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Dendritic Cells: Two-Edged Swords in Pathogenesis of Autoimmune Glomerulonephritis

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1. Introduction

Direct involvement of $CD4^+$ T cells in the pathogenesis of inflammatory glomerulonephritis such as Anti-GBM glomerulonephritis and other glomerular diseases of autoimmune nature, has been well demonstrated. Unlike antibody mediated mechanisms, regulation and/or activation of T cells requires antigen presenting cells (APC) such as dendritic cells (DC). DCs are critical for activation of pathogenic T cells, or for establishing T cell-mediated glomerular inflammation by presenting local self antigens to pathogenic T cells. Thus, recent studies have been focusing on identification of DCs and their functions in various human autoimmune glomerulonephritis or in animal models. Similar to other human autoimmune diseases, DCs involved in glomerulonephritis include diverse subpopulations, which have either pro- or anti-inflammatory functions. Understanding especially their anti-inflammatory function may lead to development of new therapeutic strategies by mimicking those natural mechanisms. Mounting evidence shows the presence of tolerogenic DCs (tDCs) in various kidney diseases, which are involved in inhibition of autoimmunity by elimination or skewing development of self reactive T cells. Several new types of DCs have been characterized in animal models. Among them, one type of tDC may arrest an existing glomerular inflammatory process. This novel tDC specifically infiltrates glomeruli under autoimmune attack and induces apoptosis in auto-reactive T cells, leading to natural recovery in certain strains of animals. Thus, this tDC is an attractive target in cellular immunotherapy for glomerulonephritis by mimicking this natural recovery mechanism.

2. What are dendritic cells (DCs)?

Adaptive immunity, which is unique to vertebrates, is much more efficient than innate immunity, which is common among all types of animals. The high effectiveness of adaptive immunity is due to its specifically defined recognition of any given antigen. Only two types of immune cells in adaptive immunity, B cells and T cells, are capable of such antigen recognition through specified receptors. In T cells, their antigen recognition receptor is the T cell receptor (TcR); in B cells, their receptor is called the B cell receptor (BcR), which in fact is a membrane-bound antibody. Unlike innate immunity, B cells and T cells do not discriminate molecular motifs of microbial antigens from other antigens, and thus, they do

not directly recognize microbial antigens, or in a broader meaning, any antigens, by themselves. Rather, they acquire antigen-recognition capacity through "education" by other immune cells. The most important process during "education" is antigen presentation, which is carried out by so-called antigen presenting cells (APCs). In this chapter, we will focus solely on APCs for $CD4^+$ T cells, since $CD4^+$ T cells play a central role in adaptive immunity, inflammatory diseases and autoimmunity including those occurring in glomeruli. A group of phagocytes can present antigens to $CD4^+$ T cells (although B cells can act as APC to $CD4^+$ T cells, it will be excluded in this chapter). We call these phagocytes "professional" APCs since their principal function is to present antigens. These phagocytes, which include monocytes, macrophages and dendritic cells, capture especially microbial antigens through their motif/pattern recognition receptors such as toll like receptors (TLRs). The captured antigens are processed into peptides, which then are presented to $CD4^+$ T cells in a complex of MHC II molecules and antigenic peptides. Thus, these professional APCs function as messengers or connections between innate and adaptive immunity: they capture antigens from microbial pathogens and use these antigens to "educate" T cells and B cells. As a result, a group of T or B cells which solely recognize this antigen would be activated to fight the original pathogens in a more effective way.

The DCs has been recognized as the most potent professional APCs since its discovery three decades ago. So far, immunologists believe that DCs are the only APCs that are able to initiate/direct an adaptive immunity by activation of naïve T cells, because DCs express special signaling molecules called co-stimulatory molecules, such as CD80 and CD86, in addition to their superb capacity in capturing and presenting antigens (1). From this point of view, DCs are also considered a critical immunoregulator. DC was first identified as a population of striking dendritic-shaped cells in the spleen by Ralph Steinman in the 1970s (2). It soon became clear that cells similar to the splenic DCs are present in all lymphoid and non-lymphoid tissues, though in a much smaller number than macrophages. However, soon immunologists realized that DCs in fact are a heterogenic group of phagocytes, which may be generated from different lineages. It seems less arguable that DCs are generated from bone marrow stem cells. As many distinct subtypes of DCs have been described or discovered, it seems difficult to give a simple definition for DCs.

What are DCs? Why did we name certain immune cells DCs? There are several common characteristics shared by the cells, which have been named as DCs (3). *First*, DCs are usually of hematopoietic origin and grow branched projections called dendrites that give the cell its name (δένδρον or déndron in Greek means "tree") at certain development/activation stages. Development of cellular projections greatly increases their cell surface area for contacting/ capturing antigens. *Second*, they are potent professional APCs, and in many cases, they can activate naïve T cells. Their APC function can be reflected by their expression of MHC II, which can be further up-regulated after stimulations, in addition to "dendrite' like cellular projections, which would increase the cell surface area for capturing antigens. In some DCs or at certain activation stages, they also express co-stimulatory molecules for T cells (4). *Third*, they also express multiple "pattern recognition receptors" such as TLRs for recognition of microbial antigens.

Different DCs migrate following a special pattern through circulation, tissue and lymphoid organs (Figure 1) (5). Thus, they express certain sets of chemokine receptors and adhesion molecule. For example, all mouse DCs express an adhesion molecules CD11c. Immature DCs or DC precursors are often found in the peripheral blood before they exit the circulation. As a first line of immune defense, DCs, such as conventional DCs, are present in tissues in contact with the external environment, such as the skin and the mucosal system.

They are actively motile and continuously sample their surroundings. Once activated after encountering invading pathogens or antigens, they migrate to the lymphoid organs where they interact with T cells and B cells to initiate and shape the adaptive immune response. However, this typical migration route may not fit to all types of DCs. For example, plasmocytoid DCs directly enter lymph nodes (6).

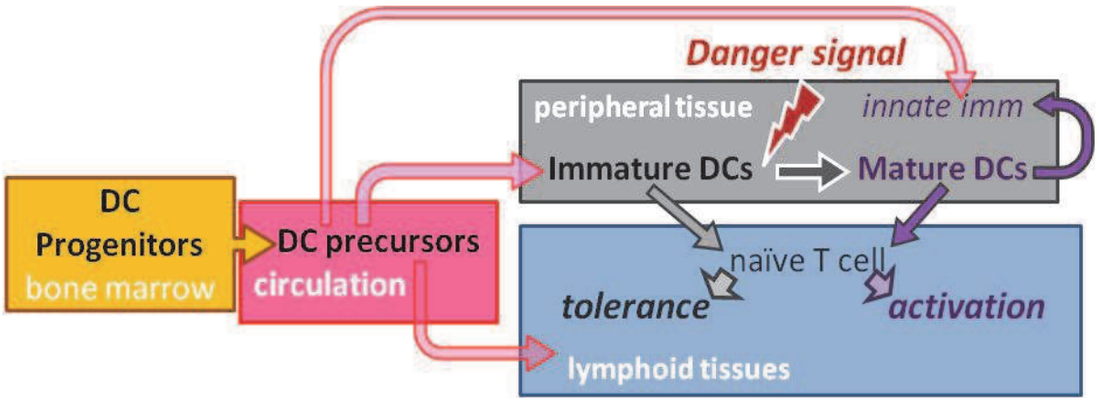

Fig. 1. Schematic diagram shows circulation of DCs, from bone marrow progenitors, precursor in circulation and immature DCs in peripheral tissues and mature DCs in lymphoid organs. This route is representative. Not all DCs migrate or mature as shown.

3. DC classification

Because of the high levels of heterogeneity among identified subsets or types of DCs, their classification is not an easy task for immunologists. DCs have been grouped by their function, lineage, markers, and migration route or residing tissues. *First*, DCs can be grouped by their locations and migration route. DCs and DC precursors can be found in the circulation, and in different anatomic locations, including lymphoid or non-lymphoid tissues. Langerhans cells are a well characterized DC residing in the skin (7). DCs in the interstitial tissue including renal tissue are named IntDC. DCs also populate the entire mucosa system. Those tissue-residing DCs develop from DC precursors in the circulation, and act as "scouts" to detect any invading antigens. Once loaded with antigens, those DCs migrate into afferent lymph, and they are called veiled cells. After migrating through the afferent lymphatic system, they are called interdigitating DCs (IDCs) in T cell areas in the paracortex of lymph nodes. IDCs may activate naïve T cells there. In lymphoid tissue, many DCs are present in the Germinal Center (GC, where B cells differentiate) and are called GC DCs, which function as a strong APC for activating T cells and B cells. In GC, there is a type of cell called follicular DC (fDC). fDC presents antigens to B cells using a totally different mechanism, and thus, is not a typical DC discussed in this chapter. *Second*, DCs have been classified by their lineage (8). For example, the terms "lymphoid DC" and "myeloid or monocyte-related" DC are used for those DCs, which probably differentiate from the same bone marrow stem cells as lymphocytes or monocytes, respectively. However, this classification is largely based on similarity in morphology and surface markers between the cells. Results from *in vitro* differentiation experiments or experiments to identify special differentiation pathways in bone marrow stem cells or DC precursors have provided some evidence to support some DCs' lineage. *Third*, more accurate classifications of DCs that are

based on a combination of their lineage, markers and function, and thus, are much more complicated, as well as some times controversial. There are several classification methods for mouse DCs, since various DCs have been well characterized in mice. It seems impossible for this chapter to cover all those classifications for DCs. Furthermore, those classifications may not be able to recover or describe several newly discovered DCs. To avoid confusion, this chapter will mainly introduce one representative classification for mouse DCs which reside in the lymphoid organs, recently summarized by Sato and Fujita (9). Despite the difficulty in comparison of the DC systems between humans and mice, recent work has revealed much common ground (10). We will then compare mouse DCs to their human counterparts.

Mouse DCs are primarily defined by their surface MHC II and CD11c in combination with CD4, CD8αα, CD11b (a myeloid marker) and several other molecules such as CD205 (IDC marker). $CD8\alpha\alpha^+$ DC has been classified as lymphoid DCs, while $CD8\alpha\alpha^-$ DC as myeloid DCs, due to their possible lineage. However, currently, both mouse and human DCs are divided into two big groups: conventional DCs (cDC) and plasmacytoid DCs (pDC) (Figure 2). DCs from two groups not only show different migration routes, but also differentiate probably from different stem cells with quite different functions. In mice, DCs in lymphoid organs have been best characterized. Mouse cDCs in lymphoid tissues can be further divided into five subsets largely based on their CD4 and CD8 expression and their location in different lymphoid tissues. There are three subsets of cDCs in the spleen, which include two of myeloid origin with phenotypes of $CD4^+CD205^-CD11b^+$ and $CD4^-CD8\alpha^-CD205^-CD11b^+$, and one of lymphoid origin with a phenotype of $CD8\alpha\alpha^+CD205^+CD11b^-$ (Figure 2)(11). It needs to be pointed out that "myeloid origin" in this chapter are not equal to "myeloid DC (mDC)", which has been widely used in other classification methods. We will explain the difference later. Each subset shows various functions, which are demonstrated largely by *in vitro* experiments (Figure 2). Both DC subsets of myeloid origin (i.e. $CD11b^+$) in the spleen (some times in lymph nodes as well) express F4/80 (a well known marker for mature macrophages). $F4/80^+$ cDCs are located in the marginal zone between white and red pulp and will migrate to the T-cell area after stimulation. Both splenic $CD8\alpha\alpha^-$ DCs of myeloid origin are able to stimulate $CD4^+$ and $CD8^+$ T cells and to initiate a Th2-type T cell response (12). Splenic DCs of lymphoid origin ($CD8\alpha\alpha^+CD205^+CD11b^-$) are found in the T-cell area; a smaller number of this cDC may also exist in lymph nodes. Interestingly, this DC is a dominant subset among thymic DCs. Several *in vitro* experiments showed that this cDC can function both as a regulator and stimulator of T cells. Although it can stimulate both $CD4^+$ and $CD8^+$ T cells, it subsequently restricts T cell proliferation by either inducing apoptosis in $CD4^+$ T cells, or limiting endogenous cytokine production in $CD8^+$ T cells. Those results suggest that this cDC subset may be responsible for maintenance of T cell tolerance in lymphoid organs in the absence of infection (13). In contrast, other studies suggest this subset cDC to be a potent T cell stimulator. This $CD8\alpha\alpha^+$ lymphoid cDC can activate both $CD4^+$ or, through cross-presentation, $CD8^+$ cytotoxic T cells. More importantly, this DC can trigger the development of a Th1 response *in vivo*, which is in agreement with the fact that activated $CD8\alpha\alpha^+$ lymphoid cDCs are the major source of the Th1-promoting cytokine interleukin-12 (IL-12)(14). In addition to the above three subsets of DCs, there are two extra myeloid DC subsets only found in lymph nodes (Figure 2). In fact, these cDCs are mature DCs which have migrated from peripheral tissues to lymph nodes through the lymphatic system after

they are loaded with antigens. The first subset has a $CD4^{-}CD8\alpha^{-}CD205^{+}CD11b^{+}$ phenotype, which is the mature form of interstitial tissue DCs (IntDCs), and the second subset is $CD8\alpha^{low}CD205^{+}CD11b^{+}$, which matures from skin-associated Langerhans cells. Migration of Langerhans cells is restricted to the skin-draining lymph nodes, and thus, $CD8\alpha^{low}CD205^{+}CD11b^{+}$ cDCs are found only in skin draining lymph nodes. On the other hand, IntDCs associated $CD4^{-}CD8\alpha^{-}CD205^{+}CD11b^{+}$ cDC may be found in all lymph nodes. Because of their migration to lymphoid tissues, Langerhans cells and IntDCs are often called "migratory DCs". Mature Langerhans cells (i.e. the $CD8\alpha^{low}CD205^{+}CD11b^{+}$ cDC subset) in lymph nodes express characteristic langerin together with high levels of MHC II and co-stimulatory molecules, representing a typical fully activated DC, which can effectively stimulate naïve $CD4^{+}$ T cells to differentiate into Th1 T cells (15). A constant migration of interstitial tissue immature DC to lymph nodes occurs even in the absence of invading pathogens at steady-state. Since presentation of antigens by immature or semi-mature DCs may lead to unresponsiveness of T cells, the migration of tissue DCs at a steady-state is believed to be critical for the DCs' involvement in the maintenance of peripheral tolerance (16). Before we sum up the classification of cDCs, it is necessary to clarify the terms "myeloid DCs (mDCs)" from DCs with "myeloid origin" described above. The term mDC has been widely used to describe a subset of DCs, which are believed to be from the same lineage of monocytes or macrophages. Some studies revealed that mDCs have at least two subsets: very common mDC-1 and rare mDC-2. However, more recent studies suggest that the mDCs are most likely equivalences of subsets of cDC with myeloid origins in the above classification. For example, mDC is the major source of IL-12. Several recent studies also thought the concept of mDC to be inappropriate (17). Thus, we try to avoid using the term mDC.

pDC is a distinct type of DC, which is characteristically different from cDCs (Figure 2). pDCs are found mainly in the spleen, as well as in bone marrow, thymus and lymph nodes (18). Historically, pDC was first identified in humans, which shared several characteristics with plasma cells (terminally differentiated B cells which secrete antibodies)(19). In fact, freshly isolated pDCs have a morphology which is big and round with only a few dendrites and very different from that of a typical DC. Furthermore, pDCs express B220 (a marker for mouse B cells) and Gr-1, together with CD8α, CD11c, CD205 and MHC II. Recently, additional surface markers, such as mPDCA-1 for mouse pDCs have been identified. While cDC subsets migrate into lymph nodes from tissues, pDCs enter lymph nodes directly from circulation by crossing the high endothelial venule (HEV) using the adhesion molecule CD62L. Freshly isolated pDCs lack expression of co-stimulatory molecules, and show poor capacity to stimulate naïve T cells, suggesting their potential role in the maintenance of peripheral tolerance under steady-state conditions. Although *in vitro* activated pDCs are capable of simulation of T cells by up-regulation of expression of MHC II, CD8α, and co-stimulatory molecules, this capacity is not in the range compatible to that of cDCs. On the other hand, mouse pDCs produce a large quantity of type I interferon (IFN) following a viral infection, suggesting its important role in antiviral responses rather than the APC function in initiation of a T cell response (10, 20). The lineage of mouse pDCs remains controversial. Recent studies showed complicity of pDC lineage, suggesting that its precursor cell may represent a unique hematopoietic lineage with high flexibility in its differentiation. Nevertheless, Flt3L (a cytokine) has been identified to be a major cytokine for the development of pDCs from hematopoietic stem cells (21).

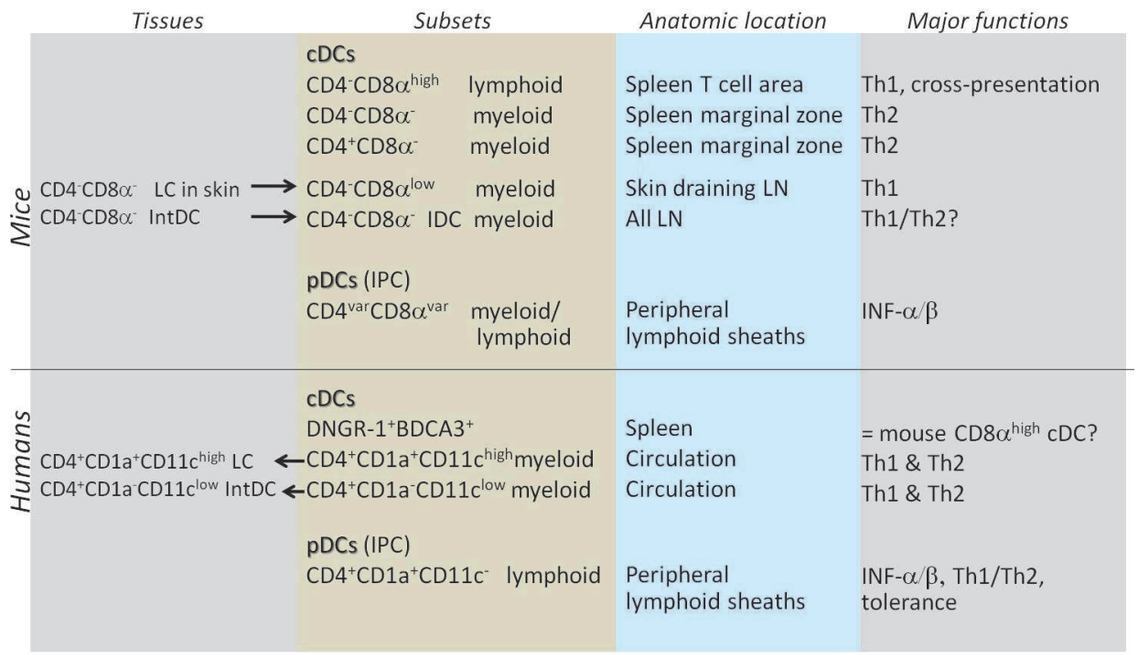

Fig. 2. Simplified classification of DC subsets in humans and mice. Each subset is named by its major markers. Their anatomic locations and major functions are listed for reference. Arrows indicate differentiation direction. *IDC*, interdigitating DC; *IntDC*, interstitial tissue DC; *IPC*, natural IFN-producing cell; *LC*, Langerhans cell; *LN*, lymph node.

Human DCs, especially those residing in the lymphoid organs, have not been characterized as well as those in mice because peripheral blood samples or, in some cases, fetus umbilical cord blood samples, are some times the only readily available source. In rare cases, investigators used human DCs isolated from lymphoid tissues, ranging from the tonsil, thymus, and spleen. Thus, human DCs from peripheral blood will be discussed for their classification. Similar to mouse DCs, human DCs also fall into two distinct groups: human cDC and pDC (9). Although all human cDCs express CD11c, human pDC does not. Thus, unlike for mouse DCs, CD11c is not a common marker for human DCs. In addition, because of a lack of available materials, migration route and maturation of human DCs are less understood. More studies are needed. Nevertheless, for human cDCs, two subsets with myeloid origin have been described in peripheral blood samples thus far, both of which co-express CD11b and CD11c (Figure 2). In addition to common CD11b, CD11c, CD4, and MHC II, the two human cDCs in the blood can be distinguished by other markers: the $CD1a^{+}BDCA\text{-}1/CD1c^{+}$ $CD11c^{high}$ subset and the $CD1a^{-}BDCA\text{-}3/CD141^{+}$ $CD11c^{low}$ subset (22, 23). These two human myeloid cDC subsets show the capacity to stimulate T cells; this capacity will be further augmented in the presence of the cytokine granulocyte-macrophage colony stimulating factor (GM-CSF). *In vitro* experiments showed that under certain culture conditions, these $CD1a^{+}BDCA\text{-}1/CD1c^{+}$ $CD11c^{high}$ subset would differentiate into the cells, which expressed several molecules such as langerin and displayed typical Birbeck granule characteristics of Langerhan cells, suggesting this subset to be the precursor of Langerhans cells. On the other hand, the $CD1a^{-}BDCA\text{-}3/CD141^{+}$ $CD11c^{low}$ subset may be the direct precursors of IntDCs (24). However, this classification is merely based on markers, and may not reflect their lineage but their maturation status. As described above, these two human

cDC subsets in the blood, in fact, are precursors of cDCs before their migration into tissue. Therefore, it is difficult to compare human cDCs to mouse cDCs, because of different locations.

Human pDCs share many common features with mouse pDCs. As we mentioned above, pDCs were first identified in humans as a rare type of cells in the paracortical areas in active lymph nodes with a morphology similar to plasma cells. However, this cell also expressed several markers for T cells and monocytes, and thus, it originally was named as plasmacytoid T cell or plasmacytoid monocyte. Recent studies have demonstrated that plasmacytoid monocytes, natural IFN-producing cells (IPCs), and immature DCs in peripheral blood and tonsils turn out to be the same cell known as the pDCs (Figure 2). Similar to mouse pDCs, human pDCs are of lymphoid origin and they poorly stimulate T cells. However, they could differentiate into IDC-like cells and acquire the ability to activate naïve T cells in the presence of IL-3 and CD40L. More studies show that pDCs not only can provoke a Th1 or Th2 responses, but also induce immune tolerance *in vivo* (25). Similar to its mouse counterpart, it can produce large amounts of type I IFN in response to certain viruses (19). Cytokines Flt3L and G-CSF are required for generation and differentiation of pDCs, respectively (26). Administration of Flt3L dramatically increases both myeloid cDCs and pDCs, whereas G-CSF only increases pDCs.

As we described above, all identified human DCs, including cDCs and pDCs, may express CD4, but never CD8. Mouse CD8αα$^+$ DCs have several special functions that other DCs lack in regulation of the T cell response. Hence, they become a promising target for clinical application to manipulate immune responses in autoimmune diseases, organ grafting, and vaccination. Failure of decades-long searching to identify human CD8αα$^+$ DCs has led to question whether CD8αα$^+$ cDCs may exist in humans. However, a recent paper may have made a breakthrough in identifying a human counterpart of mouse CD8αα$^+$ DC; this study identified a population of human DNGR-1$^+$BDCA-3$^+$ leukocytes in the spleen (27). Although this cell lacked expression of CD8, it shares many other markers/molecules, as well as several special functions, with mouse CD8αα$^+$ DCs. It is highly possible that this cell is equivalent to mouse CD8αα$^+$ DCs.

4. Roles of DCs in promoting autoimmunity and immune tolerance

It remains not fully understood how T cells and B cells decide to mount a response to a given antigen. In theory, adaptive immunity is able to mount an immune response to any given antigen, including self antigens, because it does not discriminate self or non-self antigens, or microbial antigens. Yet, our adaptive immune system normally does not respond to self antigens. In other words, the immune system seems to "ignore" the presence of self antigens. However, such unresponsiveness to, or ignorance of, self antigens is neither natural nor inherent. Rather, it is an acquired process. The process for T cells or B cells to actively "ignore" the presence of an antigen is called immune tolerance. If immune tolerance is toward self antigens, it is simply called self tolerance.

The immune system possesses a network of complicated tolerance mechanisms to avoid immune response against all potential self antigens. Self tolerance mechanisms could occur at three levels. The first level is evolutionary. Special molecular patterns of microbes have evolutionally led to the generation of pattern recognition receptors on innate immune cells, which effectively bind to certain microbial molecules. We will not discuss this level of tolerance in this chapter, as it is not related to adaptive immunity. The second level of self

tolerance mechanisms occurs prior to or during activation of naïve self reactive T cells. The mechanisms at this level would eliminate pathogenic self reactive T cells, or skew their activation, and thus avoid autoimmunity *de novo*. The majority of known self tolerance mechanisms act at this level. Those mechanisms can be further divided into two categories: central tolerance, which occurs in central lymphoid organs such as the thymus and bone marrow, or peripheral tolerance which occurs mainly in peripheral lymphoid organs. The third level of tolerance mechanisms occurs post activation of pathogenic T cells or after pathogenic T cells have initiated autoimmune tissue damage. This level of tolerance is less explored and thus, remains largely unknown. Failure in tolerance (or a break in self tolerance) to a self antigen at any level is a prerequisite for occurrence of autoimmunity.

With capacities in both promoting and inhibiting autoimmunity, DCs are considered one of the most critical manipulators/regulators in autoimmunity versus immune tolerance. Because DCs are the only APC capable of activating naïve T cells, they first play a pivotal role in breaking self tolerance in T cells as well as supporting autoimmune responses during pathogenesis of autoimmune diseases (28-30). On the other hand, numerous studies have shown that subsets of DCs, or DCs at different maturation stages, function as tolerance inducers by down-regulation of self reactive immune responses, or by skewing activation of a self reactive T cell toward a phenotype related with immune tolerance (29-31). Those DCs are named tolerogenic DCs (tDCs) (Figure 3)(32, 33). A single type of DCs may function as both an activator of an immune response or a tolerance inducer, depending on their maturation/activation status or even their location (33). In other cases, a special subset of DC may act as tDCs and play a sole role in immune tolerance.

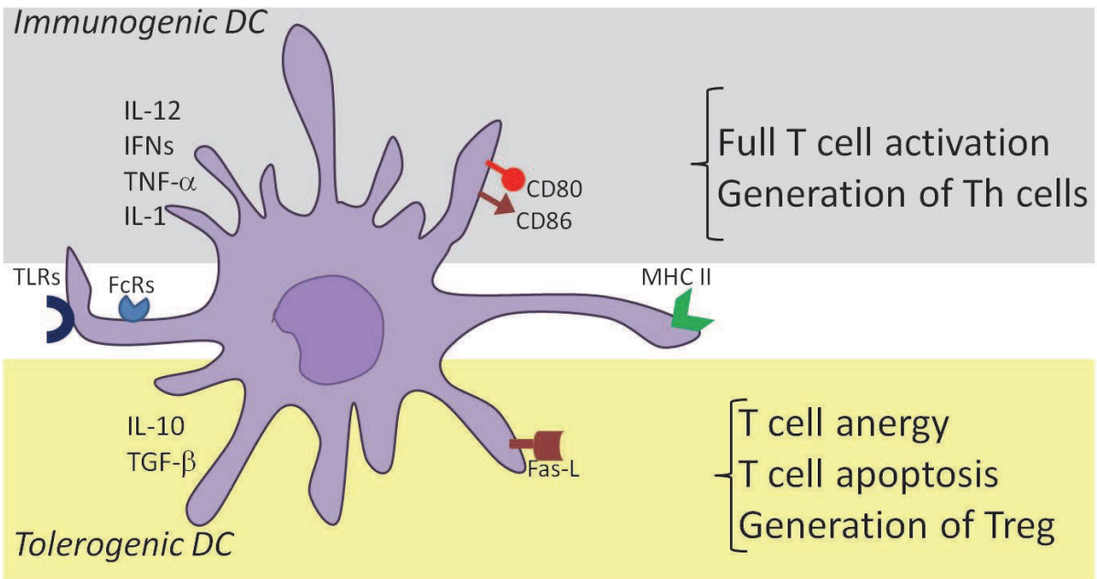

Fig. 3. Comparison of immunogenic DC and tolerogenic DC (tDC). Fates of T cells after their interaction with DCs are shown at the right. Note the differences in expression of co-stimulatory molecules and cytokines. *TLR*, Toll-like receptor; *FcR*, Fc receptor.

Due to their special functions in immunoregulation, DCs have been long investigated for their roles in autoimmune diseases since their discovery. As mentioned in the last

paragraph, it is clear that DCs could be pathogenic or protective in autoimmune diseases. From this point of view, DCs can be divided into two groups based on their functions during an autoimmune response: immunogenic DCs, which provoke an autoimmune response to an antigen, and tDCs, which induce tolerance to an antigen. A balance between the two DCs is the key to determine if autoimmunity will occur. Thus, alterations in either DCs due to genetic milieu or environmental factors may lead to unbalance, resulting in autoimmunity.

In the early years after discovery of DCs, investigations mainly focused on DCs' function in promotion or initiation of autoimmunity. It seems there are no arguments that DCs are required to activate naïve self reactive T cells, which is a pivotal player in manifestation of autoimmune diseases. DCs are the only known APCs which are capable of eliciting autoimmune responses and/or autoimmune diseases. In addition, unique functions of DCs in target tissues may further enhance autoimmune inflammation through coordinating recruitment and activation of other immune players. Those early studies have elegantly provided direct evidential support that DCs are a critical player especially in the initiation stage of autoimmunity in animal models such as experimental allergic encephalomyelitis (EAE) models for multiple sclerosis (MS) and non-obese (NOD) model for Type I diabetes. For example, transfer of DCs, which were engineered to constitutively express a T-cell epitope of a model antigen, induced destruction of the β–islet, where this model antigen was expressed (34). In an EAE model, DCs were pulsed *in vitro* with a T cell epitope of well known self antigen for MS called myelin basic protein; transfer of the DCs into untreated mice resulted in MS like symptoms (35). In addition, the role of DCs in autoimmune diseases was indirectly demonstrated, in part, by examination of DCs in tissues of human autoimmune patients. For example, a high number of DCs were detectable in the serum and synovial fluid of patients with various autoimmune diseases such as rheumatoid arthritis, Sjogren's syndrome, multiple sclerosis, thyroiditis and diabetes (36-38). One study further showed a positive association between high levels of circulating DCs secreting pro-inflammatory cytokines with severity of multiple sclerosis (39).

However, unlike in an immune response to invading organisms, the mechanisms for activation of naïve reactive T cells by a DC in an autoimmune response are unique and thus, are a main focus of investigations. Several mechanisms, by which DCs activate pathogenic T cells, have been revealed in the past. *First*, DCs will mature during an infection; the mature DCs may co-present self antigens with those from infectious agents to naïve self reactive T cells. Frequent or persistent viral infections may boost the release of self antigens in the target organ, which in turn would greatly increase the chance for DCs to "accidently" activate naïve self reactive T cells. In addition, overall anti-viral or bacterial immunity may generate cytokine-mediated bystander activation of self reactive lymphocytes. *Second*, DCs present some pathogenic antigens, which mimic certain self antigens, to naïve T cells. Some of those activated T cells may recognize self antigens and cause autoimmunity. Some mimicking peptides may have a low efficiency in stimulating naïve T cells due to a low binding affinity to their TcR. However, increased quantity of microbial antigens during infection could enhance engagement of more mimicking epitopes with TcR, leading to the activation of self reactive T cells. *Third*, certain defects in host tissues may lead to the release of increased amounts of or altered self antigens, which have been previously ignored by the immune system. For example, the defective clearance of apoptotic cell debris due to an impaired uptake may result in an autoimmunity. In this case, DCs may be activated by

apoptotic materials such as DNA. A recent study showed that binding of their surface TLR7 and TLR9 to dsDNA from dead cells activates pDCs, which in turn initiate autoimmune skin inflammation in a murine model (40). A common feature for the above three scenarios is that DCs are passively involved in activation of self reactive T cells, and thus, they are "innocent" in those scenarios. In those cases, autoimmunity occurs mainly due to the increase in available self antigens. A "threshold" model has been proposed to summarize the above cases (41). DCs constantly present self antigens, but they fail to activate T cells because antigens are under a "threshold" level. Multiple factors may influence the quantity of presented self antigens to surpass the threshold, resulting in a significant autoimmune response, and subsequently an autoimmune disease. *Fourth*, DCs are also regulated by other immune cells or molecules. DC's maturation and development are controlled by the types of pathogens/antigens as well as cytokines released by the activated T cells. One study suggested that high levels of IFN-α in systemic lupus erythematosus (SLE) may promote differentiation of monocytes to DCs, which in turn initiates an autoimmune response by picking up and further presenting more SLE-specific self antigens to self reactive T cells (42). Generally, regulatory T cells (Tregs) can suppress the maturation, activation and the subsequent production of inflammatory cytokines by recently activated DCs. However, chronically activated DCs, which may be presenting self antigens, could escape this mechanism and provoke an autoimmune response (43). *Fifth*, DCs could initiate autoimmunity because of intrinsic defects in genes controlling the DCs' functions, which results in DCs that behave deviantly. There are numerous genetic defects in DCs, which have been associated with the onset of autoimmune diseases. Unusual differentiation and/or maturation of DCs may lead to an abnormality of DCs either in quantity or quality. Loss of integrin $\alpha_v\beta_8$ on DCs causes autoimmunity and colitis in mice (44). Defects in the apoptosis of immune cells, including DCs, have been blamed for several autoimmune diseases. Abnormal co-stimulatory phenotypes of DCs have been linked to onset of severe murine lupus. By coordinating the recruitment and/or activation of other immune cells, DCs can drive the generation of ectopic lymphoid tissues, as in the case of inflamed synovia in rheumatoid arthritis (RA) and SLE. Thus, more self antigens would be presented more effectively in target organs. Normally, some DCs would be eliminated through apoptosis, because they have the potential to activate naïve self reactive T cells. However, genetic defects in DCs' apoptosis may prolong DCs' life and increase the chances for them to activate self reactive T cells. A transgenic mouse expressing the baculoviral caspase inhibitor, p35, in DCs results in their accumulation and, in turn, chronic lymphocyte activation and systemic autoimmune manifestations (45).

Despite its pivotal role in provoking an autoimmune response as sole APCs that can activate self reactive T cells, many more studies have been devoted to exploring DC's roles in self tolerance and/or autoimmunity prevention/controlling (33). It is clear now that DCs play critical roles in both central and peripheral tolerance. For central tolerance, thymic DCs function similar to but not limited to thymic epithelial cells. Both cells can selectively induce apoptosis in immature potential self reactive T cells. When immature T cells enter the thymus to be "educated", thymic DCs as well as thymic epithelia will present self antigens to immature T cells. If a T cell bears TcR which binds to the self antigens with high affinity, DCs will selectively trigger apoptosis in these potentially self reactive immature T cells. This process is called "negative selection". Unlike thymic epithelial cells, which can only present self antigens within the thymus, thymic DCs also can carry self antigens from outside tissues

to eliminate additional self reactive T cells. Furthermore, thymic pDCs or mDCs, which are activated by thymic stromal lymphopoietin, induce generation of natural $CD4^+CD25^+$ Treg.
A significant number of tDC-mediated tolerance mechanisms have been demonstrated in both humans and animals. In general, those tDC-mediated mechanisms are much more complicated and sophisticated than those in central tolerance. Elucidation of the known DC-mediated tolerance mechanisms and discovery of new ones in peripheral tissues remain a big challenge for immunologists, and thus, it is still a hot topic in immunological research today. Known tDC-mediated peripheral tolerance mechanisms, including one from our group, will be summarized in this section. There are two types of tDCs. The first type of tDCs is immature or semi-mature DCs, which are believed to be tolerogenic (33). The second type of tDCs are special types of DCs, or a specially differentiated DC subset, which act solely as an immune tolerance inducer. For the first type of tDCs, in the absence of infection or inflammation, DCs in the tissues will remain in an immature state. Those immature DCs may also capture self antigens from dead cells or accidentally released substances from cells and migrate to lymphoid organs with loaded self antigens due to homeostatic traffic. Unlike a mature DC, the immature or semi-mature DC, which has been loaded with self antigens, actively silence self reactive T cells because they lack co-stimulatory molecules for a full T cell activation. There are several mechanisms for those immature or semi-mature DCs to silence naïve self reactive T cells. Just as they do in central tolerance, some DCs may induce apoptosis in the T cells, which recognize the self antigen presented by DCs (45). Alternatively, the immature DCs induce unresponsiveness in T cells called anergy. It is believed that homeostatic traffic of DCs to silence naïve T cells is critical for maintenance of peripheral tolerance (46). Defect in molecules such as chemokine receptors, which is critical for this homeostatic migration, has been linked to several autoimmune diseases such as rheumatoid arthritis (RA) and MS. Furthermore, it has been reported that immature DCs may stimulate naïve self reactive T cells to differentiate into regulatory T cells (Treg) (47). As one of the most important immunoregulators, Tregs, in turn, actively inhibit pathogenic self reactive T cells. Several studies suggest that Treg can also inhibit maturation of DCs, and thus, more tDCs are generated. On the other hand, the second type of tDCs are specifically differentiated DCs, or from different lineages, which have the sole function of inducing an immune tolerance. Mounting evidence supports the presence of such tDCs. For example, the treatment of DC precursors with certain substances such as glucocorticoid (GC) leads to the generation of a type of DC which was morphologically similar to a mature DC, but was able to induce T cell anergy, suggesting that an anergy-inducing DC could be a special type of DCs (48). 1,25-dihydroxyvitamin D3 (1,25-vitD) has been known to inhibit autoimmune diseases in animal models, as well as in humans. Activation of vitamin D receptor (VDR) by either exogenous or endogenously generated1,25-vitD reprograms DCs to become tolerogenic (49). An experiment showed that systemic administration of *in vitro* generated tDC with TNF-α treatment ameliorates murine inflammatory arthritis, suggesting a critical role of cytokines from a tissue microenvironment in generation of tDC. Obviously, tolerogenicity of those DCs does not depend on its maturation stage but rather on their different maturation pathway. This is probably true for humans as well. A new phenotype of tDC, which induces T cell anergy, can be generated from human monocyte-derived DCs by treatment of proteases from the fungus Aspergillus oryzae (ASP)(50). A long list of substances can induce differentiation of tDCs (32). Dexamethasone-treated DCs are able to induce differentiation of Treg *in vitro* (51). Both immunologists and clinicians expect a

potential clinical application from the *in vitro* generated tDCs for inhibition of autoimmunity, and induction of immune tolerance to graft antigens. Some animal models showed encouraging results by transfer of tDC to inhibit autoimmune diseases (52). Vasoactive intestinal peptide induced regulatory dendritic cells showed therapeutic effects on autoimmune disorders (53) On the other hand, investigators are also searching for tDCs with a different lineage from the known cDCs or pDCs. A tDC, which is responsible for inhibition of $CD8^+$ T cell mediated anti-tumor activity, has been described in a murine model (54). This type of tDC has not been characterized well, and further investigation is needed. Our group is currently characterizing a new type of DC, which may be tolerogenic (55).

The common features for the above DC-mediated tolerance mechanisms can be summarized as follows: 1) DCs act on naïve T cells, and 2) DCs induce tolerance in lymphoid tissues but not in peripheral tissues. As a result, those DCs prevent autoimmunity *de novo*, because pathogenic T cells would be eliminated from lymphoid tissues before their activation. However, it is highly possible that naïve autoreactive T cells may escape the above mechanisms and be activated to further differentiate into pathogenic effecter cells through, for example, molecular mimicry or bystander activation during an infection. In fact, the presence of activated self reactive T cells has been widely reported in normal human individuals and animals. Although the tDCs described above have potential clinical applications for treatment of autoimmune diseases, it is worthwhile to emphasize that all those tDCs, either *in vitro* induced tDCs or natural tDCs, may only prevent autoimmunity *de novo*. These tDCs have shown encouraging results with a great promise in animal models. In most cases, the treatment needs to be prior to the onset of the disease. It is, therefore, questionable if these tDCs can be used to treat an existing autoimmune disease, which is common in human patients. It will be equally important to ask if any tolerance mechanisms in target tissues are able to control autoimmune diseases after pathogenic autoreactive T cells have infiltrated the target tissue and caused tissue damage. In other words, are there any tDCs which participate in the third level of immune tolerance? Fortunately, a few studies suggest the existence of tDCs in the third level of tolerance. *In vivo* depletion of pDCs by antibody to mouse pDC antigen-1 (mPDCA-1) after the onset of the disease enhanced T cell activation in target tissue but not in lymphoid organs, which exacerbated CNS inflammation in a mouse EAE model (56). This study suggests the presence of a tissue infiltrating tolerogenic pDCs, which infiltrated inflamed target tissue to inhibit a pathogenic T cell response. However, it remains to be elucidated how this pDC inhibited autoimmune inflammation. A novel DC-mediated mechanism has been recently described in a rat anti-GBM glomerulonephritis model. Unlike many other types of DCs, this DC actively infiltrates inflamed autoimmune target tissues and presents the self antigen locally (55). The DC selectively induces apoptosis in the infiltrating self reactive pathogenic T cells, which recognize the presented self antigen. Subsequently, T cell-mediated autoimmune inflammation is stopped. In contrast to many other tDC-mediated tolerance mechanisms, unique features of the above two are that 1) it contains the autoimmune disease after activation of self reactive T cells/tissue damage rather than prevents it *de novo*, and 2) it occurs in autoimmune target tissue rather than in lymphoid organs. It is conceivable that these tDCs, which are involved in the third level of immune tolerance, could be more effective in treatment of an existing autoimmune disease.

5. Renal DCs in the steady-state

As a first step to studying DCs' role in renal physiology and pathology, many studies have been devoted to identification of DCs in normal renal tissue or related draining lymph nodes in both humans and animals (mainly mice and rats). Historically, as early as 1981, a mononuclear phagocyte with expression of MHC II and a "stellate" morphology was described to reside in the renal interstitium in mice, which probably was the first confirmed DC in renal tissue (57). Since then, various types of DCs have been identified in either steady-state or under pathological conditions mainly in mice, as well as in rats and humans (58-60). Compared to the DCs in other organs or tissues, renal DCs are still poorly understood. However, it has become clear that similar to those in other tissues or organs, renal DCs are comprised of highly heterogeneous subsets (Table 1). Using $CX3CR1^{GFP+}$ transgenic mice, a network composed of a large number of $CX3CR1^{+}$ cells, which are mainly DCs, spanning the entire tubule-interstitium and enclosing all nephrons has been observed (61). Further investigations have suggested that this renal DC network in the steady-state probably is involved in maintenance of renal homeostasis and self tolerance. In addition, several functional subsets of DCs have been identified in the kidney using various markers.

Mouse renal DCs have been best analyzed among all species. Murine renal DCs can be primarily identified using a combination of CD11 and MHC II as markers. With other DC markers, at least three renal DC subsets have been characterized and classified, which have been summarized by Nelson and Kurts, respectively (Table 1)(58, 60). The majority of renal DCs belong to the first subset, which expresses the chemokine Franklin receptor CX3CR1, the macrophage marker F4/80, and the myeloid marker CD11b, but not CD8, suggesting this $CX3CR1^{+}F4/80^{+}CD11b^{+}CD8^{-}$ subset to be the equivalent to the IntDCs (i.e. cDCs of myeloid origin in lymphoid nodes) (refer to Figure 2)(10, 61, 62). This renal DC subset probably is the DCs, which form DC network surrounding renal tubules (61). A small number of the second subset is $CD8\alpha\alpha^{+}CD11c^{+}$ $CD103^{+}$, which seems similar to the $CD8\alpha\alpha^{+}$ cDCs of myeloid origin in the lymph nodes (63). Since this subset is normally observed in skin-associated lymph nodes and is associated with Langerhans cells in the skin, it will be interesting to determine their lineage and function (64). The third subset of renal DCs, which is rare, is similar to the pDCs with a phenotype of $CD11c^{+}CD8\alpha^{-}B220^{+}$, suggesting that this may be pre-pDCs (61, 65). Human renal DCs in normal kidneys also have been characterized, and several subsets have been described. At least two different $HLA\text{-}DR^{+}$ myeloid cDC subtypes have been identified in the cortex of normal kidneys, with phenotypes of $BDCA\text{-}1^{+}DC\text{-}SIGN^{+}$ and $BDCA\text{-}1^{+}DC\text{-}SIGN^{-}$ (66). The first subset is probably human cDCs of myeloid origin (see Table). In addition, a subset, which is similar to the pDCs with a phenotype of $BDCA\text{-}2^{+}DC\text{-}SIGN^{-}$, is also abundantly present in the renal tissue (66). All of those DC subsets are located in the tubulo-interstitium with a high frequency. These DCs often surround glomeruli, but are rarely observed within glomeruli. Among those subsets, $BDCA\text{-}1^{+}DC\text{-}SIGN^{+}$ DCs are most abundant and are four times as frequently present as $BDCA\text{-}2^{+}$. Thus, cDCs of myeloid origin are dominant in renal tissues in both humans and mice. In inflamed or injured renal tissue, additional subsets of DCs have been observed in both humans and mice. These pathology-related renal DCs will be discussed in the next section. Several new types of DCs, such as IFN-producing killer DC, inflammatory TNF-α-inducible nitric oxide synthase–producing DCs, and tolerogenic IDO expressing DCs, have been identified (67-69). It remains unclear whether those newly defined DCs are presented in or recruited to renal tissues.

Species	*Subset and phenotype*	*Abundance*	*Note*
Mice	$CD8^-$ cDC myeloid $CD11c^+CD11b^+F4/80^+$ $B220^-CX3CR1^+$	Many	IntDC
	$CD8^+$ cDC myeloid? $CD11c^+CD11b^-CD103^+CD205^-$ $Langerin^+$	Few	= Langerhans cells?
	pDC $CD11c^+CD11b^-CD8^-B220^+Gr1^+$	Few	Pre-pDC
	$CD8^-$ Pre-DC (inflammatory) $CD11c^+CD11b^+F4/80^+Gr\text{-}1^+$	-	Non-residential?
Humans	cDC $BDCA\text{-}1^+DC\text{-}SIGN^+$	Many	
	cDC $BDCA\text{-}1^+DC\text{-}SIGN^-$	Many	
	pDC $BDCA\text{-}2^+DC\text{-}SIGN^-$	Few	

Table 1. Subsets of DCs in the renal tissue of mice and humans at steady state

Due to the advancement in technologies and the increasing number of DC specific markers, investigators were able to examine renal DCs' function and their lineage in detail by isolation of renal DCs from either animals or humans for *in vitro* experiments, or by using gene manipulated animals or bone marrow chimeras for *in vivo* experiments. Investigations on mice DCs suggest that, like other DCs, renal DCs probably also derive from common bone marrow stem cells for macrophages and DC precursors. Renal DCs may directly derive from circulating pre-DCs (59). Based on the studies on DCs in other non-lymphoid or lymphoid organs, these bone marrow stem cells first differentiate into circulating or patrolling $Csf1r^+Gr1^+$ and $Csf1r^+Gr1^-$ monocytes in peripheral blood (70, 71). Subsets of $Csf1r^+Gr1^-$ or $Csf1r^+Gr1^+$ monocytes may become the precursor of different pre-DCs under certain conditions. However, a study suggested the presence of non-monocyte pre-DCs for DCs in other tissues such as the lung (72). On the other hand, some studies showed that diverse renal DC populations probably differentiate from $FLT3^+$ DC precursors for both pDCs and mDCs (73). Microenvironments in renal tissue may determine diversification of renal DCs from this rather flexible common DC precursor. One *in vivo* experiment showed that injection of FLT3 to mice did not alter the proportion of each DC subset in the kidney, although the DCs' number significantly increased (74). Very early studies also suggest a potential of the renal microenvironment in generation of diverse renal DCs from shared progenitors or precursors. Subsets of renal DCs of myeloid origin share several common markers among the mononuclear phagocytes such as F4/80 and CD68. This phenotypic overlap between renal DCs of myeloid origin and macrophages is different in different tissue locations within normal kidneys, suggesting that the environments may affect DCs' phenotypic changes (75). In one experiment, stimulation of the same precursor by different cytokines led to the generation of pro- or anti-inflammatory DCs (70). GM-CFS stimulated DC precursors from bone marrow promotes the generation of DCs with an inflammatory phenotype by both *ex vivo* and *in vivo* experiments (70). On the other hand, FLT3L-derived

DCs are phenotypically similar to DCs at a steady state, which are believed to be mainly anti-inflammatory. Several studies have tried to identify the local factors which determined renal DCs' differentiation. For example, CSF-1 receptor is known to be important for the differentiation and survival of myeloid DCs in general (76). Renal epithelial cells constitutively express CSF-1 (77, 78). It will be interesting to test if epithelium-expressed CFS-1 is involved in shaping renal DCs' repertoire. In summary, the majority of studies on renal DCs of myeloid origin suggest that local inductive factors shape the repertoire of renal DCs.

There are several interesting issues regarding the life cycle of renal DCs at a steady-state. First, how pre-DCs migrate or are recruited into renal tissues. Chemokines and adhesion molecules play a pivotal role in leukocyte trafficking. Thus, renal DCs or their precursors in the circulation are expected to express certain sets of chemokine receptors and adhesion molecules. Several experiments have suggested special chemokines released from renal tissue may be required for recruitment of pre-DCs to the kidney. However, information regarding expression of these two molecules in renal DCs is still lacking or controversial. The second issue is the life span for renal DCs. Using a bone marrow chimera mouse model, the life span of renal DCs in mice has been determined to be 10-14 days in homeostasis (79). On the other hand, BrdU-labeling experiments using normal mice suggest an average half-life of approximately 35 days across all subsets of renal DCs (80). The third issue is whether renal DCs can self renewal or need to be constantly recruited from the circulation. A study observed that a small percent of residential leukocytes were $CX3CR1^{high}GR1^{-}$ but lacked markers for differentiated DCs, suggesting these to be renewal DCs (61). However, more experiments are needed to answer this question.

The subsets of renal DCs, which are constantly present in normal renal tissue and form an immune surveillance network at a steady-state, may have three functions. However, those functions are largely speculated from the results for DCs in other tissues. First, they serve as sentinels in monitoring possible invading pathogens as one part of immune surveillance. Once they are activated by pathogens, mature renal DCs will migrate into renal draining lymph nodes to provoke an adaptive immune response against the pathogens (61, 81). Second, as one part of innate immunity, renal DCs may release cytokines or chemokines upon activation by pathogens to organize an innate immune attack against the pathogens by recruitment or activation of other innate immune cells (82). Third, as an important peripheral tolerance mechanism, immature renal DCs constantly capture self antigens from the tubules and glomeruli, and even some small molecules which are filtered in glomeruli (80, 83-85). Like in other tissue locations, a constant migration of renal DCs into local renal lymph nodes probably also exists (86). Through their APC function, the migrated immature DCs selectively inhibit activation of potential self reactive T cells. It has been reported that additional small self molecules may reach renal lymph nodes, where DCs capture those molecules. If these molecules are not associated with pathogenic antigens, they are used to tolerize harmful T cells by DCs (87, 88).

6. DCs in promotion of autoimmune glomerulonephritis

Like in other peripheral tissues, DCs play a critical role in provoking autoimmunity by breaking self tolerance in renal tissues including glomeruli. We have mentioned earlier that there are no DCs present in normal glomeruli. What type(s) of DCs are responsible for breaking self tolerance and for the maintenance of immune tolerance to glomerular self

antigens? It will be interesting to describe a concept called "tubuloglomerular feedback loop" hypothesis (Figure 4). This hypothesis may explain renal DCs' involvement in both self tolerance to tubular/glomerular self antigens, and provoking autoimmune inflammatory kidney diseases including glomerulonephritis (84, 89). In steady-state, this mechanism may prevent autoimmunity in a similar way to that in mucosal tolerance in the intestinal tract, especially for antigens of low molecular mass, although this remains to be formally demonstrated (90). A large population of $CX3CR1^{+}F4/80^{+}$ $CD8^{-}$ DCs, which lines the outer medullary tubules to form a DC network, has been described earlier. There is also a smaller population of renal $CD8\alpha\alpha^{+}$ DCs. Cellular self antigens released from normal apoptotic death or small molecules filtered through glomeruli will reach the lumen of renal tubules; tubular epithelial cells will transfer the self antigens to renal $CD8\alpha\alpha^{-}$ DCs in the renal DC network or $CD8\alpha\alpha^{+}$ DCs directly uptake those antigens (80, 83-85). The self antigens will then be presented to $CD4^{+}$ T cells by renal $CD8\alpha\alpha^{-}$ DCs to induce their unresponsiveness, or cross-presented by renal $CD8\alpha\alpha^{+}$ DCs to $CD8^{+}$ T cells to induce their apoptosis, probably in a similar way to other tissue locations at steady-state (91). Thus, tolerance to normally released self glomerular antigens is induced or maintained. On the other hand, mechanical/chemical, biological renal injury, or autoimmunity would induce cell necrosis, which in turn will release a new set of self antigens called damage-associated molecular patterns (DAMPs), some of which could be ligands for TLRs and serve as a "danger signal". When renal DCs pick up and present these DAMPs as danger antigens under an inflammatory milieu, they may activate self reactive T cells and cause tubulointerstitial inflammation first. The autoimmune response to glomerular antigens will be "feedbacked" to the glomerulus either directly or through a periglomerular infiltration. One recent study showed that renal DCs could become pathogenic during crescentic glomerulonephritis, suggesting that abnormal tissue damages in glomeruli are required for differentiation of pro-inflammatory DCs (92). However, it remains unclear where those pathogenic DCs originate.

Studies, which aimed to demonstrate how and what types of renal or non-renal DCs participate in pathogenesis of glomerulonephritis, remain scarce. However, it is clear that DCs also play a critical role in various renal diseases including autoimmune glomerulonephritis at several levels; these roles are mutually related. *First*, DCs are required to activate pathogenic T cells against renal self antigens. It is not only true for autoimmune glomerulonephritis, but also for other glomerular diseases, as glomerular chronic inflammation may lead to autoimmunity. There is evidence that upon encountering maturation stimuli such as DAMPs or microbial antigens, renal DCs migrate to the renal draining lymph nodes (86) where they activate specific T cells (93). This process is believed to be very similar to the canonical life-cycle of tissue residing DCs extrapolated from the paradigm of Langerhans cells in the skin (73, 91, 94). Activation of self reactive T or B cells in renal draining lymph nodes has been demonstrated in animal models for lupus glomerulonephritis and anti-GBM glomerulonephritis (95, 96). However, renal DCs or renal infiltrating DCs may also activate T cells locally in a lupus model which will be described later. Rodent nephrotoxin nephritis is a model for human crescentic glomerulonephritis. Sheep antibody to mouse GBM will be "embedded" in the host GBM after injection. GBM-"embedded" sheep antigens are taken up by DCs in lymphatic organs, and are used to activate specific Th1 cells and B cells. As a result, glomerular inflammation, characteristic of T cell mediated delayed hypersensitivity, occurs. Although renal DCs show a protective role at early stages (97), later they act as two types of APCs to promote inflammation (60). First, renal DCs migrate to local lymph nodes to cross-

present glomerular antigens to $CD8^+$ T cells, which in turn cause glomerular damage. Second, renal DCs present the self antigen from the damage to $CD4^+$ T cells, which in turn orchestrate and maintain glomerular inflammation.

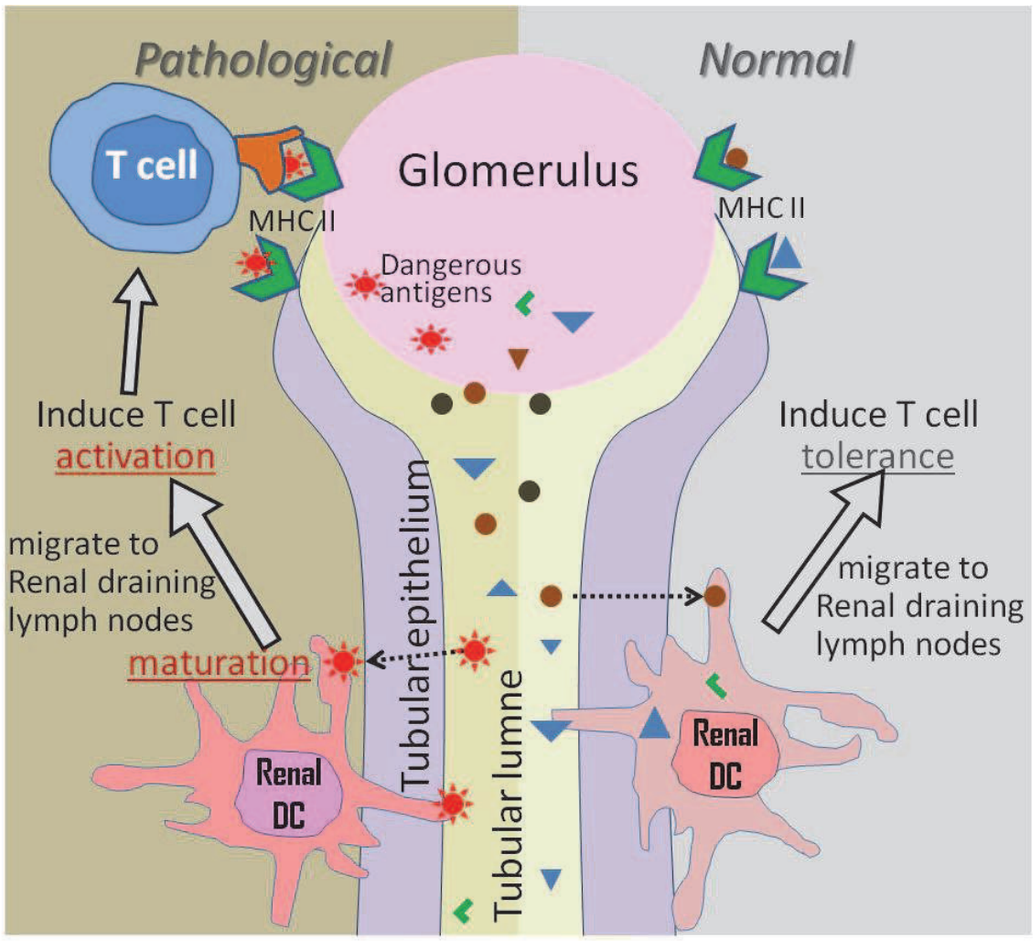

Fig. 4. Diagram shows the tubuloglomerular feedback loop under normal and pathologic conditions in kidneys. In normal kidney, self antigens from glomeruli are released to the lumen of the tubules. The antigens then are up-take by renal DCs, or transferred to renal DCs (arrows) by tubular epithelium. Renal DCs will migrate into renal draining lymph node to induce tolerance toward the glomerular antigens. If renal DCs encounter dangerous antigens from glomeruli, they will mature and induce T cell activation. Activated T cells will in turn attack glomeruli with dangerous pathogens/antigens by recognition of MHC II-antigen complex expressed by Bowman's capsule.

Second, renal DCs also play a role in establishing glomerular inflammation as an innate immune cell. Renal DCs may release a set of pro-inflammatory cytokines and chemokines upon stimulation from injuries, and subsequently orchestrate an acute inflammation. It is important to re-emphasize that such environmental milieu of acute inflammation may in turn provide renal DCs an opportunity to break self tolerance and provoke a pathogenic autoimmunity post acute inflammation. Using two models for renal injury, DCs' roles in establishing acute inflammation post renal injury have been investigated in quite detail.

Ischaemia-reperfusion injury (IRI) is a model to mimic renal transplantation. Renal F4/80$^+$ CD11c$^+$ subset DCs are the earliest source of TNF-α (80), which in turn causes an influx of circulating immune cells including pro-inflammatory DC subsets, monocytes/macrophages and T cells (98). Orchestrated actions of these cells contribute to kidney parenchymal damage. Renal DCs' capacity to stimulate T cells remarkably increased 24 hours post renal injury (80). Since T cells have been known to play critical roles in IRI (99, 100, 101), as well as in glomerular diseases and in transplant rejection, T cell activation by renal DCs may contribute to disease progression. One report showed that renal DCs can be activated under hypoxia with the transcription factor HIF-1a and LPS (102). However, it remains questionable as LPS is not present in the injured renal tissue. Interestingly, renal DCs may also display an anti-inflammatory function in this model, which will be discussed later in this section. In the other model, unilateral urethral obstruction results in progressive renal fibrosis, which mimics human progressive renal diseases (103). Although infiltrating macrophages, which release the profibrotic and pro-inflammatory cytokines TGF-β and TNF-α, are mainly responsible for renal fibrosis, F4/80$^+$ renal DCs are an early source of TNF-α. The importance of this early TNF-α from DCs was demonstrated by depletion of DCs with Clo-liposome. The depletion led to attenuated renal fibrosis, accompanied by reduced TNF-α and TGF-β levels in obstructed kidneys (104). However, some studies suggest that attenuated fibrosis is probably due to a failure in activation of IL-17 secreting Th17 or INF-γ-secreting Th1 T cells by renal DCs (105). Thus, DCs may not directly participate in fibrosis. However, it needs to be identified which renal DCs are involved in the activation of T cells.

In many cases, renal DCs may play dual roles in tandem in the promotion of autoimmune pathogenesis. At earlier stages, renal DCs act as an innate cell to establish an inflammation, and at later stages they function as a potent APC to break self tolerance. This is well exemplified by lupus glomerulonephritis. Lupus is initiated by glomerular deposition of immune complexes formed by autoantibodies and nuclear self antigens, and undergoes two stages during progression: antibody-complex mediated acute lupus nephritis and subsequent chronic glomerulonephritis with T cell involvement. The roles of DCs in this disease have recently been addressed in human patients and animal models. During the first stage, an antibody complex triggers complement activation and production of pro-inflammatory cytokines/chemokines, leading to acute glomerular inflammation. The roles of DCs in this stage can be summarized as 1) a systemic role in breaking T cell tolerance leading to production of autoantibodies, and 2) a local role in establishing glomerular inflammation. Because the systemic role of DCs as a APC in autoantibody generation is less kidney-specific, we will focus on DCs' local role. In addition to renal DCs, DCs have been found to infiltrate glomeruli in lupus glomerulonephritis (95, 106). At least two types of pre-DCs, Gr1$^+$ inflammatory monocyte or Gr1^{low} patrolling monocyte, have been found to infiltrate inflamed glomeruli (107). Those infiltrating DCs are able to produce the Th1–driving cytokine IL-12 within glomeruli, suggesting their ability to provide a pro-inflammatory milieu (104). Blockage of co-stimulatory molecules of DCs together with cyclophosphamide reduced the number of renal CD11c$^+$ cells, as well as T cell infiltration during lupus' chronic stage. This suggests renal DCs themselves function not only as an innate cell population in the promotion/ establishment of renal inflammation but also as APCs to break T cell tolerance. It remains unclear how self reactive T cells are primed. T cell activation and expansion in the renal draining lymph nodes has been reported, suggesting that migration of renal DCs into lymph nodes is necessary (95). Another possibility is that renal DCs may stimulate T cells within glomeruli.

7. DCs in the prevention of autoimmune glomerulonephritis

As we discussed earlier, one of the functions for renal DCs in the steady-state is to maintain peripheral tolerance to renal self antigens. We also mentioned earlier a concept of tubuloglomerular "feedback" loop. This hypothesis may explain how a renal DC network maintains self tolerance to glomerular antigens since no DCs are present in this tissue location. Thus, self tolerance to glomerular self antigens is established indirectly, in a similar way to "oral tolerance". Consequently, non-dangerous self antigens released from glomeruli will be tolerized. This mechanism will prevent glomerular autoimmunity *de novo*. However, recent studies also demonstrated that under acute tissue damage caused by ischemia reperfusion, renal DCs still could control inflammation and probably induce tolerance to the abnormal self antigens leaked from the damage (108), suggesting that this mechanism may also play a role in maintenance of limited self tolerance post acute tissue damages.

In addition to this renal DC network, several subsets of DCs, including residential and infiltrating DCs, also play roles in inhibition of autoimmunity during or post tissue injuries. Those renal DCs induce self tolerance or inhibit glomerular inflammation through several ways. First, the renal DCs may inhibit autoimmune inflammation in glomeruli as APCs to eliminate or anergize pathogenic T cells in glomeruli. In a murine nephrotoxin nephritis model, early depletion of $CD11c^+$ cells aggravated renal damage. Because only DCs in mice express a high level of CD11c, this study suggested a protective role of renal DCs in glomerulonephritis, at least at an early stage of development (97). Mechanistic analysis revealed that renal DCs from nephritic mice stimulated a potent T cell proliferation with the expression of cytokine IL-10. In general, IL-10 is considered an anti-inflammatory. Further study has shown that blockage of IL-10 production aggravated glomerulonephritis. Thus, renal DCs during tissue damage may induce differentiation of T cells into an anti-inflammatory phenotype such as Tregs. A similar phenomenon has been observed in a cisplatin induced nephritis model. In this model, renal tubular cells are first damaged by the toxin and consequently undergo necrotic cell death. Depletion of $CD11c^+$ cells, which are largely murine cDCs but not pDCs, exacerbated renal injury (109). The underlying molecular mechanisms may be similar to that in the lung. An increased expression of inducible costimulatory ligand (ICOS-L) on DCs can suppress T cells (110). In the above two cases, renal cDCs inhibit glomerular inflammation through their APC function to promote generation of anti-inflammatory T cells. Second, renal DCs may also function as anti-inflammatory immune cells to inhibit autoimmune glomerular inflammation. In a murine model, myeloid cells of the kidney, probably renal DCs, have been shown to attenuate ischaemia-reperfusion injury, by production of single Ig IL-1-related receptor (SIGIRR) (111). SIGIRR is a negative regulator of TLR−IL-1 receptor signaling. It inhibits Th17 T cell development, and is an immunosuppressive mediator expressed by DCs and macrophages. The deficiency of this mediator worsened tissue damage. This situation could be reversed by liposome-mediated depletion of phagocytes including renal DCs, suggesting a potential of renal DCs or other renal phagocytes in prevention of further tissue damage by releasing anti-inflammatory molecules such as SIGIRR. However, it needs to be proven if renal DCs expressing SIGIRR actively contain tissue damage. Interestingly, a study by the same group on a murine lupus model also suggested protective roles in renal injury using SIGIRR-deficient mice. Mice that lacked SIGIRR showed aggravated hydrocarbon oil-induced lupus (112).

Despite the above tolerance mechanisms in kidneys, a keen question still remains: why abnormal tissue damage such as an infection in glomeruli usually does not result in autoimmunity, despite the fact that both cell necrosis and microbial antigens provide DAMPs and a danger signal? Thus, other tolerance mechanisms must exist to prevent autoimmunity at the third level (i.e. after self reactive T cells have been activated or autoimmune glomerular damage has been initiated). Indeed, a few studies, including one from our group, suggest the existence of such DC-mediated tolerance mechanisms. As we mentioned before, our group reported a new type of DC with a phenotype of $CD8\alpha\alpha^{+}CD11b/c^{+}MHC\text{-}II^{+}ED1^{-}OX62^{-}$ in our rat model for anti-GBM glomerulonephritis (55). This DC is not residential, but rather is selectively recruited into inflamed glomeruli. Both in vivo and in vitro experiments have shown that this DC induces T cell apoptosis in the glomeruli, leading to termination of glomerular inflammation (Figure 5). Further experiments suggest that this DC is responsible for natural recovery from early glomerulonephritis in a disease resistant rat strain by termination of T cell-mediated glomerular inflammation (113, unpublished data, Lou). Importantly, transfer of $CD8\alpha^{+}$ DCs of a resistant strain cured glomerulonephritis at an early stage in a disease prone strain. This mechanism is very attractive and logical, and could be used for development of a novel cell-based immunotherapeutic strategy for autoimmune glomerulonephritis. DCs have been the target for immunotherapy for treating various diseases including cancer and autoimmune diseases (114). However, more studies are needed to ensure if a similar mechanism also exits in humans (115).

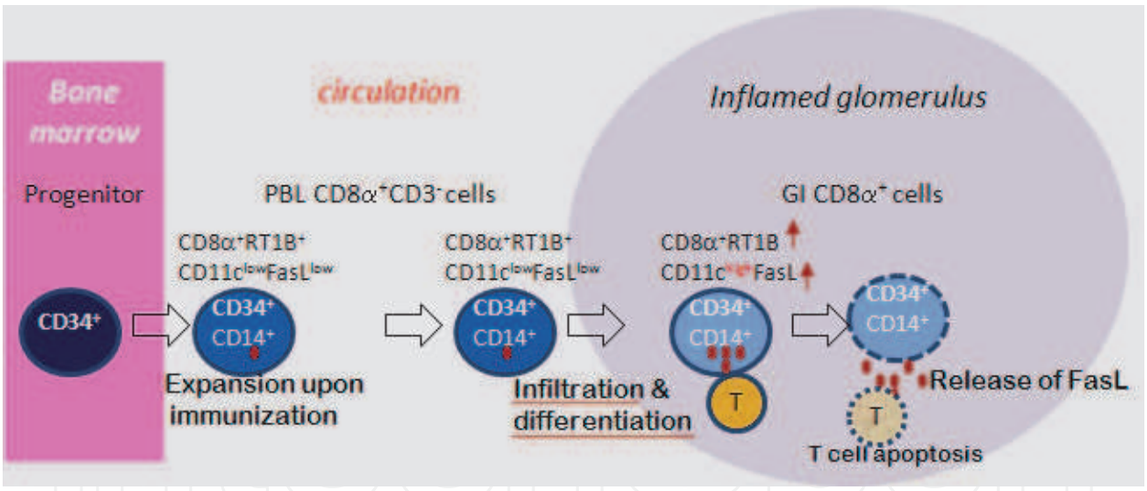

Fig. 5. Diagram for the mechanism, by which a new type of $CD8\alpha^{+}$ DC terminates glomerular inflammation by active infiltration of inflamed glomeruli and induction of T cell apoptosis through Fas-L. Development of this $CD8\alpha^{+}$ DC is also shown. *GI CD8α⁺ cells*, glomeruli-infiltrating $CD8\alpha^{+}$ cells; *RT1B*, rat MHC II molecule. This model used rats as experimental animals.

8. Conclusive remarks

Like in other tissue locations, multiple subsets of both cDCs and pDCs reside in normal renal tissues both in humans and mice. Heterogeneity of residential renal DCs is due to their different precursors and more importantly, renal microenvironmental factors. At a steady-

state, these residential renal DCs form an immune surveillance network for detecting pathogens and for maintaining immune tolerance to renal self antigens. Although glomeruli lack residential DCs, those surrounding tubules may monitor antigens from the glomeruli, self or non-self, through the tubuloglomerular feedback loop. During acute glomerular injury, the majority of residential renal DCs play a critical role in controlling tissue damage through their anti-inflammatory function. Under immunological changes in glomeruli, including chronic inflammation and autoimmune attacks, both renal residential DCs and infiltrating DCs are involved in the process. DCs in the renal draining lymph nodes serve as the sole APC to activate naïve self reactive T cells, or those in the renal tissue maintain glomerular inflammation by presenting self antigens locally to pathogenic T cells. However, tolerogenic DCs inhibit autoimmunity in glomeruli by induction of anergy or apoptosis in self reactive T cells, or by inducing differentiation of regulatory T cells (Tregs). It is important to discover new DC subsets, especially tolerogenic DCs, and elucidate their differentiation and function. Using artificially generated tolerogenic DCs, we may be able to develop a novel antigen-specific immunotherapeutic strategy for treatment of glomerular diseases.

9. Acknowledgement

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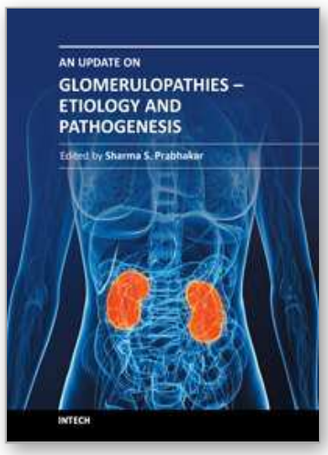

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The book has fourteen chapters which are grouped under different sections: Immune System and Glomerulonephritis, Animal Models of Glomerulonephritis, Cytokines and Signalling Pathways, Role of Cells and Organelles in Glomerulonephritis and Miscellaneous. While the purpose of this volume is to serve as an update on recent advances in the etio-pathogenesis of glomerulopathies, the book offers the current and broad based knowledge in the field to readers of all levels in the nephrology community.

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