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Dendritic Cells: Versatile Players in Renal Transplantation

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Dendritic cells (DCs) induce and regulate adaptive immunity through migrating and maturing in the kidney. In this procedure, they can adopt different phenotypes—rejection-associated DCs promote acute or chronic injury renal grafts while tolerogenic DCs suppress the overwhelmed inflammation preventing damage to renal functionality. All the subsets interact with effector T cells and regulatory T cells (Tregs) stimulated by the ischemia–reperfusion procedure, although the classification corresponding to different effects remains controversial. Thus, in this review, we discuss the origin, maturation, and pathological effects of DCs in the kidney. Then we summarize the roles of divergent DCs in renal transplantation: taking both positive and negative stages in ischemia–reperfusion injury (IRI), switching phenotypes to induce acute or chronic rejection, and orchestrating surface markers for allograft tolerance *via* alterations in metabolism. In conclusion, we prospect that multidimensional transcriptomic analysis will revolute researches on renal transplantation by addressing the elusive mononuclear phagocyte classification and providing a holistic view of DC ontogeny and subpopulations.

Keywords: dendritic cells, renal transplantation, rejection, tolerance, ischemic–reperfusion injury

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INTRODUCTION

In all tissues, DCs function in a network of mononuclear phagocytes with many innate immune cells taking center stage (1). This network in the kidney is complex and heterogeneous, highly relying on macrophages and DCs (2). Discovered by Metchnikoff 150 years ago, macrophages can mediate fibrosis after renal transplantation, whereas DCs were first described in 1973 by Steinman and Cohn as even elongated or stellate cells to present antigens. Given that DCs and macrophages are both involved in innate immune networks, DCs should have overlapping functionalities as macrophages in tissue homeostasis, promoting pathogen defense and contributing to acute or chronic rejection (2, 3). But compared with macrophages, the unique roles of DCs in rejection or tolerance are still ambiguous and undefined partly because they often share similar surface markers (4–7). Equipped with increasingly available kidney biopsy data, the recent outbreak in the high-dimensional analysis of single-cell has sparked instructions for the classification of these immune cells (8–11). In this review, we first describe the consensus of DC ontogeny encompassing the origins, maturation, and pathological effects of DCs

in the kidney. We then summarize the major roles of kidney DCs in three major aspects of renal transplantation, including ischemic injury when grafts are removed from the donors, rejection including acute and chronic process, and tolerance including induced or natural genic tolerance. Finally, we point out certain obstacles and disadvantages to prospect the value of multidimensional transcriptomic analysis.

DC-LINKED PATHOLOGICAL PROCEDURE IN RENAL TRANSPLANTATION

The Origin and Migration of DCs in Kidney Allograft Rejection

Like other tissues, dendritic cells in the kidney are derived from bone hematopoietic stem cells (**Figure 1**). Traditionally, cell surface markers were used to subdivide cDCs into cDC1 and cDC2 (12). Human cDC1 mainly expressed CD11c, CD141, CLEC9A (C-type lectin domain family 9 member A) and highly expressed MHC (major histocompatibility complex) class II, while cDC2 mainly expressed CD11c, high- affinity Fc receptor for immunoglobin E, CD1c, CD1a and highly expressed CD11c and MHC class II. CD11c, MHC class II, CD26, and interferon-regulatory factor 8 (IRF8) are highly expressed in murine cDC1, and CLEC9A, XCR1, and CD103 are also expressed. In mice, cDC2 expresses high CD11c, MHC class II, CD11b, CD26, CX3CR1, interferon-regulatory factor 4, dendritic cell inhibitory receptor 2 but expresses low IRF8 and F4/80 (**Table 1**).

Moreover, traditional DC subsets are described by lineage-specific transcription factors including DNA binding inhibitor 2 and interferon regulatory factor 4. In mice, the conventional DC group 1 (cDC1) express neither SiglecH nor Ly6C, while the precursor of the conventional DC group 2 (cDC2) express no SiglecH but Ly6C (21). Based on these transcription factors, phagocytes expressing major histocompatibility complex (MHC) class II and integrin CD11c are named cDCs. Another independent subgroup, unconventional plasma-like dendritic cells, expressed transcription factor E2-2 and its myeloid antigen but did not express CD123. Whether they are related to traditional DC is still doubtable.

During circulation, the precursor dendritic cells develop and differentiate into kidney-specific dendritic cells (22). In the kidney, no more than 5% of dendritic cells are cDC1 expressing CD103; most DCs express CD11b and CX3CR1 and can be categorized into cDC2. Compared with dendritic cells in other parts of the body, kidney-specific dendritic cells can be

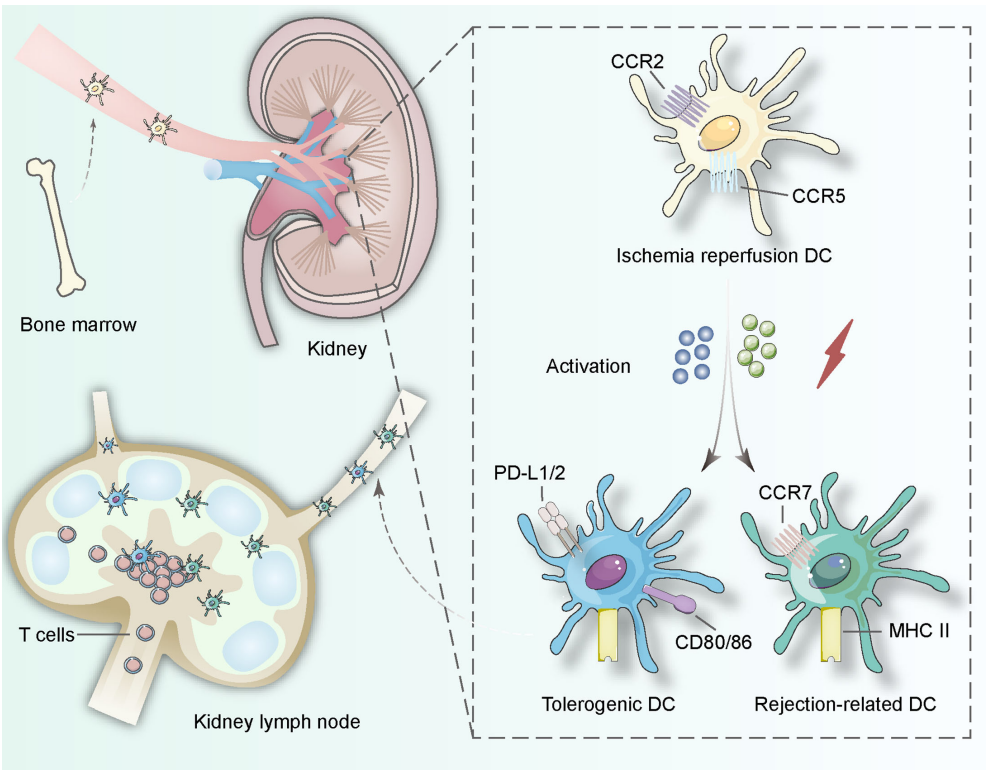

FIGURE 1 | DCs in the kidney originate from bone hematopoietic stem cells and involve in lymphatic recycling *in vivo*. When ischemia–reperfusion occurs, immature DCs start to search for interactions with T lymphocytes and change their surface proteins including CCR2, CCR5 to induce tolerance procedure (expressing PD-L1/2 and CD80/86) or rejection procedure (expressing CCR7 and MHC class II). The activation can be derived from pathogen-associated molecular patterns and danger-associated molecular patterns in the procedure of ischemia-reperfusion.

TABLE 1 | Remarkable features of three different types of DCs in renal transplantation.

Clinical subsets	General functions	Key markers	References
DCs in IRI	Promotion of both inflammation and anti-inflammation	CD45, CD11c, MHC-II, TNF-α, CD80, CD86, CD40, CD54, C1d, CD8 α, but not CD4 and CD205	(13, 14)
Rejection-related DCs	Promoting acute rejection and chronic rejection *via* different interaction with T cells	CD11c, MHC class II, CD1c, FcεRI	(15)
Tolerogenic DCs	Inducing anti-rejection effects *via* suppressing various types of T cells and activating Treg cells	poor expression of MHC, T cell co-stimulatory molecules like CD40, CD80/86, and T cell co-inhibitory ligands (*e.g.*, programmed death ligand-1 and death-inducing ligands)	(16–20)

FcεRI, high- affinity Fc receptor for IgE; MHC, major histocompatibility complex.

located in the lymph nodes around the kidney and the kidney itself, which is essential for the control of adaptive immunity (23) (**Figure 1**). In the kidney, most of these phagocytes with the ability to activate T cells are located in the cortex. It can be confirmed that cDC1 is located near the blood vessels, while most of these cells near the subcapsular and arterial connective tissue have the morphology of macrophages. The high osmotic pressure of transplanted medulla may inhibit the antigen presentation of DCS to $CD8^+$ T cells, but the specific type of DCs still needs to be further studied.

Chemokines and corresponding receptors induce the migration of kidney-specific DCs. Chemokines are detected by receptors on the surface of precursor DCs and precursor DCs can migrate along the inverse chemical gradient pathway to the source. Receptor expression determines the specificity of kidney DCs. CX3CR1 and CCR2 are incorporated into the action of leaving the bone marrow, and CXCR4 helps precursor DCs retention in the marrow (24–26). But the inflammatory conditions after transplantation possibly alter the migration mechanism to mediate both rejection and tolerance, which remain unidentified and might be potential intervention sites in the future (**Figure 1**).

The Maturation of DCs in Kidney Allograft Rejection

With no stimuli, immature kidney DCs inhibit T and B lymphocytes, which also can coordinate tolerance (25). Danger-associated molecular patterns occur when ischemia and reperfusion happen, activating TLR4 (toll-like receptor 4) and leading to the maturation of DCs (27–29). This maturation induces inflammation and provokes adaptive immunity to specific antigens, such as alloantigen and so on (30, 31). According to Sporri and Reis e Sousa's report, danger-associated molecular patterns (DAMPs) cannot make DCs promote T-helper responses, but exposure to pathogen-associated molecular patterns can (32). Taken together, DAMPs are not the most crucial pathway to activate DCs for allograft rejection (33–36). Furthermore, rejection can happen in T lymphocyte deficient conditions, implying that the maturation of DCs might be more than a complex mechanism triggered by DAMPs or pathogen-associated molecular patterns (37–40).

The Possible Downstream Effects of DCs in Kidney Allograft Rejection

Conventional hypothesis indicated donor DCs activate anti-donor rejection *via* migration to the host second lymphoid nodes providing alloantigen to recipient T cells (41). This hypothesis resulted from observations on mouse models: T lymphocytes respond to antigen-presenting cells with non-self-MHC (major histocompatibility complex) *in vivo* (42, 43). Moreover, depleting leukocytes in the allografts drives long-term survival, whereas injecting donor DCs into the host restores acute rejection (44–49). Later research established that donor and recipient DCs play equal roles in mediating the rejection process, and recipient DCs are even more stable to present antigens. Deleting recipient DCs prolonged allograft survival significantly but depleting donor DCs did not (50). Also, DCs lacking MHC or CD80/86 molecules are killed by recipient natural killer cells during migration to the lymphoid nodes (50–53). Recently, donor DCs are viewed as transporters of antigen rather than presenters of antigen (54). MHC molecules can be exchanged between the donor and recipient DCs (55, 56). Therefore, recipient DCs gain non-self MHC from donor DCs, capable to activate T lymphocytes originated from recipients through both non-self MHC and self MHC (57–62).

The basic function of mouse cDC1 is to use MHC class I molecules on its surface to extract antigens from $CD8^+$ cytotoxic T cells and induce them to kill target cells. This plays a decisive role in the process of renal transplantation and may be directly related to cellular immunity. Also, mouse cDC1 can induce regulatory T cells in lymphatic circulation (63, 64). The function of human cDC1, which is different from that of mice, needs further study. However, compared with cDC1, cDC2 generally does not have the aforementioned antigen targeted by cytotoxic T cells (65–67). Therefore, in renal transplantation, cDC2 will not be killed by cytotoxic T cells but can induce B cells to respond through helper T cells, which may be the mechanism of antibody-mediated immune rejection (68). Finally, it has been revealed that cDC2 cells induce T helper cells to stimulate the production of pro-inflammatory mediators in the chronic renal inflammation model, so in the same chronic rejection, cDC2 may also be the center of inflammation and participate in the pathogenesis of immune effectors including antibodies.

DCs IN IRI

IRI happens frequently following renal transplantation *via* recruitment of immune cells including DCs by pro-inflammatory cytokines like tumor necrosis factor derived from hypoxic endothelial cells (13, 69) (**Figure 2**). The DCs involved in IRI have not been completely defined. Current studies tend to

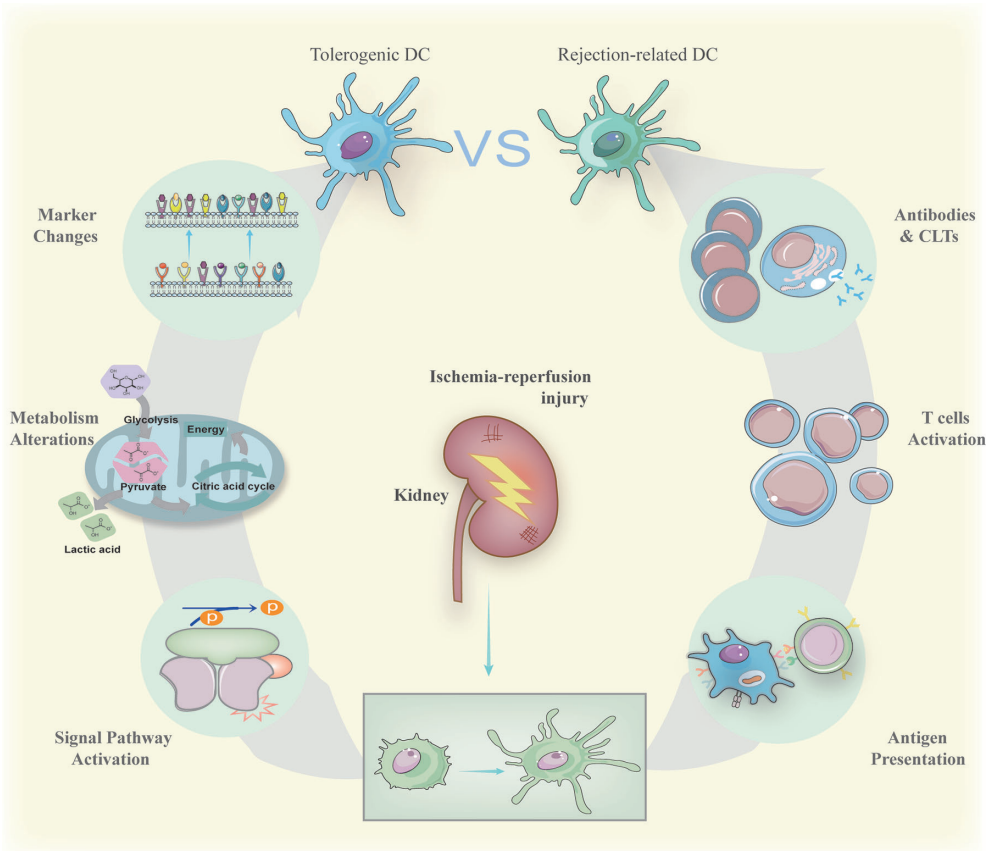

FIGURE 2 | Immature DCs can be activated by antigens derived from ischemia-reperfusion and act as the role of powerful antigen-presenting cells to trigger antibody-mediated rejection and cell-mediated rejection. The result of antibody-mediated rejection is activated B cell releasing harmful antibodies while active cytotoxic T cells kill donor cells forming cell-mediated rejection. On the contrary, when treated by specific drugs, immature DCs can also maintain their surface markers to suppress possible inflammation caused by transplantations *via* signal pathways activation regulating metabolism alterations. The signal pathways include NF-κB and mTOR summarized in the section *The Generation of Tolerogenic DCs*. The metabolism alterations involve glycometabolism and lipid metabolism with more details in the section *The Generation of Tolerogenic DCs*.

claim that DCs involved in IRI express CD45, CD11c, MHC-II, TNF-α, CD80, CD86, CD40, CD54 (ICAM), C1d, CD8 α, but not CD4 and CD205. All the markers might be useful in further investigations (**Table 1**). Then hypoxia-inducible factor 1α induces kidney DC maturation, damaging renal functionality (70–72). DCs can promote harmful activations of immune effects *in vivo*, but they are also associated with protecting renal function from IRI. Since immature DCs are less stimulatory than mature DCs, some researchers supposed that kidney DCs' role is to harm allograft (73–76). DCs feature in IL-10 as well as single Ig IL-1-related receptor, therefore, exhibiting the inhibiting effects on inflammation in IRI (77). On the contrary, immature kidney DCs can serve as an adverse player to mature DCs, preventing IRI (78, 79). Thrombin could release IL-12, IL-17, and C3a thus causing T helper-1 bias to influence kidney DCs' behaviors and determine the outcomes of IRI (80). High concentrations of tissue factors in the kidney may also contribute to IRI (81). Further studies are warranted to clarify the discrepancy about kidney DCs, especially the relationship between rejection-related DCs and tolerogenic DCs (**Figure 2**).

REJECTION-RELATED DCs IN ALLOGRAFTS

The traditional function of DCS is to mediate the rejection of harmful non-autogenous substances or abnormal autogenous materials, so the research on rejection-related DCs mostly employs traditional surface markers of cDCs. Although it is not recommended to judge the types of DCs based on only one surface marker, the comprehensive use of different surface markers can still accurately define rejection-related DCs (**Table 1** for specific markers).

Acute Rejection Based on the DC-Dependent Mechanism

The interaction between DCs and T lymphocytes triggers a so-called acute rejection through the conventional pathway—donor DCs present alloantigen to recipient T cells directly (82, 83) (**Figure 2**). At first, the ischemia–reperfusion condition drives donor DCs to induce acute rejection (14). Secondly, active DCs search for immature or memory T cells attracted by the chemical

gradient of CCR7 to present the allografts (84). Early studies usually located this process in second lymphoid organs (85), while later observation indicated that second lymphoid organs are not necessary for acute rejection: acute rejection occurs even when lacking secondary lymphoid organs (86, 87). The identical role of DCs in acute renal rejection could be separated into interaction with memory T cells and naive T cells, which happens in many different places including the second lymphoid organs. Taken different DCs into consideration, recipient DCs may be germane to the acute rejection as well as donor DCs (88).

Chronic Rejection Based on the DC-Dependent Mechanism

Owing to a longer lifespan, recipient DCs are more likely to mediate the chronic rejection rather than donor DCs. According to observations in mouse kidney grafts, the recipient DCs replace most of the donor DCs within 24 h after surgery, and over 90% DCs are derived from recipients on the 7th day after transplantation (57). Subsequently, these DCs originated from monocytes in the host, but a few donor DCs still survive to activate T cells (57). The interaction between DCs and T cells has been more stable and prolonged since DCs reach into the renal cortex to arrest antigen-specific T cells around the endothelium with no regard to the chemical gradient. Independent of the chemical gradient, interruption of the protracted connection with T cells induces tolerance (89, 90). Also, infiltrating DCs activate B cells to promote chronic allograft rejection with the assist of T helper cells. This procedure depends on recipient DCs presenting antigen to recipient T helper cells, but the molecular mechanism remains elucidated (91–94). A few clinical trials are targeting this approach, whereas more current studies are paying attention to mediate tolerance taking advantage of the tolerogenic DCs and Tregs (95).

TOLEROGENIC DCs IN RENAL TRANSPLANTATION

Remarkable Features of Tolerogenic DCs

As a pivotal part of innate immunity, tolerogenic DCs are usually defined as immature rejection-related DCs (96, 97). Tolerogenic DCs, also called DCregs, circulate in the body quiescently responding to endogenous or exogenous stimuli, for example, endogenous alarmins. These tolerogenic DCs exhibit poor expression of MHC, T cell co-stimulatory molecules like CD40, CD80/86, as well as T cell co-inhibitory ligands (*e.g.*, programmed death ligand-1 and death-inducing ligands), presenting non-phagocyte properties (16–20) (**Table 1**). Meanwhile, these DCs express a larger amount of the macrophage inhibitor cytokine than rejection-related DCs (98). Moreover, tolerogenic DCs can change the amount of C1q on its surface approaching the mature state with the assistance of globular C1q receptors (99, 100). C1q, a complement subunit, mediates IL-10 secretion involved in the interaction between DCs and myeloid or lymphoid cells (101–103). Besides, tolerogenic DCs confine promoting inflammatory factors including IL-12p70 into a low level while producing a high level of anti-inflammatory molecular-like transforming growth factor β as well as IL-10 (104) (**Figure 3**).

According to transcription analysis, the Wnt/β-catenin pathway programs tolerogenic DCs to maintain a series of unique molecular markers (105–108), and tolerogenic DCs specifically express some genes, including CNGA1, CCL18, C1QB, MUCL1, MAP7, C1QC, CYP7B1, and CYP24A1 (109). Compared to immunologic DC, tolerogenic DCs possess a steady oxidative phosphorylation program and favor fatty acid oxidation associated with decreased reactive oxygen species (110). Based on these features, tolerogenic DCs stimulate T cells weakly or even suppress the function of T cells *via* anergy or apoptosis for long-term immaturity (111). Additionally, tolerogenic DCs can spare, expand, and induce Tregs as shown in **Figure 3** (111–113). The interaction between tolerogenic DCs and divergent T cells results in conditions such as allograft rejection, hematopoietic stem cell transplantation, graft-*versus*-host diseases, and autoimmune disorders (111, 114–116). But the specific mechanism buried in these phenomena remains elusive. Therefore, an increasing number of studies incorporate tolerogenic DCs into clinical trials in organ transplantation and autoimmune diseases (117–119).

Tolerogenic DCs Possible Anti-Rejection Effects

DCs inducing tolerance was first discovered in 1995/1996 (120, 121). Tolerogenic DCs have the potential to suppress allograft rejection because DCs with $CD16^-$ markers exist in transplant recipients compared with healthy people using single-cell RNA sequence (122). Also, infusion of tolerogenic DCs appears to be reliable and acceptable with or without immunosuppressive agents, which probably provides anti-rejection therapy in the future (111, 123). Ezzelarab et al. infused donor-derived tolerogenic DCs processed by vitamin D3, IL-10 into rhesus macaque models, showing that graft survival prolonged with no evidence of host sensitization (124). Autologous tolerogenic DC infusion could also lengthen the survival time of grafts, and murine IL-10-induced DCs can function as rejection inhibitors *in vivo* and *in vitro* expressing lower levels of MHCII, CD40, CD86, CD205 (125–127).

Donor-derived tolerogenic DCs can interact with alloreactive memory T cells including $CD8^+$ and $CD4^+$ cells (128, 129) (**Figure 3**). In specific, tolerogenic DCs increase allograft survival time relying on co-inhibition of cytotoxic T lymphocyte antigen-4 (CTLA-4) downregulation (128) (**Figure 3**), and coinhibitory CTLA-4 blocker treatment has the potential to improve prognosis in renal allografts (130, 131). Moreover, DC-induced $CD95^+$ memory T cells could be an immunosuppressive phenotype with increased expression of programmed death-1 as well as coinhibitory CTLA-4 *via* Eomesodermin (an essential transcription factor maintenance) (124, 128, 132). Thereafter, the infusion of coinhibitory CTLA-4 immune globulin and tolerogenic DCs promotes transplant tolerance (129, 133). In this promotion, high expression of

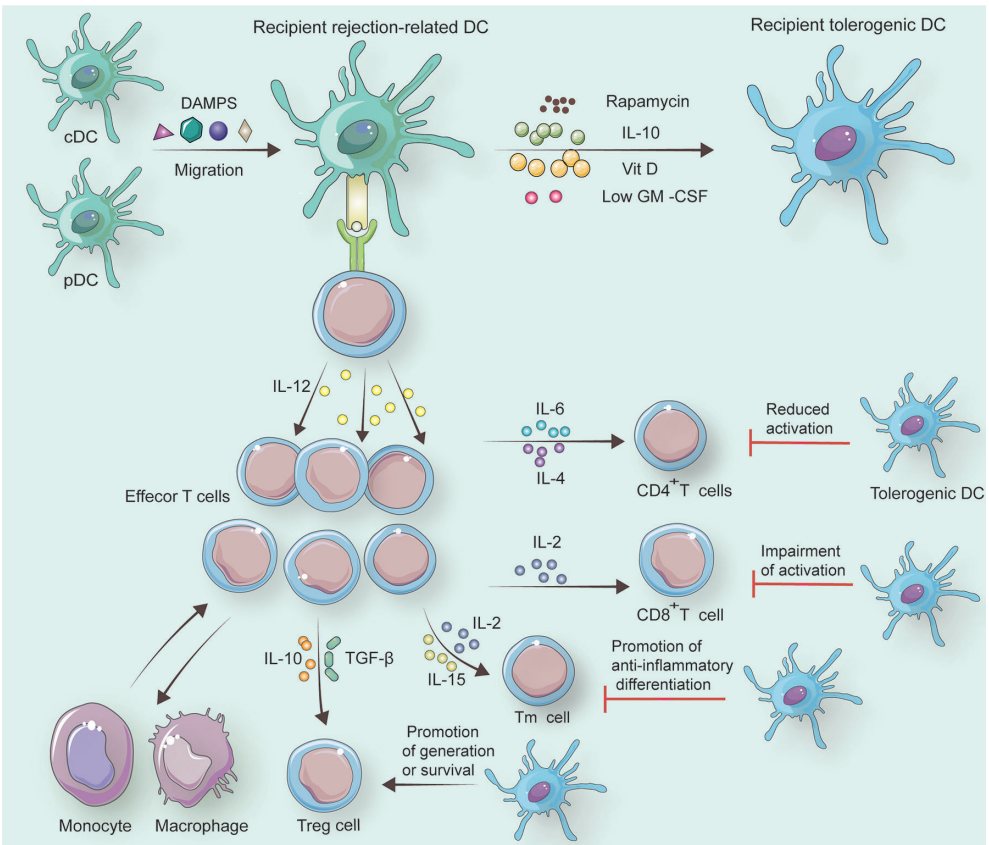

FIGURE 3 | In response to specific factors including DAMPs, recipient cDCs and pDCs change into recipient rejection-related DCs. If rapamycin, IL-10, Vit D, or a low dose of GM-CSF is employed to treat recipient rejection-related DCs, recipient tolerogenic DCs can be generated. Under the control of recipient rejection-related DCs, naive T cells differentiate to $CD8^+$ T cells with the help of IL-2 and differentiate to $CD4^+$ T cells assisted by IL-6 and IL-4. Memory T cells (Tm cells) also originate from naïve T cells, and this alteration is associated with IL-2 and IL-15. Treg cells can occur when IL-10 and TGF-β are secreted by recipient rejection-related DCs. Besides, tolerogenic DCs reduce $CD4^+$ T cell activation, and they can impair active $CD8^+$ T cells. Furthermore, Tm cells tend to be anti-inflammatory promoted by tolerogenic DCs. Treg cells survive for a longer period with tolerogenic DCs than with rejection-related DCs.

immune-globulin-like transcript 3 and immune-globulin-like transcript 4 causes $CD4^+CD45RO^+CD25^+$ T cells to become Tregs mediated by the enzyme indoleamine 2, 3-dioxygenase in allografts (134) (135). As a result, the identical indoleamine-2,3-dioxygenase and immunoglobulin-l like transcript 3 as well as high expressions of both MAP7 and MUCL1 genes occur in the mechanism of vitamin D3 inducted tolerogenic DCs (136–140) (**Figure 3**).

Donor-derived tolerogenic DCs can prolong graft survival time: treatment of these DCs ensures graft survival another 50 to 300 days (125). Donor tolerogenic DCs regulate $CD8^+$ as well as $CD4^+$ memory T cell responses, and this regulation prevents potential rejections (141–145). These DCs capture vesicles containing allograft antigens but choose an anti-inflammation phenotype: the number of donor-reactive IL-17^+ T cells remains low (125, 146). Further, donor-derived tolerogenic DCs induced by vitamin D3 and IL-10 moderate IL-17 associated inflammation and maintain stability even exposed to inflammatory molecules (124, 147). Most importantly, humans produce no specific antibody against injecting tolerogenic DCs (124). Moreover, without active recipient T cells, harmful antibodies derived from B cells will be reduced (148). Besides, multiple subsets of freshly isolated human DCs, including non-conventional plasmacytoid DCs, can regulate immune responses as well (107, 108, 149). **Table 2** summarizes the versatile roles of DCs targeting solving rejection problems in renal transplantation, implying future evaluable clinical advances (153).

The Generation of Tolerogenic DCs

Various cytokines and similar materials serve as triggers *in vivo*. Exposure to donor blood and immunosuppressive mediators, rapamycin, for example, might be a useful method in a non-human primate model (124, 129). Also, effective tolerogenic DCs can be endogenous. However, recipients' natural killer cells tend to kill donor-derived DCs that can mediate Tregs. Addressing this issue, Morelli and colleagues deleted host DCs to protect the donor-derived DCs from being killed (154). Through this method, recipient DCs acquired exosomes released by the donor tolerogenic DCs and amplified the effect of tolerance *via* the third mechanism mentioned in *The Possible Downstream*

TABLE 2 | Versatile roles of DCs in renal transplantation.

Animal Models	Interventions	Results	Functional roles or mechanisms	References
Rat	i.v. tolerogenic DCs derived from donors	increasing content of CD4+CD25 +Foxp3+Tregs and up-regulated secretion of Th2 cytokines	The enzyme indoleamine 2, 3-dioxygenase in tolerogenic DCs may induce allograft immunotolerance.	(135)
Monkey	i.v. CTLA-4 immunoglobulin and tapered rapamycin	Graft median survival time prolongation as well as IL-17 production attenuation combined with no circulating anti-donor antibody	The beneficial effect of donor Ag-pulsed autologous tolerogenic DC on nonhuman primate graft survival may be modest but not statistically significant.	(125)
Monkey	i.v. donor-derived regulatory dendritic cell	Tolerogenic DC-mediated tolerance with or without cytotoxic T-lymphocyte-associated antigen activation.	Pre-transplant DCreg infusion promotes tolerance after transplantation with no regard to CD28 blockade.	(129)
Mouse	Renal DCs were studied in collagenase-digested mouse kidneys	DCs migrate from the renal interstitial to renal lymph node within 48 h accompanied by increased DCs	Renal DCs respond to localized or systemic acute kidney injury by increasing the transport of protein antigens from the kidney to lymph nodes.	(74)
Mouse	Antigen coupled to an anti-CD205 antibody	Antigen-specific CD8 T-cell deletional tolerance	DEC-205 provides an effective receptor mechanism for DCs to deal with MHC class I presentation *in vivo*, which makes DCs produce stable immune tolerance and immune response after maturation.	(150)
Rhesus monkey	i.v. MD-3 anti- intercellular adhesion molecule antibody combined with low dose rapamycin and CD154	Long-term survival of pig xenoislets	The maturation of DCs relies on intercellular adhesion molecule-1 and anti-intercellular adhesion molecule-1-induced antigen-specific T cell tolerance.	(151)
Humanized mouse	i.v. MD-3 antibody before transplantation	Xenospecific T-cell tolerance; prevention of xenoislet rejection	The maturation of DCs relies on intercellular adhesion molecule-1 and anti-intercellular adhesion molecule-1 -induced antigen-specific T cell tolerance.	(151)
Cynomolgus monkey	i.d. immunization with antigen fused to anti-DC-asialoglycoprotein receptor antibody every 5–6 weeks after the flu virus	Ag-specific, IL-10 producing Tregs *in vivo*	human DCs can generate antigen-specific suppressive CD4 T cells that produce interleukin 10 *via* DC-asialoglycoprotein receptor but not Dectin-1 or DC-specific intercellular adhesion molecule-3-grabbing nonintegrin.	(152)
Rhesus macaques	i.v. DCreg + B7-CD28 costimulation blocking agent cytotoxic T-lymphocyte-associated antigen immunoglobin, 7 days before renal transplantation and for up to 8 weeks	Median graft survival time was 39.5 days in control monkeys and 113.5 days in tolerogenic DCs treated animals	Tolerogenic DCs generated from cytokine-mobilized donor blood monocytes in vitamin D3 and IL-10 moderate combined T cell- and antibody-mediated rejection.	(124)

Effects of DCs in Kidney Allograft Rejection (60). A few cytokines are able to induce tolerogenic DCs *in vitro*, for example, IL-10 and TGF-β (optimal inducible factors) (155) (**Figure 4**). IL-10 decreases MHC-II expression and costimulatory molecules in DC (156, 157). TGF-β increases the expression level of programmed death-ligand 1 and Fas-ligand on DC, inducing T cell apoptosis, and Treg differentiation (158, 159). Also, valuable methods can be used to produce tolerogenic DCs *in vitro* such as soluble Schistosoma Mansoni egg antigen, tumor necrosis factor α-induced protein 8 like-1, human soluble CD83, and prostaglandin E2 (PGE2). Soluble Schistosoma Mansoni egg antigen increases IL-10 level and suppresses Il-12p40 secretion, implying a novel method of tolerogenic DC generation (160). Except for IL-10 and TGF-β, tumor necrosis factor α-induced protein 8 like-1 could control the T cell activation procedure (161, 162). Human soluble CD83 alone achieves kidney allograft tolerance (>100 days) involving tolerogenic DC generation and indoleamine 2,3-dioxygenase activation (163). Mature DCs treated with PGE2 could inhibit inflammation *via* IL-10 secretion (164, 165). Traditional immunosuppressants can also serve as inducers of tolerogenic DCs, for instance, rapamycin and dexamethasone (166–170). Tolerogenic DCs generated from dexamethasone exhibit few costimulatory molecules or pro-inflammatory cytokines (171). Besides, metastasis-associated lung adenocarcinoma transcript 1, mesenchymal stem cells, nuclear paraspeckle assembly transcript 1, LF 15-0195, and pluripotent stem cells have a potential capacity to facilitate the tolerogenic DCs since they have been proven in other organ transplants (172–174).

Tolerogenic DC activation relies on adenosine triphosphate derived from glycolysis and tricarboxylic acid. Thus, control of glycolysis regulates DCs in renal transplantation especially in a few key active sites (175, 176). For instance, insufficient energy support causes morphological alteration and disorders in migration to lymph nodes (177). Lipopolysaccharide, complement component C1q subcomponent-binding protein, 2-deoxyglucose, and 1,25-dihydroxy vitamin D3 are associated with oxidative phosphorylation, fatty acid oxidation, and reactive oxygen species. In glycolysis, lipopolysaccharide mediates fatty acid synthesis forming adenosine triphosphate to trigger DC activation (178). C1q subcomponent-binding protein participates in the tricarboxylic acid cycle *via* regulating pyruvate dehydrogenase as a chaperone protein (179). 2-deoxyglucose plays an essential role in reducing CD40, CD86,

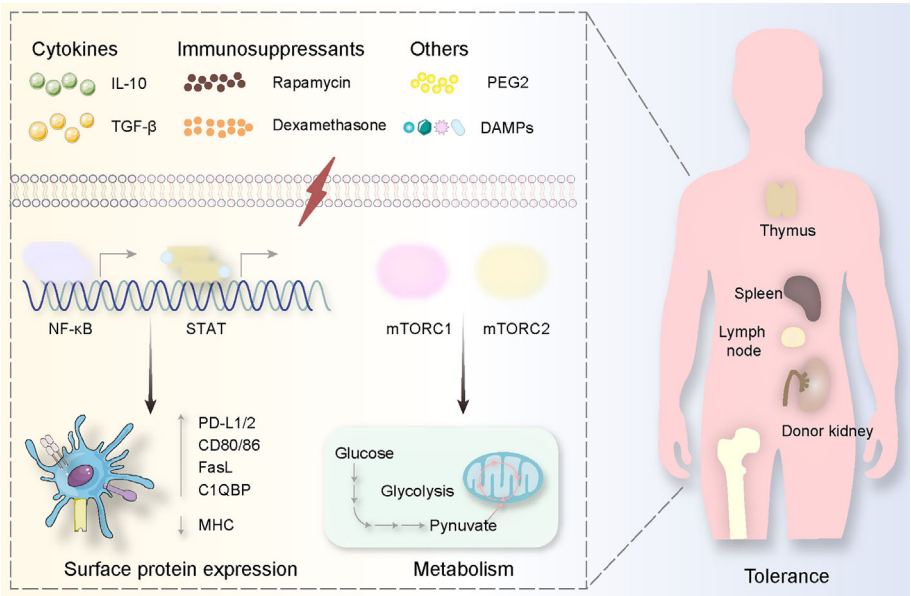

FIGURE 4 | Tolerogenic DCs are usually generated *via* specific substances. These stimulations derived from cytokines (IL-10, TGF-β), immunosuppressants (Rapamycin, Dexamethasone), and others (PEG2, DAMPs) mediate signal pathways involving NF-κB and mTOR activation, causing surface protein expression alterations (highly expressing PD-L1/2, CD80/86, FasL C1QBP while decreasing MHC expression) and metabolism changes (from glucose to pynuvate). All these procedures happen in the donor kidney and the immune organs including the thymus, spleen, lymph node, and bone marrow.

and MHC-II expression and secreting IL-6, IL-12p70, and TNF, which can be defined as features of tolerogenic DCs (178). Oxidative phosphorylation and fatty acid oxidation can be regulated by paracrine-derived Wnt5a protein linked tolerogenic DC generation, vitamin D3 or 1,25-dihydroxy vitamin D3 induction of tolerogenic DCs, and dexamethasone mediated tolerance (109, 180, 181). Specifically, these materials generate tolerogenic DCs through inducible nitric oxide synthase, nuclear factor E2-related factor 2: inducible nitric oxide synthase reduces oxidative phosphorylation and fatty acid oxidation, but nuclear factor E2-related factor 2 decreases the amount of inducible nitric oxide synthase expression (182, 183). As for the relationship between oxidative phosphorylation and fatty acid oxidation, miR-142 links to carnitine palmitoyltransferase-1a and induces more active fatty acid oxidation and further increases glycolysis promoting pro-inflammatory cytokines (184). Fatty acid inhibits oxidative phosphorylation and facilitates reactive oxygen species leading to more severe inflammation (185–187).

In addition to general metabolism, it is accurate and stable to induce tolerogenic DCs employing regulating signal pathways. The most well-known pathway that has been focused on is mTOR (mammalian target of rapamycin) involving mTOR complex 1 (mTORC1) as well as mTOR complex 2 (mTORC2) (**Figure 4**). The inhibition of mTOR produces tolerogenic DCs associated with glucose metabolism. GM-CSF, IL-4, rapamycin, alum, and graphene quantum dots have effects on mTOR mediating potential tolerance *via* lower adenosine triphosphate generation (167, 188–190). Specifically, mTORC2 decreases adenosine triphosphate generated from mTORC1 mediating glycolysis, and mTORC1 takes crucial tasks in DC maturation (191) (**Figure 4**). Also, the upstream and downstream molecules contribute to the generation of tolerogenic DCs (**Figure 2**). An upstream complex called adenosine monophosphate-activated protein kinase can be suppressed by polyphenol resveratrol causing poor expression of mTOR (192). A downstream complex named after the peroxisome proliferators-activated receptor plays a metabolic role in DC maturation through targeting at mTORC1 and hypoxia-inducible factor-1a as a downstream complex serves to reprogram glycolysis for DC maturation *via* mTOR activation (177, 193–195). Reprogramming glycolysis in DCs can be finished by another kinase known as spleen tyrosine kinase depending on the production of IL-1b through a different mechanism compared with infection (196, 197).

STAT and NF-κB have also been incorporated into the maturity of DC as a family containing STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6 as well as inhibiting STAT1, STAT2, and STAT5, and activating STAT3 induces tolerogenic DCs (198, 199) (**Figures 2**, **4**). Targeting at STAT1, flavonoids decrease the expression of programmed death-ligand 1 to enable DCs more mature (200, 201). Silencing STAT1 with small interfering RNA in DCs causes low expression of CD83 and CD86, implying anti-inflammatory effects (202). STAT2 functions as a co-worker with STAT1 mediating cross-presentation of DC, and thus STAT2 should be suppressed when tolerogenic DCs are needed (203). STAT3 activation provides tolerogenic DCs because IFN-α-induced programmed death-ligand 1 expression is inhibited by suppressed STAT3, and STAT3-

deficient DC could increase pro-inflammatory cytokines, promote antigen-dependent T cell activation (204, 205). With STAT5 inhibited by JQ1 in lipopolysaccharide-mediated DCs, the level of IL-12p70 secretion is decreased (206). Moreover, materials preventing NF-κB like small interfering RNA and Bay11-7082 have the potential to generate tolerogenic DCs in that they can serve as immunosuppressive tools in other organ transplants (207, 208) (**Figure 4**).

CONCLUSIONS AND POSSIBLE THERAPEUTIC PROSPECTS

Compared with macrophages in kidney transplantation, renal DCs' roles in ischemia–reperfusion, rejection or tolerance still need to clarify. For further investigation, a unified standard to separate kidney DCs from macrophages must be established based on the current level, since macrophages and DCs are both essential parts of innate immunity and they often function together inducing rejection or tolerance. This objective can be promoted by high-dimensional analysis of single-cell because increasing kidney biopsy samples provide an opportunity for revealing the markers and transcription different from macrophages. Additionally, the comparison of normal kidney and rejected kidney engenders valuable hypothesis and remarkable conclusions analyzed by artificial intelligence. In some respects, researchers tend to establish mouse models in experiments and this choice produces numerous discoveries and hinders translational medicine. Kidney transplantation saves tens of thousands of patients' lives every year and costs millions of dollars handling rejection-associated problems meanwhile. Although donor DCs might mediate tolerance *in vivo*, patients still rely on traditional glucocorticoids and non-specific immunosuppress drugs. As a result, translational medicine should be emphasized immediately after the roles of DCs in renal transplantation being clarified. Finally, the relationship between rejection and tolerance and DCS is relatively clear, but the relationship between DCs and other complications of renal transplantation is still in a vague state. For example, infection related to renal transplantation may be related to intestinal flora, and the effect of intestinal flora on host immune status is likely to be achieved through DCs. In addition, the lifespan of donor DCS is not as long as that of recipient DCs, so the details of the interaction between the two DCS will also be the key to anti-rejection intervention at different time points after renal transplantation. On this basis, the understanding of the interaction between DCs and T cells of each transcript will also provide support for the development of anti-rejection drugs after transplantation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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