novel migration pathway for rat dendritic cells from the blood: hepatic sinusoids-lymph translocation. *J. Exp. Med.* 185 (4), 777–784. doi:10.1084/jem.185.4.777
- Kuhn, S., Hyde, E. J., Yang, J., Rich, F. J., Harper, J. L., Kirman, J. R., et al. (2013). Increased numbers of monocyte-derived dendritic cells during successful tumor immunotherapy with immune-activating agents. *J. Immunol.* 191 (4), 1984–1992. doi:10.4049/jimmunol.1301135
- Kuhn, S., Yang, J., and Ronchese, F. (2015). Monocyte-Derived Dendritic Cells Are Essential for CD8(+) T Cell Activation and Antitumor Responses After Local Immunotherapy. *Front. Immunol.* 6, 584. doi:10.3389/fimmu.2015.00584
- Lämmermann, T., Bader, B. L., Monkley, S. J., Worbs, T., Wedlich-Söldner, R., Hirsch, K., et al. (2008). Rapid leukocyte migration by integrin-independent flowing and squeezing. *Nature* 453 (7191), 51–55. doi:10.1038/nature06887
- LaRosa, D. F., Rahman, A. H., and Turka, L. A. (2007). The innate immune system in allograft rejection and tolerance. *J. Immunol.* 178 (12), 7503–7509. doi:10.4049/jimmunol.178.12.7503
- Le Borgne, M., Etchart, N., Goubier, A., Lira, S. A., Sirard, J. C., van Rooijen, N., et al. (2006). Dendritic cells rapidly recruited into epithelial tissues via CCR6/CCL20 are responsible for CD8+ T cell crosspriming *in vivo*. *Immunity* 24 (2), 191–201. doi:10.1016/j.immuni.2006.01.005
- Lechler, R., Ng, W. F., and Steinman, R. M. (2001). Dendritic cells in transplantation—friend or foe? *Immunity* 14 (4), 357–368. doi:10.1016/s1074-7613(01)00116-9
- Lee, L. M., Zhang, H., Lee, K., Liang, H., Merlev, A., Vincenti, F., et al. (2021). A Comparison of *Ex Vivo* Expanded Human Regulatory T Cells Using Allogeneic Stimulated B Cells or Monocyte-Derived Dendritic Cells. *Front. Immunol.* 12, 679675. doi:10.3389/fimmu.2021.679675
- Lehtonen, A., Veckman, V., Nikula, T., Lahesmaa, R., Kinnunen, L., Matikainen, S., et al. (2005). Differential expression of IFN regulatory factor 4 gene in human monocyte-derived dendritic cells and macrophages. *J. Immunol.* 175 (10), 6570–6579. doi:10.4049/jimmunol.175.10.6570
- León, B., López-Bravo, M., and Ardavin, C. (2007). Monocyte-derived dendritic cells formed at the infection site control the induction of protective T helper 1 responses against *Leishmania*. *Immunity* 26 (4), 519–531. doi:10.1016/j.immuni.2007.01.017
- Levitsky, J., Goldberg, D., Smith, A. R., Mansfield, S. A., Gillespie, B. W., Merion, R. M., et al. (2017). Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients. *Clin. Gastroenterology Hepatology* 15 (4), 584–593. doi:10.1016/j.cgh.2016.07.035
- Lewis, K. L., Caton, M. L., Bogunovic, M., Greter, M., Grajkowska, L. T., Ng, D., et al. (2011). Notch2 receptor signaling controls functional differentiation of dendritic cells in the spleen and intestine. *Immunity* 35 (5), 780–791. doi:10.1016/j.immuni.2011.08.013
- Liu, Q., Rojas-Canales, D. M., Divito, S. J., Shufesky, W. J., Stolz, D. B., Erdos, G., et al. (2016). Donor dendritic cell-derived exosomes promote allograft-targeting immune response. *J. Clin. Investigation* 126 (8), 2805–2820. doi:10.1172/JCI84577
- Liu, Y.-J. (2005). IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. *Annu. Rev. Immunol.* 23, 275–306. doi:10.1146/annurev.immunol.23.021704.115633
- Lu, L., Li, W., Zhong, C., Qian, S., Fung, J. J., Thomson, A. W., et al. (1999). Increased apoptosis of immunoreactive host cells and augmented donor leukocyte chimerism, not sustained inhibition of B7 molecule expression are associated with prolonged cardiac allograft survival in mice preconditioned with immature donor dendritic cells plus anti-CD40L mAb. *Transplantation* 68 (6), 747–757. doi:10.1097/00007890-199909270-00006
- Lu, L., Qian, S., Hershberger, P. A., Rudert, W. A., Lynch, D. H., and Thomson, A. W. (1997). Fas ligand (CD95L) and B7 expression on dendritic cells provide counter-regulatory signals for T cell survival and proliferation. *J. Immunol.* 158 (12), 5676–5684. doi:10.4049/jimmunol.158.12.5676
- Lu, L., and Thomson, A. W. (2002). Manipulation of dendritic cells for tolerance induction in transplantation and autoimmune disease. *Transplantation* 73 (1), S19–S22. doi:10.1097/00007890-200201151-00008
- Lu, L., Woo, J., Rao, A. S., Li, Y., Watkins, S. C., Qian, S., et al. (1994). Propagation of dendritic cell progenitors from normal mouse liver using granulocyte/macrophage colony-stimulating factor and their maturational development in the presence of type-1 collagen. *J. Exp. Med.* 179 (6), 1823–1834. doi:10.1084/jem.179.6.1823
- Lukacs-Kornek, V., and Schuppan, D. (2013). Dendritic cells in liver injury and fibrosis: shortcomings and promises. *J. Hepatology* 59 (5), 1124–1126. doi:10.1016/j.jhep.2013.05.033
- Lutz, M. B., and Schuler, G. (2002). Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? *Trends Immunol.* 23 (9), 445–449. doi:10.1016/s1471-4906(02)02281-0
- Ma, B., Yang, J.-Y., Song, W.-J., Ding, R., Zhang, Z.-C., Ji, H.-C., et al. (2016). Combining Exosomes Derived from Immature DCs with Donor Antigen-Specific Treg Cells Induces Tolerance in a Rat Liver Allograft Model. *Sci. Rep.* 6, 32971. doi:10.1038/srep32971
- Macedo, C., Tran, L. M., Zahorchak, A. F., Dai, H., Gu, X., Ravichandran, R., et al. (2021). Donor-derived regulatory dendritic cell infusion results in host cell cross-dressing and T cell subset changes in prospective living donor liver transplant recipients. *Am. J. Transplant.* 21 (7), 2372–2386. doi:10.1111/ajt.16393



- Maldonado, R. A., and von Andrian, U. H. (2010). How tolerogenic dendritic cells induce regulatory T cells. *Adv. Immunol.* 108, 111–165. doi:10.1016/B978-0-12-380995-7.00004-5
- Manicassamy, S., and Pulendran, B. (2011). Dendritic cell control of tolerogenic responses. *Immunol. Rev.* 241 (1), 206–227. doi:10.1111/j.1600-065X.2011.01015.x
- Marín, E., Cuturi, M. C., and Moreau, A. (2018). Tolerogenic Dendritic Cells in Solid Organ Transplantation: where Do We Stand? *Front. Immunol.* 9, 274. doi:10.3389/fimmu.2018.00274
- Marino, J., Babiker-Mohamed, M. H., Crosby-Bertorini, P., Paster, J. T., LeGuern, C., Germana, S., et al. (2016). Donor exosomes rather than passenger leukocytes initiate alloreactive T cell responses after transplantation. *Sci. Immunol.* 1 (1), aaf8759. doi:10.1126/sciimmunol.aaf8759
- Martin-Gayo, E., Sierra-Filardi, E., Corbí, A. L., and Toribio, M. L. (2010). Plasmacytoid dendritic cells resident in human thymus drive natural Treg cell development. *Blood* 115 (26), 5366–5375. doi:10.1182/blood-2009-10-248260
- Mastoridis, S., Londoño, M.-C., Kurt, A., Kodela, E., Crespo, E., Mason, J., et al. (2021). Impact of donor extracellular vesicle release on recipient cell "cross-dressing" following clinical liver and kidney transplantation. *Am. J. Transplant.* 21 (7), 2387–2398. doi:10.1111/ajt.16123
- Matsuno, K., and Ezaki, T. (2000). Dendritic cell dynamics in the liver and hepatic lymph. *Int. Rev. Cytol.* 197, 83–136. doi:10.1016/S0074-7696(00)97003-7
- Matsuno, K., Ezaki, T., Kudo, S., and Uehara, Y. (1996). A life stage of particle-laden rat dendritic cells *in vivo*: their terminal division, active phagocytosis, and translocation from the liver to the draining lymph. *J. Exp. Med.* 183 (4), 1865–1878. doi:10.1084/jem.183.4.1865
- Mellor, A. L., Keskin, D. B., Johnson, T., Chandler, P., and Munn, D. H. (2002). Cells expressing indoleamine 2,3-dioxygenase inhibit T cell responses. *J. Immunol.* 168 (8), 3771–3776. doi:10.4049/jimmunol.168.8.3771
- Mempel, T. R., Henrickson, S. E., and Von Andrian, U. H. (2004). T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases. *Nature* 427 (6970), 154–159. doi:10.1038/nature02238
- Menezes, S., Melandri, D., Anselmi, G., Perchet, T., Loschko, J., Dubrot, J., et al. (2016). The Heterogeneity of Ly6Chi Monocytes Controls Their Differentiation into iNOS+ Macrophages or Monocyte-Derived Dendritic Cells. *Immunity* 45 (6), 1205–1218. doi:10.1016/j.immuni.2016.12.001
- Merad, M., Sathe, P., Helft, J., Miller, J., and Mortha, A. (2013). The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. *Annu. Rev. Immunol.* 31, 563–604. doi:10.1146/annurev-immunol-020711-074950
- Mildner, A., Yona, S., and Jung, S. (2013). A close encounter of the third kind: monocyte-derived cells. *Adv. Immunol.* 120, 69–103. doi:10.1016/B978-0-12-417028-5.00003-X
- Miller, M. J., Safrina, O., Parker, I., and Cahalan, M. D. (2004). Imaging the single cell dynamics of CD4+ T cell activation by dendritic cells in lymph nodes. *J. Exp. Med.* 200 (7), 847–856. doi:10.1084/jem.20041236
- Moreau, A., Alliot-Licht, B., Cuturi, M.-C., and Blancho, G. (2017). Tolerogenic dendritic cell therapy in organ transplantation. *Transpl. Int. Official J. Eur. Soc. For Organ Transplant.* 30 (8), 754–764. doi:10.1111/tri.12889
- Morelli, A. E., and Thomson, A. W. (2007). Tolerogenic dendritic cells and the quest for transplant tolerance. *Nat. Rev. Immunol.* 7 (8), 610–621. doi:10.1038/nri2132
- Moseman, E. A., Liang, X., Dawson, A. J., Panoskaltis-Mortari, A., Krieg, A. M., Liu, Y.-J., et al. (2004). Human plasmacytoid dendritic cells activated by CpG oligodeoxynucleotides induce the generation of CD4+CD25+ regulatory T cells. *J. Immunol.* 173 (7), 4433–4442. doi:10.4049/jimmunol.173.7.4433
- Munn, D. H., Sharma, M. D., Hou, D., Baban, B., Lee, J. R., Antonia, S. J., et al. (2004). Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. *J. Clin. Investigation* 114 (2), 280–290. doi:10.1172/JCI21583
- Murphy, T. L., Grajales-Reyes, G. E., Wu, X., Tussiwand, R., Briseño, C. G., Iwata, A., et al. (2016). Transcriptional Control of Dendritic Cell Development. *Annu. Rev. Immunol.* 34, 93–119. doi:10.1146/annurev-immunol-032713-120204
- Nakano, R., Yoshida, O., Kimura, S., Nakao, T., Yokota, S., Ono, Y., et al. (2021). Donor plasmacytoid dendritic cells modulate effector and regulatory T cell responses in mouse spontaneous liver transplant tolerance. *Am. J. Transplant.* 21 (6), 2040–2055. doi:10.1111/ajt.16412
- Navarro-Barriuso, J., Mansilla, M. J., and Martínez-Cáceres, E. M. (2018). Searching for the Transcriptomic Signature of Immune Tolerance Induction-Biomarkers of Safety and Functionality for Tolerogenic Dendritic Cells and Regulatory Macrophages. *Front. Immunol.* 9, 2062. doi:10.3389/fimmu.2018.02062
- Nitschké, M., Aebischer, D., Abadier, M., Haener, S., Lucic, M., Vigl, B., et al. (2012). Differential requirement for ROCK in dendritic cell migration within lymphatic capillaries in steady-state and inflammation. *Blood* 120 (11), 2249–2258. doi:10.1182/blood-2012-03-417923
- Oberbarnscheidt, M. H., Zeng, Q., Li, Q., Dai, H., Williams, A. L., Shlomchik, W. D., et al. (2014). Non-self recognition by monocytes initiates allograft rejection. *J. Clin. Investigation* 124 (8), 3579–3589. doi:10.1172/JCI74370
- Ochando, J., and Braza, M. S. (2017). Nanoparticle-Based Modulation and Monitoring of Antigen-Presenting Cells in Organ Transplantation. *Front. Immunol.* 8, 1888. doi:10.3389/fimmu.2017.01888
- Ochando, J. C., Homma, C., Yang, Y., Hidalgo, A., Garin, A., Tacke, F., et al. (2006). Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. *Nat. Immunol.* 7 (6), 652–662. doi:10.1038/ni1333
- Ochando, J., Ordikhani, F., Jordan, S., Boros, P., and Thomson, A. W. (2020). Tolerogenic dendritic cells in organ transplantation. *Transpl. Int. Official J. Eur. Soc. For Organ Transplant.* 33 (2), 113–127. doi:10.1111/tri.13504
- Ono, Y., Perez-Gutierrez, A., Nakao, T., Dai, H., Camirand, G., Yoshida, O., et al. (2018). Graft-infiltrating PD-L1hi cross-dressed dendritic cells regulate antidonor T cell responses in mouse liver transplant tolerance. *Hepatology* 67 (4), 1499–1515. doi:10.1002/hep.29529
- Palomares, O., Rückert, B., Jartti, T., Küçüksezer, U. C., Puhakka, T., Gomez, E., et al. (2012). Induction and maintenance of allergen-specific FOXP3+ Treg cells in human tonsils as potential first-line organs of oral tolerance. *J. Allergy Clin. Immunol.* 129 (2), 510–520. doi:10.1016/j.jaci.2011.09.031
- Penna, G., Vulcano, M., Sozzani, S., and Adorini, L. (2002). Differential migration behavior and chemokine production by myeloid and plasmacytoid dendritic cells. *Hum. Immunol.* 63 (12), 1164–1171. doi:10.1016/S0198-8859(02)00755-3
- Pillarisetty, V. G., Shah, A. B., Miller, G., Bleier, J. I., and DeMatteo, R. P. (2004). Liver dendritic cells are less immunogenic than spleen dendritic cells because of differences in subtype composition. *J. Immunol.* 172 (2), 1009–1017. doi:10.4049/jimmunol.172.2.1009
- Plantinga, M., Williams, M., Vanheerswynghe, M., Deswarte, K., Branco-Madeira, F., Toussaint, W., et al. (2013). Conventional and monocyte-derived CD11b(+) dendritic cells initiate and maintain T helper 2 cell-mediated immunity to house dust mite allergen. *Immunity* 38 (2), 322–335. doi:10.1016/j.immuni.2012.10.016
- Poulin, L. F., Rey, Y., Uronen-Hansson, H., Schraml, B. U., Sancho, D., Murphy, K. M., et al. (2012). DNGR-1 is a specific and universal marker of mouse and human Batf3-dependent dendritic cells in lymphoid and nonlymphoid tissues. *Blood* 119 (25), 6052–6062. doi:10.1182/blood-2012-01-406967
- Pulendran, B. (2015). The varieties of immunological experience: of pathogens, stress, and dendritic cells. *Annu. Rev. Immunol.* 33, 563–606. doi:10.1146/annurev-immunol-020711-075049
- Que, W., Guo, W.-Z., and Li, X.-K. (2020). Manipulation of Regulatory Dendritic Cells for Induction Transplantation Tolerance. *Front. Immunol.* 11, 582658. doi:10.3389/fimmu.2020.582658
- Rahman, A. H., and Aloman, C. (2013). Dendritic cells and liver fibrosis. *Biochimica Biophysica Acta* 1832 (7), 998–1004. doi:10.1016/j.bbadis.2013.01.005
- Raïch-Regué, D., Glancy, M., and Thomson, A. W. (2014). Regulatory dendritic cell therapy: from rodents to clinical application. *Immunol. Lett.* 161 (2), 216–221. doi:10.1016/j.imlet.2013.11.016
- Raker, V. K., Domogalla, M. P., and Steinbrink, K. (2015). Tolerogenic Dendritic Cells for Regulatory T Cell Induction in Man. *Front. Immunol.* 6, 569. doi:10.3389/fimmu.2015.00569
- Rastellini, C., Lu, L., Ricordi, C., Starzl, T. E., Rao, A. S., and Thomson, A. W. (1995). Granulocyte/macrophage colony-stimulating factor-stimulated hepatic dendritic cell progenitors prolong pancreatic islet allograft survival. *Transplantation* 60 (11), 1366–1370.
- Reis e Sousa, C. (2006). Dendritic cells in a mature age. *Nat. Rev. Immunol.* 6 (6), 476–483. doi:10.1038/nri1845
- Reizis, B., Bunin, A., Ghosh, H. S., Lewis, K. L., and Sisirak, V. (2011). Plasmacytoid dendritic cells: recent progress and open questions. *Annu. Rev. Immunol.* 29, 163–183. doi:10.1146/annurev-immunol-031210-101345
- Reizis, B. (2019). Plasmacytoid Dendritic Cells: development, Regulation, and Function. *Immunity* 50 (1), 37–50. doi:10.1016/j.immuni.2018.12.027
- Rich, F. J., Kuhn, S., Hyde, E. J., Harper, J. L., Ronchese, F., and Kirman, J. R. (2012). Induction of T cell responses and recruitment of an inflammatory dendritic cell subset following tumor immunotherapy with Mycobacterium smegmatis. *Cancer Immunol. Immunother.* CII 61 (12), 2333–2342. doi:10.1007/s00262-012-1291-8
- Robbins, P. D., and Morelli, A. E. (2014). Regulation of immune responses by extracellular vesicles. *Nat. Rev. Immunol.* 14 (3), 195–208. doi:10.1038/nri3622
- Rogers, N. M., Isenberg, J. S., and Thomson, A. W. (2013). Plasmacytoid dendritic cells: no longer an enigma and now key to transplant tolerance? *Am. J. Transplant.* 13 (5), 1125–1133. doi:10.1111/ajt.12229
- Romani, N., Koide, S., Crowley, M., Witmer-Pack, M., Livingstone, A. M., Fathman, C. G., et al. (1989). Presentation of exogenous protein antigens by dendritic cells to T cell clones. Intact protein is presented best by immature, epidermal Langerhans cells. *J. Exp. Med.* 169 (3), 1169–1178. doi:10.1084/jem.169.3.1169
- Ronca, V., Wootton, G., Milani, C., and Cain, O. (2020). The Immunological Basis of Liver Allograft Rejection. *Front. Immunol.* 11, 2155. doi:10.3389/fimmu.2020.02155
- Rosas, M., Thomas, B., Stacey, M., Gordon, S., and Taylor, P. R. (2010). The myeloid 7/4-antigen defines recently generated inflammatory macrophages and is synonymous with Ly-6B. *J. Leukoc. Biol.* 88 (1), 169–180. doi:10.1189/jlb.0809548
- Ruben, J. M., García-Romo, G. S., Breman, E., van der Kooij, S., Redeker, A., Arens, R., et al. (2018). Human plasmacytoid dendritic cells acquire phagocytic capacity by



- TLR9 ligation in the presence of soluble factors produced by renal epithelial cells. *Kidney Int.* 93 (2), 355–364. doi:10.1016/j.kint.2017.08.006
- Russo, E., Teixeira, A., Vaahromeri, K., Willrodt, A.-H., Bloch, J. S., Nitschké, M., et al. (2016). Intralymphatic CCL21 Promotes Tissue Egress of Dendritic Cells through Afferent Lymphatic Vessels. *Cell Rep.* 14 (7), 1723–1734. doi:10.1016/j.celrep.2016.01.048
- Saeki, H., Moore, A. M., Brown, M. J., and Hwang, S. T. (1999). Cutting edge: secondary lymphoid-tissue chemokine (SLC) and CC chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes. *J. Immunol.* 162 (5), 2472–2475. doi:10.4049/jimmunol.162.5.2472
- Sallusto, F., Schaerli, P., Loetscher, P., Schaniel, C., Lenig, D., Mackay, C. R., et al. (1998). Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. *Eur. J. Immunol.* 28 (9), 2760–2769. doi:10.1002/(SICI)1521-4141(199809)28:09<2760::AID-IMMU2760>3.0.CO;2-N
- Sander, J., Schmidt, S. V., Cirovic, B., McGovern, N., Papanonopoulou, O., Hardt, A.-L., et al. (2017). Cellular Differentiation of Human Monocytes Is Regulated by Time-Dependent Interleukin-4 Signaling and the Transcriptional Regulator NCOR2. *Immunity* 47 (6), 1051–1066. doi:10.1016/j.immuni.2017.11.024
- Sato, T., Yamamoto, H., Sasaki, C., and Wake, K. (1998). Maturation of rat dendritic cells during intrahepatic translocation evaluated using monoclonal antibodies and electron microscopy. *Cell Tissue Res.* 294 (3), 503–514. doi:10.1007/s004410051201
- Satpathy, A. T., Briseño, C. G., Lee, J. S., Ng, D., Manieri, N. A., Kc, W., et al. (2013). Notch2-dependent classical dendritic cells orchestrate intestinal immunity to attaching-and-effacing bacterial pathogens. *Nat. Immunol.* 14 (9), 937–948. doi:10.1038/ni.2679
- Satpathy, A. T., Wu, X., Albring, J. C., and Murphy, K. M. (2012). Re(de)fining the dendritic cell lineage. *Nat. Immunol.* 13 (12), 1145–1154. doi:10.1038/ni.2467
- Schlitzer, A., McGovern, N., and Ginhoux, F. (2015). Dendritic cells and monocyte-derived cells: two complementary and integrated functional systems. *Seminars Cell & Dev. Biol.* 41, 9–22. doi:10.1016/j.semcdb.2015.03.011
- Schmid, M. A., Kingston, D., Boddupalli, S., and Manz, M. G. (2010). Instructive cytokine signals in dendritic cell lineage commitment. *Immunol. Rev.* 234 (1), 32–44. doi:10.1111/j.0105-2896.2009.00877.x
- Schuler, G., and Steinman, R. M. (1985). Murine epidermal Langerhans cells mature into potent immunostimulatory dendritic cells *in vitro*. *J. Exp. Med.* 161 (3), 526–546. doi:10.1084/jem.161.3.526
- Schumann, K., Lämmermann, T., Brückner, M., Legler, D. F., Polleux, J., Spatz, J. P., et al. (2010). Immobilized chemokine fields and soluble chemokine gradients cooperatively shape migration patterns of dendritic cells. *Immunity* 32 (5), 703–713. doi:10.1016/j.immuni.2010.04.017
- Segura, E., Touzot, M., Bohineust, A., Cappuccio, A., Chiochia, G., Hosmalin, A., et al. (2013). Human inflammatory dendritic cells induce Th17 cell differentiation. *Immunity* 38 (2), 336–348. doi:10.1016/j.immuni.2012.10.018
- Serbina, N. V., Salazar-Mather, T. P., Biron, C. A., Kuziel, W. A., and Pamer, E. G. (2003). TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. *Immunity* 19 (1), 59–70. doi:10.1016/s1074-7613(03)00171-7
- Shariat, A., Karimi, M. H., Mokhtariyazad, T., Moazzeni, S. M., Geramizadeh, B., MalekHosseini, S. A., et al. (2014). Maturation state and function of monocyte derived dendritic cells in liver transplant recipients. *Iran. J. Immunol.* 11 (3), 153–165.
- Sharma, M. D., Baban, B., Chandler, P., Hou, D.-Y., Singh, N., Yagita, H., et al. (2007). Plasmacytoid dendritic cells from mouse tumor-draining lymph nodes directly activate mature Tregs via indoleamine 2,3-dioxygenase. *J. Clin. Investigation* 117 (9), 2570–2582. doi:10.1172/JCI31911
- Spiering, R., Jansen, M. A. A., Wood, M. J., Fath, A. A., Eltherington, O., Anderson, A. E., et al. (2019). Targeting of tolerogenic dendritic cells to heat-shock proteins in inflammatory arthritis. *J. Transl. Med.* 17 (1), 375. doi:10.1186/s12967-019-2128-4
- Steinman, R. M., and Banchereau, J. (2007). Taking dendritic cells into medicine. *Nature* 449 (7161), 419–426. doi:10.1038/nature06175
- Steinman, R. M., and Cohn, Z. A. (1973). Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J. Exp. Med.* 137 (5), 1142–1162. doi:10.1084/jem.137.5.1142
- Steptoe, R. J., Fu, F., Li, W., Drakes, M. L., Lu, L., Demetris, A. J., et al. (1997). Augmentation of dendritic cells in murine organ donors by Flt3 ligand alters the balance between transplant tolerance and immunity. *J. Immunol.* 159 (11), 5483–5491. doi:10.4049/jimmunol.159.11.5483
- Steptoe, R. J., Patel, R. K., Subbotin, V. M., and Thomson, A. W. (2000). Comparative analysis of dendritic cell density and total number in commonly transplanted organs: morphometric estimation in normal mice. *Transpl. Immunol.* 8 (1), 49–56. doi:10.1016/s0966-3274(00)00010-1
- Sumpter, T. L., Dangi, A., Matta, B. M., Huang, C., Stolz, D. B., Vodovotz, Y., et al. (2012). Hepatic stellate cells undermine the allostimulatory function of liver myeloid dendritic cells via STAT3-dependent induction of IDO. *J. Immunol.* 189 (8), 3848–3858. doi:10.4049/jimmunol.1200819
- Süss, G., and Shortman, K. (1996). A subclass of dendritic cells kills CD4 T cells via Fas/Fas-ligand-induced apoptosis. *J. Exp. Med.* 183 (4), 1789–1796. doi:10.1084/jem.183.4.1789
- Swiecki, M., and Colonna, M. (2010). Unraveling the functions of plasmacytoid dendritic cells during viral infections, autoimmunity, and tolerance. *Immunol. Rev.* 234 (1), 142–162. doi:10.1111/j.0105-2896.2009.00881.x
- Tacke, F., Alvarez, D., Kaplan, T. J., Jakubzick, C., Spanbroek, R., Llodra, J., et al. (2007). Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J. Clin. Investigation* 117 (1), 185–194. doi:10.1172/JCI28549
- Tadayon, S., Dunkel, J., Takeda, A., Eichin, D., Virtakoivu, R., Elima, K., et al. (2021). Lymphatic Endothelial Cell Activation and Dendritic Cell Transmigration Is Modified by Genetic Deletion of Clever-1. *Front. Immunol.* 12, 602122. doi:10.3389/fimmu.2021.602122
- Tal, O., Lim, H. Y., Gurevich, I., Milo, I., Shipony, Z., Ng, L. G., et al. (2011). DC mobilization from the skin requires docking to immobilized CCL21 on lymphatic endothelial and intralymphatic crawling. *J. Exp. Med.* 208 (10), 2141–2153. doi:10.1084/jem.20102392
- Tang-Huau, T.-L., and Segura, E. (2019). Human *in vivo*-differentiated monocyte-derived dendritic cells. *Seminars Cell & Dev. Biol.* 86, 44–49. doi:10.1016/j.semcdb.2018.02.018
- Thomson, A. W., and Knolle, P. A. (2010). Antigen-presenting cell function in the tolerogenic liver environment. *Nat. Rev. Immunol.* 10 (11), 753–766. doi:10.1038/nri2858
- Thomson, A. W., and Lu, L. (1999). Are dendritic cells the key to liver transplant tolerance? *Immunol. Today* 20 (1), 27–32. doi:10.1016/s0167-5699(98)01378-4
- Thomson, A. W., Metes, D. M., Ezzelarab, M. B., and Raïch-Regué, D. (2019). Regulatory dendritic cells for human organ transplantation. *Transplant. Rev. Or. Fla* 33 (3), 130–136. doi:10.1016/j.trre.2019.05.001
- Thomson, A. W., Vionnet, J., and Sanchez-Fueyo, A. (2020). Understanding, predicting and achieving liver transplant tolerance: from bench to bedside. *Nat. Rev. Gastroenterol. Hepatol.* 17 (12), 719–739. doi:10.1038/s41575-020-0334-4
- Tokita, D., Sumpter, T. L., Raimondi, G., Zahorchak, A. F., Wang, Z., Nakao, A., et al. (2008). Poor allostimulatory function of liver plasmacytoid DC is associated with proapoptotic activity, dependent on regulatory T cells. *J. Hepatology* 49 (6), 1008–1018. doi:10.1016/j.jhep.2008.07.028
- Ueta, H., Xu, X.-D., Yu, B., Kitazawa, Y., Yu, E., Hara, Y., et al. (2021). Suppression of liver transplant rejection by anti-donor MHC antibodies via depletion of donor immunogenic dendritic cells. *Int. Immunol.* 33 (5), 261–272. doi:10.1093/intimm/dxaa076
- Ulvmar, M. H., Werth, K., Braun, A., Kelay, P., Hub, E., Eller, K., et al. (2014). The atypical chemokine receptor CCRL1 shapes functional CCL21 gradients in lymph nodes. *Nat. Immunol.* 15 (7), 623–630. doi:10.1038/ni.2889
- Uwatoku, R., Suematsu, M., Ezaki, T., Saiki, T., Tsujii, M., Irimura, T., et al. (2001). Kupffer cell-mediated recruitment of rat dendritic cells to the liver: roles of N-acetylgalactosamine-specific sugar receptors. *Gastroenterology* 121 (6), 1460–1472. doi:10.1053/gast.2001.29594
- Van den Bergh, J. M. J., Smits, E. L. J. M., Berneman, Z. N., Hutten, T. J. A., De Reu, H., Van Tendeloo, V. F. I., et al. (2017). Monocyte-Derived Dendritic Cells with Silenced PD-1 Ligands and Transpresenting Interleukin-15 Stimulate Strong Tumor-Reactive T-cell Expansion. *Cancer Immunol. Res.* 5 (8), 710–715. doi:10.1158/2326-6066.CIR-16-0336
- Villadangos, J. A., and Young, L. (2008). Antigen-presentation properties of plasmacytoid dendritic cells. *Immunity* 29 (3), 352–361. doi:10.1016/j.immuni.2008.09.002
- Wilson, N. S., and Villadangos, J. A. (2004). Lymphoid organ dendritic cells: beyond the Langerhans cells paradigm. *Immunol. Cell Biol.* 82 (1), 91–98. doi:10.1111/j.1440-1711.2004.01216.x
- Wolf, A. A., Yáñez, A., Barman, P. K., and Goodridge, H. S. (2019). The Ontogeny of Monocyte Subsets. *Front. Immunol.* 10, 1642. doi:10.3389/fimmu.2019.01642
- Yin, X., Chen, S., and Eisenbarth, S. C. (2021). Dendritic Cell Regulation of T Helper Cells. *Annu. Rev. Immunol.* 39, 759–790. doi:10.1146/annurev-immunol-101819-025146
- Yona, S., Kim, K.-W., Wolf, Y., Mildner, A., Varol, D., Breker, M., et al. (2013). Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. *Immunity* 38 (1), 79–91. doi:10.1016/j.immuni.2012.12.001
- Yoneyama, H., Matsuno, K., Zhang, Y., Murai, M., Itakura, M., Ishikawa, S., et al. (2001). Regulation by chemokines of circulating dendritic cell precursors, and the formation of portal tract-associated lymphoid tissue, in a granulomatous liver disease. *J. Exp. Med.* 193 (1), 35–49. doi:10.1084/jem.193.1.35
- Yu, B., Ueta, H., Kitazawa, Y., Tanaka, T., Adachi, K., Kimura, H., et al. (2012). Two immunogenic passenger dendritic cell subsets in the rat liver have distinct trafficking patterns and radiosensitivities. *Hepatol. Baltim. Md* 56 (4), 1532–1545. doi:10.1002/hep.25795
- Zahorchak, A. F., DeRiggi, M. L., Muzzio, J. L., Sutherland, V., Humar, A., Lakkis, F. G., et al. (2023). Manufacturing and validation of Good Manufacturing Practice-compliant regulatory dendritic cells for infusion into organ transplant recipients. *Cytotherapy* 25 (4), 432–441. doi:10.1016/j.jcyt.2022.11.005

- Zahorchak, A. F., Macedo, C., Hamm, D. E., Butterfield, L. H., Metes, D. M., and Thomson, A. W. (2018). High PD-L1/CD86 MFI ratio and IL-10 secretion characterize human regulatory dendritic cells generated for clinical testing in organ transplantation. *Cell. Immunol.* 323, 9–18. doi:10.1016/j.cellimm.2017.08.008
- Zecher, D., van Rooijen, N., Rothstein, D. M., Shlomchik, W. D., and Lakkis, F. G. (2009). An innate response to allogeneic nonself mediated by monocytes. *J. Immunol.* 183 (12), 7810–7816. doi:10.4049/jimmunol.0902194
- Zheng, L., Li, Z., Ling, W., Zhu, D., Feng, Z., and Kong, L. (2018). Exosomes Derived from Dendritic Cells Attenuate Liver Injury by Modulating the Balance of Treg and Th17 Cells After Ischemia Reperfusion. *Cell. Physiology Biochem.* 46 (2), 740–756. doi:10.1159/000488733
- Zhuang, Q., Liu, Q., Divito, S. J., Zeng, Q., Yatim, K. M., Hughes, A. D., et al. (2016). Graft-infiltrating host dendritic cells play a key role in organ transplant rejection. *Nat. Commun.* 7, 12623. doi:10.1038/ncomms12623
- Zubizarreta, I., Flórez-Grau, G., Vila, G., Cabezón, R., España, C., Andorra, M., et al. (2019). Immune tolerance in multiple sclerosis and neuromyelitis optica with peptide-loaded tolerogenic dendritic cells in a phase 1b trial. *Proc. Natl. Acad. Sci. U. S. A.* 116 (17), 8463–8470. doi:10.1073/pnas.1820039116
- Zuidwijk, K., de Fijter, J. W., Mallat, M. J. K., Eikmans, M., van Groningen, M. C., Goemaere, N. N., et al. (2012). Increased influx of myeloid dendritic cells during acute rejection is associated with interstitial fibrosis and tubular atrophy and predicts poor outcome. *Kidney Int.* 81 (1), 64–75. doi:10.1038/ki.2011.289