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Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands☆

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Abstract

Vitamin D receptor (VDR) ligands, in addition to controlling calcium metabolism, exert important effects on the growth and differentiation of many cell types and possess pronounced pro-tolerogenic immunoregulatory activities. VDR ligands can act directly on T cells, but antigen-presenting cells (APCs), and in particular dendritic cells (DCs), appear to be primary targets for their tolerogenic properties. The capacity of VDR ligands to target APCs and T cells is mediated by VDR expression in both cell types and by the presence of common targets in their signal transduction pathways, such as the nuclear factor NF-*k*B that is down-regulated in APCs and in T cells. VDR ligands can induce in vitro and in vivo tolerogenic DCs able to enhance $CD4^+CD25^+$ suppressor T cells that, in turn, inhibit Th1 cell responses. These mechanisms of action can explain some of the immunoregulatory properties of VDR ligands, and are potentially relevant for the treatment of Th1-mediated autoimmune diseases and allograft rejection.

Keywords: Dendritic cell; VDR; APC

1. Introduction

$1,25(OH)_2D_3$, the activated form of Vitamin D, has, in addition to its central function in calcium and bone metabolism, important effects on the growth and differentiation of many cell types, and pronounced immunoregulatory properties [1–3]. The biological effects of $1,25(OH)_2D_3$ are mediated by the Vitamin D receptor (VDR), a member of the superfamily of nuclear hormone receptors functioning as a ligand-activated transcription factor that binds to specific DNA sequence elements (Vitamin D responsive elements, VDRE) in Vitamin D responsive genes and ultimately influences their rate of RNA polymerase II-mediated transcription [4]. The presence of VDR in most cell types of the immune system [5], in particular in antigen-presenting cells (APCs) such as macrophages [5] and dendritic cells (DCs) [6], as well as in both $CD4^+$ and $CD8^+$ T lymphocytes (reviewed in ref. [7]), prompted the investigation of the potential for VDR ligands as immunomodulatory agents able to modulate T cell responses.

APCs, and notably DCs, are key targets of VDR ligands, both in vitro and in vivo. DCs, a highly specialized APC system critical for the initiation of $CD4^+$ T cell responses are present, in different stages of maturation, in the circulation as well as in lymphoid and non-lymphoid organs [8]. Immature DCs, such as Langerhans cells in the skin, are found in non-lymphoid tissues, where they exert a sentinel function. After antigen uptake, they migrate through the afferent lymph to T-dependent areas of secondary lymphoid organs where priming of naive T cells may occur. During migration to lymphoid organs, DCs mature into potent APCs by increasing their immunostimulatory properties while decreasing antigen-capturing capacity [8]. Recently, it has become clear that DCs cannot only be immunogenic but also tolerogenic, both intrathymically and in the periphery [9]. In particular immature DCs have been found to have tolerogenic properties and to induce T cells with suppressive activity [10].

2. Induction of tolerogenic dendritic cells by VDR ligands

A number of studies has clearly demonstrated that $1,25(OH)_2D_3$ and its analogues inhibit the differentiation

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Table 1
Phenotypic and functional modifications induced by VDR ligands in human myeloid dendritic cells

Phenotype/function	Effect
Maturation marker expression	
CD83	Decreased
DC-LAMP	Decreased
Antigen uptake	
Mannose receptor expression	Increased
Costimulatory molecule expression	
CD40	Decreased
CD80	Decreased
CD86	Decreased
Inhibitory molecule expression	
ILT3	Increased
ILT4	Unmodified
B7-H1	Unmodified
Cytokine production	
IL-10	Increased
IL-12	Decreased
Chemokine production	
CCL2	Increased
CCL17	Decreased
CCL18	Increased
CCL20	Decreased
CCL22	Increased
Chemokine receptor expression	
CCR7	Decreased
Apoptosis	
Maturation-induced	Increased
T-cell activation	
Response to alloantigens	Decreased

Compiled from refs. [11,48] and from the authors' unpublished data.

and maturation of DCs [11–16]. These studies, performed either on monocyte-derived DCs from human peripheral blood or on bone-marrow derived mouse DCs, have consistently shown that in vitro treatment of DCs with $1,25(OH)_2D_3$ and its analogues leads to downregulated expression of the costimulatory molecules CD40, CD80, CD86 and to decreased IL-12 and enhanced IL-10 production, resulting in decreased T-cell activation. The block of maturation, coupled with abrogation of IL-12 and strongly enhanced production of IL-10, highlight the important functional effects of $1,25(OH)_2D_3$ and its analogues on DCs and are, at least in part, responsible for the induction of DCs with tolerogenic properties. In addition, VDR ligands have other important effects on the phenotype and function of DCs (Table 1), such as the upregulation of the inhibitory receptor ILT3 that has been associated with tolerance induction [17], and the modulation of chemokine production. The combination of these effects can explain the capacity of VDR ligands to induce DCs with tolerogenic properties that favor suppressor T cell enhancement. DCs are able to synthesize $1,25(OH)_2D_3$ in vitro as a consequence of increased 1alphaOHase expression [18], and this could also contribute to promote suppressor T cell induction. It is also possible that $1,25(OH)_2D_3$ may contribute to the physiological control of immune responses, as suggested by the enlarged lymph nodes containing a higher frequency of mature DCs in VDR-deficient mice [19].

3. Tolerogenic dendritic cells induced by VDR ligands lead to enhancement of suppressor T cells

The prevention of DC differentiation and maturation as well as the modulation of their activation and survival leading to DCs with tolerogenic phenotype and function play an important role in the immunoregulatory activity of $1,25(OH)_2D_3$. These effects are not limited to in vitro activity: $1,25(OH)_2D_3$ and its analogues can also induce DCs with tolerogenic properties in vivo, as demonstrated in models of allograft rejection by oral administration directly to the recipient [20] or by adoptive transfer of in vitro-treated DCs [19]. Tolerogenic DCs induced by a short treatment with $1,25(OH)_2D_3$ are probably responsible for the capacity of this hormone to induce $CD4^+CD25^+$ suppressor T cells ($CD25^+$Ts) that are able to mediate transplantation tolerance [20].

Interest in the role of Ts cells has recently resurged and, among the various populations of Ts cells, naturally occurring thymic and peripheral $CD4^+$ T cells that co-express CD25 are currently the most actively investigated [21]. Although several surface molecules expressed by $CD25^+$Ts cells have been suggested to provide key molecular signals for immunosuppression, multiple mechanisms are probably operative. Based on the essential role of cell–cell contact for suppressive activity in vitro, the appropriate localization of $CD25^+$Ts cells could be crucial for their function not only in directing their immunosuppressive activity but also in regulating their homeostasis by guiding them to microenvironmental sources of instruction, survival and/or proliferation signals. CCR4, CCR5 and CCR8, a pattern of chemokine receptors selectively expressed by $CD25^+$Ts cells, could guide them to their cellular targets and control their interaction with APCs and T cells [22].

Two DC subsets, myeloid (M-DCs) and plasmacytoid DCs (P-DCs) have been identified. These subsets are characterized by a distinct expression of pathogen-associated pattern recognition receptors and costimulatory molecules, and by the selective production of immunomodulatory cytokines [23]. We have recently documented that in contrast to the high production by circulating human M-DCs, the CCR4 ligands CCL17 and CCL22 are poorly produced by P-DCs [24]. It is noteworthy that blood-borne M-DCs, in contrast to P-DCs, constitutively produce CCL17 and CCL22 ex vivo [24]. This selective constitutive production of CCR4 ligands by immature M-DCs lead to the preferential attraction of $CD25^+$Ts cells, ultimately favoring tolerance induction. Intriguingly, the production of CCL22, a CCR4 ligand, by M-DCs is markedly enhanced by $1,25(OH)_2D_3$ and its ana-

logues (Table 1). In contrast, the lack of secretion of significant amounts of chemokines targeting any of the receptors so far identified on $CD25^+$Ts cells by immature P-DCs, argues against a similar function for these cells. Besides maintaining peripheral immunological tolerance in homeostatic conditions, Ts cells could turn-off and limit ongoing inflammatory responses. Inflammatory signals strongly induce maturation and influx of both M-DCs and P-DCs to secondary lymphoid tissues [23], and maturation of M-DCs and P-DCs enhances their production of several proinflammatory chemokines that can potentially attract different T-cell subsets. Interestingly, maturing P-DCs, similarly to activated B cells, produce large quantities of the CCR5 ligand CCL4 [24]. Thus, in analogy with the proposed role for CCL4 in $CD25^+$Ts-cell attraction by activated B cells, mature P-DCs could recruit these cells to limit inflammatory responses.

Because DCs are pleiotropic modulators of T-cell activity, pharmacologic agents that manipulate DC function to favor the development of Ts cells could be exploited in the treatment of autoimmune diseases and graft rejection. VDR ligands could be ideally suited for this purpose, as shown by their capacity to enhance $CD25^+$Ts cells and promote tolerance induction in transplantation [20] and autoimmune disease [25] models. In both models, treatment with VDR ligands has a profound effect on the migration of effector T cells, preventing their entry into the pancreatic islets [20,25]. It remains to be seen if these agents can also affect the migration of $CD25^+$Ts cells by regulating their chemokine receptor expression or by modulating chemokine production in target tissues such as pancreatic islets. Our preliminary experiments show evidence for the latter possibility.

However, tolerogenic DCs may not always be necessarily involved in the generation of Ts cells by VDR ligands. A combination of $1,25(OH)_2D_3$ and dexamethasone has been shown to induce human and mouse naive $CD4^+$ T cells to differentiate in vitro into Ts cells, even in the absence of APCs [26]. These cells produced IL-10, but no IL-5 nor IFN-γ, thus distinguishing them from the previously described Tr1 cells [27]. Upon transfer, the IL-10-producing T cells could prevent central nervous system inflammation, indicating their capacity to exert a suppressive function in vivo [26]. Thus, although DCs appear to be primary targets for the immunomodulatory activities of VDR ligands, they can also act directly on T cells, as expected by VDR expression in both cell types and by the presence of common targets in their signal transduction pathways, such as the nuclear factor NF-*k*B that is down-regulated in APCs [28] and in T cells [26].

4. Translation of immunoregulatory properties of VDR ligands into clinical applications in the treatment of autoimmune diseases and allograft rejection

VDR ligands have gained widespread clinical application, notably in the treatment of secondary hyperparathyroidism and psoriasis [29,30], but hypercalcemia is a dose-limiting effect that prevents sustained systemic administration. To overcome this limitation, a number of $1,25(OH)_2D_3$ analogues, with a wider therapeutic window than $1,25(OH)_2D_3$ itself, have been synthesized and shown effective in experimental models of autoimmune diseases [3] and allograft rejection [31]. Although the structure-activity relationship of VDR ligands remains difficult to define, the recent elucidation of the crystal structure of the VDR bound to its natural ligand [32] should facilitate the development of $1,25(OH)_2D_3$ analogues with enhanced potency, lower calcemic liability, and increased tissue specificity, leading to the design of novel analogues with selective immunoregulatory properties potentially applicable to the treatment of autoimmune diseases and allograft rejection.

The induction of tolerogenic DCs, which leads to an enhanced number of $CD4^+CD25^+$ regulatory T cells renders VDR ligands appealing for clinical use, especially for the control of allograft rejection and for the prevention and treatment of autoimmune diseases. The immunoregulatory properties of $1,25(OH)_2D_3$ and its analogues have been studied in different models of autoimmune diseases. Notably, $1,25(OH)_2D_3$ and its analogues can prevent systemic lupus erythematosus in *lpr/lpr* mice, experimental allergic encephalomyelitis (EAE), collagen-induced arthritis, Lyme arthritis, inflammatory bowel disease and autoimmune diabetes in non-obese diabetic (NOD) mice [3]. $1,25(OH)_2D_3$ analogs are able not only to prevent but also to treat ongoing autoimmune diseases, as demonstrated by their ability to inhibit the recurrence of autoimmune disease after islet transplantation in the NOD mouse [33], and to ameliorate significantly the chronic-relapsing EAE induced in Biozzi mice by spinal cord homogenate [34]. Additive and even synergistic effects have been observed between VDR ligands and immunosuppressive agents, such as CsA and sirolimus, and these effects have been confirmed in vivo in models of autoimmune diabetes and EAE [35].

$1,25(OH)_2D_3$ and its analogues can significantly prolong allograft survival in heart, kidney, liver, pancreatic islets, skin and small bowel allografts [31]. In general, these effects have been achieved at the maximum tolerated dose, without inducing hypercalcemia, the major side effect of treatment with VDR ligands. In most experimental models, the acute rejection has been further delayed by combining VDR ligands with a suboptimal dose of CsA or other immunosuppressive agents. Although treatment with VDR ligands has consistently shown efficacy in delaying the acute allograft rejection, the effects on chronic rejection are probably the most interesting.

VDR ligands can inhibit, in association with low doses of Cyclosporin A (CsA), not only acute but also chronic allograft rejection, as documented by inhibition of adventitial inflammation and intimal hyperplasia in rat aortic allografts [36]. While the prevention of leukocyte infiltration into the adventitia is probably due to the immunomodulatory properties of VDR analogs, the inhibition of intimal

cell proliferation, both endothelial and smooth muscle cells, is likely induced by their capacity to regulate cell growth. The $1,25(OH)_2D_3$ analogue MC 1288 also reduced clinical and histological signs of chronic graft rejection in rat kidney allografts [37], and renal graft loss has been found decelerated, in a retrospective study, in patients treated with $1,25(OH)_2D_3$ [38], further suggesting its clinical applicability to inhibit chronic graft rejection.

The induction of tolerogenic DCs by VDR ligands, which leads to an enhanced number of $CD4^+CD25^+$ regulatory T cells in vivo [20,25] are likely to play an important role in controlling graft rejection, both acute and chronic, and in favoring the establishment of transplantation tolerance. A short treatment with $1,25(OH)_2D_3$ and mycophenolate mofetil, a selective inhibitor of T and B cell proliferation [39] that also modulates APCs [40], induces tolerance to islet allografts associated with an increased frequency of $CD4^+CD25^+$ regulatory T cells able to adoptively transfer transplantation tolerance [20]. The induction of tolerogenic DCs could indeed represent a therapeutic strategy promoting tolerance to allografts [41] and the observation that immature myeloid DCs can induce T cell tolerance to specific antigens in human volunteers represents an important proof of concept for this approach [42]. Also the direct effects of VDR ligands on T cells, in particular the inhibition of IL-2 and IFN-γ production, could play a role in inhibiting graft rejection. $1,25(OH)_2D_3$ inhibits IL-2 secretion by impairing the formation of the transcription factor complex NF-AT [43,44], and IFN-γ through interaction of the ligand-bound VDR complex with a VDRE in the promoter region of the cytokine [45]. A combination of $1,25(OH)_2D_3$ and low-dose CsA inhibited the expression of IL-2 and IL-12, and increased significantly IL-10 expression levels in kidney allografts [46]. Additional mechanisms could rely on the capacity of $1,25(OH)_2D_3$ to significantly reduce bioactive renal TGF-β1 by interacting with Smad proteins, important regulators of TGF-β signal transduction [47]. Since TGF-β has a pronounced pro-fibrotic activity, its decrease in the kidney tissue may inhibit the evolution of chronic rejection in kidney transplants.

5. Conclusions

VDR ligands have pleiotropic immunoregulatory activities that could be exploited therapeutically. APCs and T cells can be direct targets of the hormone, leading to the inhibition of pathogenic effector T cells and enhancing the frequency of T cells with suppressive properties, largely via induction of tolerogenic DCs. VDR ligands can also modulate chemokine secretion, enhancing the production of chemokines able to recruit suppressor T cells. These immunoregulatory activities, coupled with the absence of major side effects once calcemia is under control, have been translated into effective immunointervention in a variety of autoimmune disease and graft rejection models. This body of knowledge represents a sound basis to further explore the immunoregulatory properties of VDR ligands in chronic inflammatory conditions sustained by autoreactive or alloreactive immune responses.

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