CTMI (2005) 293:133–150

Dendritic Cells: Key Cells for the Induction of Regulatory T Cells?

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Abstract Even though dendritic cells (DCs) are well known for their capacity to induce immune responses, recent results show that they are also involved in the induction of tolerance. These two contrary effects of otherwise homologous DCs on a developing immune response may be explained by different DC developmental stages, i.e., different subsets of DCs may exist and/or different spatial distribution of DCs in the body might influence their function. However, independently from the subtype(s), it is obvious that the ability of DCs to act in a tolerogenic fashion depends on the maturation status, since immature DCs are prone to induce regulatory T cells and hence promote tolerance, whereas mature DCs stimulate effector T cells, facilitating immunity. The means by which DCs convey tolerance are not entirely clear yet, but secretion of

suppressive cytokines such as IL-10 and induction of regulatory lymphocytes are involved. In this review we focus on the interaction between DCs and T cells and highlight some mechanisms in the decision-making process of whether immunity or tolerance is induced.

1 Introduction

Dendritic cells (DCs) were originally characterized by their strong immunostimulatory properties. They express large amounts of MHC class II molecules and T cell costimulatory molecules of the B7 family on their surface. Therefore DCs, as compared to other types of antigen-presenting cells, posses the unique feature of inducing immune reactions de novo.

Recently several results emerged showing that DCs are also key cells in induction of tolerance, most likely by the means of induction of regulatory T cells. At first glance, these two opposite functions of one and the same DC, i.e., induction of effector T cells on one hand and Treg on the other hand, are hard to reconcile. However, different DC developmental stages or different subsets of DCs as well as different spatial distribution of DCs may explain these opposite functions. The main focus of this report is to review different pathways utilized by DCs to induce or stimulate regulatory T cells (Treg).

Regulatory T cells (Treg), in broader terms, consist of different subsets of T cells that are characterized by their ability to suppress proliferation of conventional effector T cells by various means. To date, three main groups of Treg can de distinguished, mainly by their functional properties (for review, see [1]) Briefly, T regulatory (Tr)-1 cells as well as T helper (Th)-3 T cells express common T cell markers such as CD4 and are characterized by secretion of IL-10 and TGF-β, which provides a means by which proliferation of conventional $CD4^+$ cells is blocked. In contrast, genuine Treg, which are characterized by their expression of CD25, block T cell proliferation by an unknown cell-to-cell contact-dependent mechanism.

However, there are many overlapping features shared by the different subtypes of regulatory T cells (i.e., production of IL-10) and some of the reports reviewed here do not further characterize the subtype of Treg. Therefore we use the term “regulatory T cells” in a broader sense, without necessarily implying that Treg generated by DCs are naturally occurring “genuine Treg,” as originally described by Shevach and Sakagucchi [2, 3].

2
Activation and Maturation Status of DCs Determines the Outcome of an Immune Response

2.1
Immature DCs as Inducers of Treg

After initial protocols were published describing the in vitro generation of DCs either from bone marrow (in mouse) or from $CD14^+$ monocytes (human), numerous experiments addressing the immunostimulatory function of DCs were conducted. These experiments used either in vitro generated or in vitro cultivated DCs, hence all of these DCs were manipulated ex vivo as opposed to the in situ situation. Accordingly, most of the experiments conducted demonstrated the superior ability of these activated DCs to stimulate T cell proliferation and to induce T effector functions. In retrospect, it is now conceivable that the in vitro cultivation of the DCs most likely lead to activation and/or maturation of the DCs, and obviously this status differs significantly from the steady-state DCs, which reside in situ in uninflamed tissues.

A first hint that the resting DCs in vivo may be different from in vitro matured DCs can be deducted from early experiments of Schuler et al. [4]. These reports showed that freshly prepared Langerhans cells (skin-derived DCs) required maturation before they were able to stimulate T cell proliferation in a mixed lymphocyte reaction (MLR). Thus, the immunostimulatory capacity of DCs seems strongly connected with a mature and/or activated phenotype.

However, since the main readout for DC function was their immunostimulatory capacity as determined by MLRs, immature or resting DCs were long regarded as inactive cells that needed proper stimulation (e.g., by invading microorganisms or infectious stimuli) in order to execute their function.

First evidence that these immature DCs are not just inactive, but instead are able to induce tolerance, derived from results obtained with in vitro differentiated immature human DCs. Jonuleit et al. could show that peripheral $CD4^+$ T cells acquire regulatory properties after repeated in vitro stimulation with immature DCs [5]. In these experiments, DCs were generated from peripheral blood monocytes by incubation with GMCSF and IL-4, but terminal differentiation with proinflammatory agents such as interleukin (IL)-1, IL-6 and prostaglandin E2 was omitted. Thereafter, $CD4^+$ T cells were repeatedly incubated with these in vitro generated immature DCs, and after three periods of co-incubation, the T cells were co-cultured with freshly isolated $CD4^+$ T cells and stimulated with anti-CD3 and anti-CD28 antibodies. Normally, incubation of T cells with CD3/CD28 induces vigorous T cell proliferation, but when T cells precultivated with immature DCs were present, no T cell proliferation could be recorded, i.e., the precultivated T cells were able to block

proliferation of conventional effector T cells. This inhibition was mediated by cell–cell contact and was independent of soluble mediators. Moreover, the precultured T cells themselves were hyporesponsive to anti-CD3/CD28 stimulation, did not produce IL-2 and expressed the surface molecule CD25. Therefore, these T cells induced by repeated stimulation with immature DC fulfill the criteria for genuine regulatory T cells (Treg), as first described by Shevach and Sakaguchi in the murine system [2, 6]. That these Treg do indeed also play a role in vivo in humans was further substantiated by results showing that trace amounts of $CD4^+/CD25^+$ Treg are present in the peripheral blood of healthy volunteers (approx. 5% of all $CD4^+$ T cells) and that these cells posses similar immunosuppressive capacities as compared to their in vitro generated counterparts [7]. In aggregate, these results have demonstrated that immature DCs are able to induce Treg in vitro; however, in search of an in vivo correlate experiments in mice had to be conducted.

In these experiments, DCs were loaded with antigens in situ by antibody targeting, thus avoiding further activation of the DCs by isolation or cultivation methods. As described by Hawiger and Mahnke, model antigens such as Ovalbumin (OVA) or hen egg lysozyme (HEL) were biochemically coupled with anti-DEC-205 antibodies and injected into mice [8–10]. These antigen-antibody conjugates target to the DC-specific antigen receptor DEC-205 that mediates uptake and presentation without further activating the DCs in situ. The following analysis of the immune response revealed that presentation of OVA to T cell by DCs in the steady state in vivo led to induction of $CD4^+CD25^+$ T cells. These T cells had regulatory properties, as they were able to inhibit proliferation of conventional $CD4^+$ T cells in MLR assays in a cell–cell contact-dependent manner.

In contrast, the induction of Treg as well as the deletion of antigen-specific $CD4^+$ T cells was abolished when DCs activating stimuli such as anti-CD40 antibodies or CpGs were injected simultaneously with the antigen–antibody conjugates. Thus, these findings underline that immature DCs are mandatory for the induction of Treg and lead to the concept that steady-state DCs show how peripheral tolerance is maintained (Fig. 1).

In this concept, it is conceivable that the maturation status of DCs determines whether immunity or tolerance is induced [11]. For example, in the absence of pathogens and inflammation, DCs residing in the periphery mainly pick up self-peptides and cell detritus without being activated. Therefore DCs remain immature and upon antigen presentation to T cells tolerance ensues. In contrast, during inflammation, DCs become activated via their pattern recognition receptors and toll-like receptors (TLRs), which are engaged by the pathogens. This leads to upregulation of T cell stimulatory molecules such as B7-1, B7-2, MHC-class II and CD40, and results in T cell activation. This

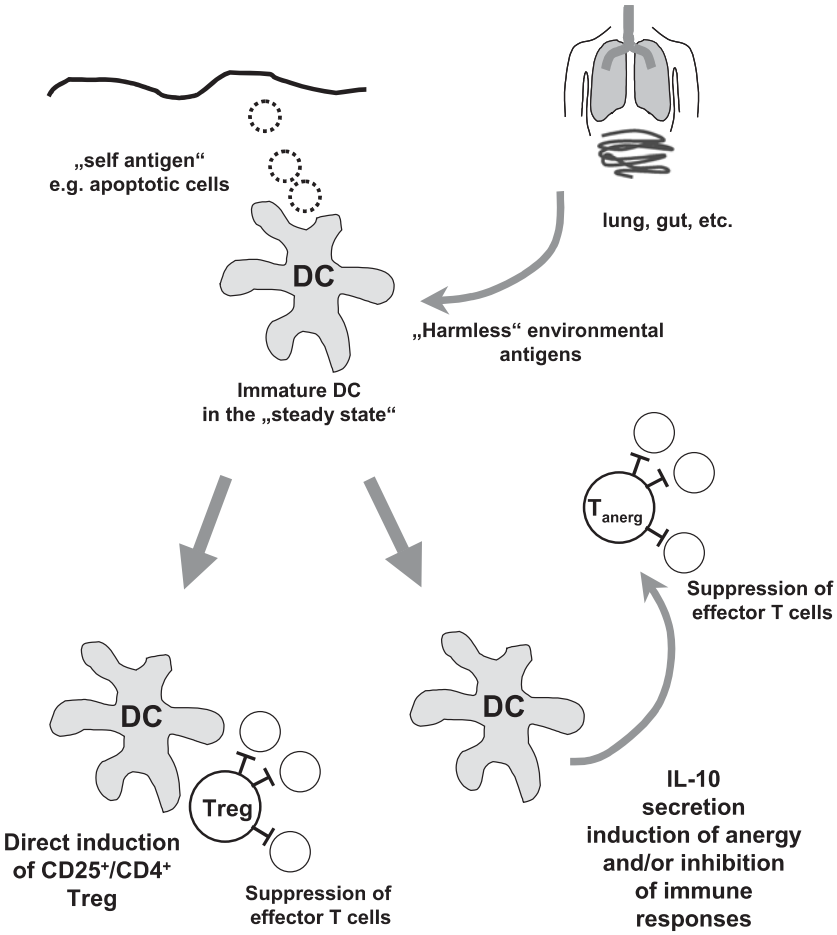

Fig. 1 DCs in peripheral tissues as sentinels for Treg induction. DCs residing in peripheral tissues take up self-antigens, e.g., via apoptotic vesicles or cellular debris. Also subsets of specialized DCs are located in areas that are exposed to innocuous environmental antigens, e.g., the gut and the lung. In the absence of inflammation, these steady-state DCs migrate towards lymphoid organs and induce $CD4^+/CD25^+$ regulatory T cells by direct contact or develop into IL-10-producing DCs that anergize T cells. Either way, these DC-induced Treg cells are able to curb proliferation of effector T cells and thus contribute to maintenance of peripheral tolerance

hypothesis is attractive since it explains observations that the DCs in the periphery possess tolerogenic as well as stimulatory capacities under different physiological circumstances [12].

3 Cytokines and Pharmaceuticals Affect the Ability of DCs to Induce Regulatory T Cells

3.1 TNFα and Semi-mature DCs

The term "immature" is not accurately defined in many aspects and according to a long-standing definition true immature DCs are only found in peripheral tissues, whereas the impetus to migrate towards regional lymph nodes requires at least some activation. Indeed there are reports showing that lung-derived migratory DCs (and hence partly activated DCs) account for the induction of regulatory T cells [13]. Therefore tolerogenic DCs found in the lymph node may be differentially activated or semi-mature.

In this regard, TNFα may play a role, since it has been shown that injection of DCs cultivated in presence of TNFα acted in a tolerogenic fashion [14]. In these experiments, DCs were able to block autoimmunity in a murine model of multiple sclerosis (EAE). This suppressive effect was mediated by the induction of IL-10-producing regulatory T cells. The subsequent phenotypic analysis revealed that the DCs expressed regular amounts of MHC class II and T cell co-stimulatory molecules, i.e., according to the authors these DCs displayed a mature phenotype as judged by their surface-marker expression. In contrast, these DCs failed to secrete IL-1β, IL-6, TNFα and in particular IL-12. The importance of IL-12 production for full maturation of DCs and acquisition of an immunostimulatory phenotype is further substantiated by results showing that IL-10 as well as cAMP are potent agonists of IL-12p70 secretion. In fact, DCs treated with these agents are resistant to terminal maturation and induce T cell unresponsiveness in vitro [15]. In conclusion, maturity of DCs may not merely be judged by their surface-marker expression; instead cytokine expression also has to be taken into account and only upregulation of several different indicators warrant a fully activated phenotype of DCs.

3.2 Interleukin-10 Modulates DCs for Tolerance Induction

IL-10 was originally described as cytokine-synthesis-inhibiting factor (CSIF) with regard to its effects exerted on IFNγ production of TH1 T cells. Meanwhile, it has been found to exert suppressive effects on a wide range of different populations of lymphocytes. When human or murine DCs are exposed to IL-10 in in vitro culture systems, the cells display reduced surface expression of MHC class I and MHC class II molecules and reduced expression of T cell

co-stimulatory molecules of the B7 family. In addition, the release of pro-inflammatory cytokines, i.e., IL-1β, IL-6, TNFα and most markedly IL-12, is abolished after IL-10 treatment [16, 17]. However, all of these effects could only be recorded when immature DCs were exposed to IL-10. In contrast, mature DCs are insensitive to IL-10 and display a stable phenotype in the presence of IL-10 once they have matured [18, 19].

According to their reduced MHC and B7 expression, the IL-10-treated DCs are inferior in T cell stimulation as opposed to their fully activated counterparts, but IL-10 does not merely keep DCs in an immature state, instead there is evidence that IL-10 modulates DC maturation enabling DCs to induce T cells with regulatory properties. For example, freshly isolated Langerhans cells inhibit proliferation of TH1 cells after exposure to IL-10 but had no effect on TH2 cells [20]. Moreover, it has been shown that IL-10-modulated DCs from peripheral blood induce alloantigen-specific anergy or anergy in melanoma-specific $CD4^+$ and $CD8^+$ T cells [21, 22]. Further analysis of these anergic T cells revealed reduced IL-2 and IFN-γ production and in contrast to genuine Treg, reduced expression of the IL-2 receptor α-chain CD25. However, in addition to these anergic T cells, some authors have also observed the emergence of genuine Treg after injection of IL-10 as indicated by $CD25^+$ upregulation and cell–cell contact requirement for their suppressive activity [23].

The therapeutic use of these IL-10-modulated DCs is under investigation since injection of in vitro generated, IL-10-modified DCs can prevent autoimmunity in a murine model of multiple sclerosis (EAE) and prolonged graft survival significantly in a murine GVHD model [24, 25]. Although most of these protocols involved in vitro exposure of DCs to IL-10, there is recent evidence that IL-10-driven DC modulation may also play a role in generation of regulatory T cells in vivo. For instance, Wakkach et al. not only confirmed previous in vitro results showing that addition of IL-10 to in vitro cultures differentiated DCs to a $CD45^{high}$ tolerogenic phenotype, but also demonstrated that this tolerogenic phenotype, along with regulatory Tr1 cells, is significantly enriched in spleens of IL-10 transgenic mice [23]. Thus these data show that IL-10 plays an important role in rendering DCs not merely immature but also modifies their ability to induce regulatory T cells in vivo.

3.3 Pharmaceuticals Interfere with DC Maturation

In accordance with the concept that immature DCs induce Treg rather then effector T cells, several pharmaceuticals have been tested for their ability to induce Treg by affecting the maturation status of DCs. Among them are the

vitamin D3 methobolite 1α,25-$(OH)_2D_3$, N-acethyl-L-cysteine and common immunosuppressive drugs such as corticosteroids, cyclosporin A, rapamycin and aspirin [26–31]. All of them have been shown to suppress DC maturation and as a consequence, anergy and/or regulatory T cells were induced. The effects are numerous and in the following examples are only outlined.

Direct induction of Treg in vitro by pharmacologically treated DCs has been observed after exposure of DCs to *N*-acetyl-L-cysteine, and injection of DCs exposed to a mixture of vitamin-D3 and mycophenolate mofetil induced full tolerance in a murine allograft model [32]. Interestingly, adoptive transfer of T cells from such tolerant mice into previously untreated mice prevented the rejection of respective allografts, thus indicating that probably regulatory T cells had been induced by vitamin D3 treated DCs in vivo. Furthermore, administration of rapamycin in clinically relevant doses prevented the full maturation of DCs and downregulated their IL-12 secretion and their capacity to induce T cell proliferation in vitro. Upon adoptive transfer of these rapamycin-treated DCs, an allo-antigen specific T cell hyporesponsiveness could be observed in the recipients [33]. In conclusion, there is plenty of evidence showing that drugs affecting DC maturation by the means of preventing DC maturation are also most likely inducers of Treg in vivo.

3.4 RelB Translocation is Crucial for DC Maturation

Although most pharmaceuticals mentioned above have no structural similarities, it is most likely that their suppressive effects were mediated by the same mechanism, namely inhibition of maturation of DCs. On a molecular level, DC maturation is guided by relB, a subunit of the NFκB transcription factor. RelB has been shown to play a major role in DC function by regulating CD40 and MHC expression. Upon stimuli exerted by TNFα, LPS or virus-derived IL-1, relB translocates to the nucleus and promotes transcription of CD40, CD80/86 and MHC genes, all of which are indicators of DC activation [34, 35]. Accordingly, blockage of this translocation can lock DCs in an immature state, as indicated by results using RelB-deficient mice. However, most of the pharmaceuticals that inhibit DC maturation as discussed above, also interact with the relB pathway. For instance there is evidence that mycophenolate mofetil, glucocorticoids and vitamin D3 all downregulate NFκB expression. After exposure of DCs to these drugs, their function is indeed modulated in a way that induction of regulatory T cells is promoted [32, 36–38].

In addition to IL-10 secretion and surface-marker expression, relB may also be a useful marker to qualify DC as Treg-inducing DCs. Evidence derives from observations showing that nuclear relB is absent in steady-state DCs lo-

cated in peripheral tissues, whereas relB becomes upregulated in the nucleus in DCs residing in inflamed or lymphoid tissues [39]. Overall, nuclear translocation of relB in DC is a reliable marker for DC activation and application of pharmaceuticals preventing or delaying nuclear relB expression in vivo may provide a tool by which regulatory T cells are induced via immature DCs.

4 Subsets of DCs That Induce Regulatory T Cells

4.1 $CD8^-$ Versus $CD8^+$

Teleologically it seems plausible that in the absence of microbial infection and inflammation the induction of regulatory T cells is the default function of DCs. Because in the steady state, the majority of foreign antigens to which DCs are exposed are innocuous and are derived from cell detritus or harmless environmental antigens [40].

Since DCs are constantly sampling the tissue environment, presentation of these self-antigens followed by induction of regulatory T cells might provide a means by which peripheral tolerance is maintained (Fig. 1). However, it cannot be excluded that beyond the immature vs. mature phenotype, different subsets of DCs exist that are intrinsically programmed to induce regulatory T cells regardless of their activation status.

A great deal of work has been done to distinguish specialized subsets of DCs by surface-marker expression and their capacity to induce or prevent immune reactions. CD8 was among the first molecules that defined DC subsets and these subsets have indeed a differential impact on tolerance vs. immunity. Ken Shortman's laboratory has found early evidence that different lineages of DCs, as determined by the CD8 expression in mice, may exist [41,42]. A subset of $CD8\alpha^+$ DCs were identified in thymus and in spleen, and it has been suggested to be of lymphoid origin as opposed to conventional, $CD8^-$ DCs that presumably are derived from myeloid precursors. Similarly, so-called lymphoid DCs were also identified in humans.

Initial experiments pointed towards tolerizing properties of these DCs, as they were inferior in inducing T cell proliferation and were able to limit IL-2 production [43, 44]. Moreover, further results from Suess et al. showed enhanced FasL expression by these cell, allowing the killing of potentially autoreactive lymphocytes [45]. However, recent results show that $CD8^+$ DCs are not exclusively involved in induction of regulatory T cells but are also able to stimulate T cell responses [46, 47]. Accordingly, in that context the characterization of $CD8^+$ DCs as "veto cells" was too bold [48, 49].

However, although not all $CD8^+$ DCs are assigned to a tolerogenic phenotype, current results suggest that at least $CD8^+$ DCs residing in lymphoid tissues are responsible for induction self-tolerance to tissue-associated antigens. For instance, it has been shown that a $CD8^+$ subset presents self-antigens and apoptotic bodies to $CD4^+$ as well as $CD8^+$ T cells, resulting in tolerance [44, 50]. In addition to these direct suppressive effects, it has also been shown that $CD8^+$ DCs are involved in direct induction of regulatory T cells in vivo [51].

Although the CD8 marker has not been proven to be an exclusive marker for Treg-inducing DCs, its value to characterize and isolate possibly tolerizing DCs for clinical applications has formally been established. For example, O'Connel et al. [52] selectively expanded $CD8^+$ DCs in mice by injection of Flt3L and after adoptive transfer of these purified DCs into syngeneic mice, increased allograft survival was recorded. Interestingly, this effect was independent of the maturation status of the transferred DCs, since in vitro matured $CD8^+$ DCs exerted similar tolerogenic effects. Moreover, even early precursors of DCs expressing the CD8 marker promote the engraftment of allogeneic hematopoietic stem cells in mice [53].

Thus these data show that in vivo among $CD8^+$ DCs (a) subpopulation(s) exist, which induce Treg and future investigations have to elucidate these tolerogenic phenotype(s) in particular.

4.2 Plasmacytoid DCs

Recently a novel subset of DCs has been characterized, so-called plasmacytoid DCs (pDCs). They are the main source of IFN type I and upon viral infection these cells presumably prime naive T cells to produce IFNγ and IL-10. However, pDCs also have the capacity to induce T cell anergy. For instance, Kuwana et al. reported that freshly isolated pDCs induced Ag-specific anergy in $CD4^+$ T cells [54]. Although pDCs are able to secrete IL-10, soluble factors do not seem to play a role in anergy induction; instead inhibitory cell surface molecules such as the Ig-like transcript (ILT) 3 and 4 are involved [55]. It has also been reported that pDCs induce naive human $CD8^+$ T cells into IL-$10^{high}IFN^{lo}$ producing T cells that were able to suppress bystander proliferation of conventional $CD8^+$ T cells. Interestingly, these pDCs had to be activated with CD40L, hence immaturity of pDC does not seem to be required in order to induce regulatory T cells [56].

Although most of the data regarding tolerogenic properties of pDCs was generated using in vitro culture systems, there is limited evidence that pDCs might be a useful tool for therapeutical regimens. In Rhesus macaques, large

numbers of potentially tolerogenic pDCs can be found in the blood stream after treatment with Flt3L or G-CSF [57, 58], and in parallel it has been shown that G-CSF-treated blood cells from humans reduced severity of human GVHD upon infusion [59, 60]. However, the impact of in vivo mobilized pDCs on immunity and whether they provide a tool for tolerance induction in therapeutic settings remains to be determined in further trials.

5 Spatial Distribution of Tolerogenic DC Phenotypes

The search for specialized subsets of DCs that are able to induce regulatory T cells remains complex since several markers overlap between immature DCs and possibly tolerogenic subsets, and refined characterization of DCs of different spatial origin complicates reliable classification as tolerogenic or immunostimulatory subsets. For instance, Wakkach et al. [23] isolated $CD11c^{low}$, $CD45^{high}$ DCs from the lymph nodes and the spleen of mice that secrete high levels of IL-10 and induce Tr1 regulatory T cells in vitro and in vivo. In comparison to other DCs, these DCs are characterized by their weak expression of CD11c, their expression of CD45 (normally expressed by T cells) and their plasmacytoid morphology. Further nonclassical DC markers, such as B220 and CD8 were identified on a subset of thymic and peripheral DCs [61]. These DCs secrete measurable amounts of type 1 interferon and are able to induce Treg in vitro. In addition to thymic DCs, another $B220^{+}$ DC subset that may take part in peripheral tolerance was identified by Lu et al. They were able to isolate a $B220^{+}$, $CD19^{-}$, DEC-205^{+} subset of DCs that even after activation with IL-3 and CD40 induces Tr1 cells [62]. Given that thymus and liver are intrinsically tolerizing organs, one can speculate that these organs contain high amounts of Treg-inducing DCs and the mere activation status of the DCs is not the crucial factor deciding tolerance vs. immunity.

The notion that the anatomical side might have an impact on whether regulatory T cells or T effector cells are induced by the DCs is corroborated by results obtained with DCs residing in mucosal surfaces. For example, in the lung and in the gut DCs are constantly exposed to numerous innocuous antigens and thus regulatory T cells that curb overboarding immune reactions have to be present. Accordingly, lung [13] as well as Peyer's patch DCs [63] have been shown to produce large amounts of IL-10 that in turn can promote differentiation of Tr1 cells by either keeping incoming DCs in an immature status or by direct effects on Tr1 differentiation [51, 64].

6
Feedback Mechanisms Between Treg and DCs

Many results support the concept that DCs are inducers of Treg under certain circumstances. However, recent results imply that Treg, on the other hand, also affect DC functions [65]. For example, Misra et al. have shown that DC co-cultured with Treg remain in an immature state as judged by surface-marker expression [19]. These Treg-exposed DCs were inferior in induction of T cell proliferation and produced significant amounts of IL-10. In another murine cardiac transplantation model, increased numbers of splenic $CD4^+/CD25^+$ Treg and immature DC were observed after treatment of the recipients with 15-deoxyspergualin, a commonly used anti-rejection drug [66]. As expected, these immature DC purified from tolerant recipients induced the generation of $CD4^+/CD25^+$ Treg when incubated with naive T cells. Surprisingly, when these Treg isolated from tolerant recipients were incubated with DC progenitors, generation of DCs with tolerogenic properties, i.e., inferior T cell stimulatory capacity and IL-10 production was observed. In conclusion, these results

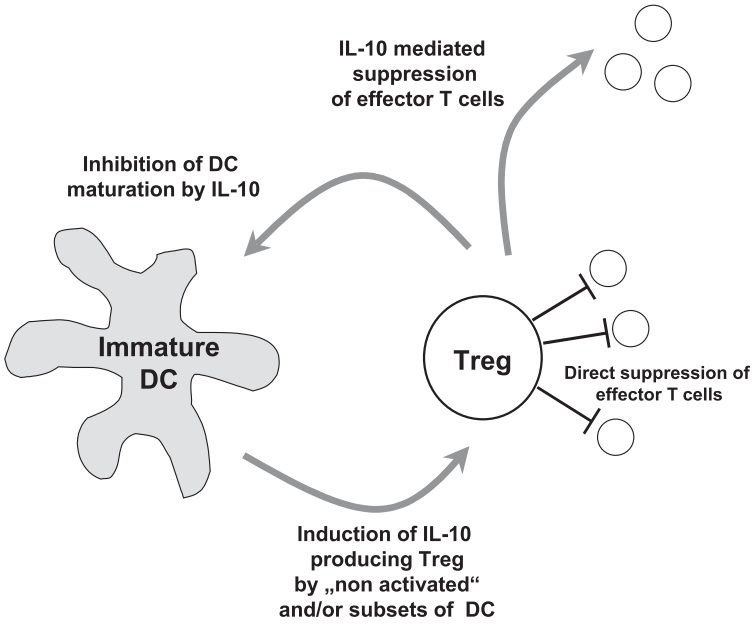

Fig. 2 DCs as part of a self-maintaining regulatory loop. DCs induce regulatory T cells either by cell–cell contact or by cytokine secretion. Treg, on the other hand, produce IL-10 and/or TGF-β, which in turn keeps DCs in an immature tolerogenic state that further promotes Treg induction

support the notion that IL-10 is a critical factor in a self-maintaining feed back loop, i.e., IL-10 derived from regulatory T cells has been shown to play a role in locking immature DCs in a tolerogenic state, which in turn induces further regulatory T cells that may contribute to IL-10 production [19]. However, this positive feed back loop can ensure prolonged immunosuppression and does not only rely on the cell–cell contact required by genuine Treg (Fig. 2).

7 Conclusion

There is strong evidence that DCs have immunosuppressive properties mainly by inducing regulatory T cells. Although the exact mechanisms are not clear yet, a number of reports support the notion that the activation and/or maturation status is crucial for the decision on whether tolerance or immunity is induced. In the absence of inflammatory stimuli, DCs remain in the steady state, which allows them to induce regulatory T cells.

Although many different T cell subpopuations are induced (reports ranging from Treg to Tr1 to TH3-like T cells), the common denominator is their capacity to curb T cell activation. Their impact for tolerance is indeed substantiated by results, showing that removal of different subpopulations of Treg commonly results in autoimmune diseases in different animal models. Therefore steady-state DCs seem crucial for maintenance of peripheral tolerance, since they may serve as sentinels for self-antigens in the peripheral tissues. In the steady state, DCs in noninfected peripheral tissues mainly encounter self-antigens (e.g., cell detritus, apoptotic bodies) or harmless environmental antigens that are transported to regional lymph nodes. Upon contact with T cells, these nonactivated DCs induce regulatory T cells, which in turn suppress potentially self-reactive effector T cells.

Therefore, the constant generation of Treg by nonactivated DCs may be a way to maintain peripheral tolerance.

In the future, biological agents that increase and/or mobilize immature DCs in vivo or block maturation of DCs may be suitable candidates for the development of novel therapeutics to treat allergic and autoimmune diseases.

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Part II
Involvement of Disease Models