

The many routes of dendritic cells to ensure immune regulation

Oscar Palomares, PhD,^{a,b} Liam O'Mahony, PhD,^a and Cezmi A. Akdis, MD^a *Davos, Switzerland, and Madrid, Spain*

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Several studies have demonstrated that the vitamin D metabolite 1,25(OH)₂D3 (VitD3) and related compounds display potent immunosuppressive properties. Although the underlying mechanisms operating in such effects are not yet fully elucidated, the modulation of the dendritic cell (DC) functions and the appearance of regulatory T (Treg) cells have been postulated as key events of the observed beneficial effects of VitD3 and analogous compounds. In this issue of the *Journal*, van der Aar et al¹ shed light on the mechanisms involved in the immunosuppressive effects of VitD3 through induction of different Treg cell subsets by different DC subsets, which might well be exploited to improve the current treatments of skin diseases, such as psoriasis or atopic dermatitis.

Treg cells constitute a heterogeneous population of T cells with the ability to suppress immune responses through several inhibitory pathways.² Treg cells are generally divided into 2 groups: the thymus-derived naturally occurring CD4⁺CD25⁺ forkhead box protein 3 (FOXP3)⁺ Treg cells³ and the inducible Treg cells generated outside the thymus after antigenic stimulation, which include IL-10-producing Treg cells (T_R1 cells)⁴ and the TGF-β-producing T_H3 cells.⁵ The induction of Treg cells represents a primary mechanism of tolerance induction that is favored in particular microenvironments,⁶ and in these processes DCs play a pivotal role. In the context of allergic diseases, it is well accepted that allergen-specific Treg cells play a central role in controlling allergic T_H2 immune responses. Although different studies on immune responses to allergens in healthy subjects, as well as in patients successfully treated with immunotherapy, have

demonstrated that the induction and maintenance of allergen-specific Treg cells constitutes a key factor in healthy immune responses to allergens,^{7,8} the molecular mechanisms operating in Treg cell generation, as well as the specific DC subsets involved in these processes, remain to be fully elucidated. In this issue van der Aar et al¹ provide new insights into the potential mechanisms operating in some of the above mentioned processes. In particular, they describe the molecular and cellular events underlying the immunosuppressive effects of VitD3, which have been previously shown to influence the severity of inflammatory skin diseases, such as psoriasis or atopic dermatitis.¹ In human subjects T-cell responses in the skin mainly depend on 2 different conventional DC subsets, known as epidermal Langerhans cells (LCs) and dermal dendritic cells (DDCs).⁹ In this study the authors elegantly demonstrate that VitD3-treated epidermal LCs are able to generate functional FOXP3⁺ Treg cells through a mechanism that is partially dependent on TGF- β . In contrast, VitD3-treated DDCs generate functional IL-10⁺FOXP3⁻ Tr₁ cells in an IL-10-dependent fashion. These results significantly enhance our current knowledge on how VitD3 is able to induce DC subset-specific programs, which generate functional Treg cells, thereby supporting the reported *in vivo* immune-suppressive properties of this metabolite.

Several studies have previously shown at the molecular level that different DC subsets play distinct roles in the modulation of T cell-mediated adaptive immunity, thus supporting the concept of functional DC subsets with opposing or complementary effects on T-cell polarization.¹⁰⁻¹² The data presented by van der Aar et al additionally contribute to this concept. Although VitD3 promotes tolerogenic epidermal LCs and DDCs, both subsets are able to generate Treg cells with different effector functions through fully distinct mechanisms (Fig 1). The immunobiology of epidermal LCs is highly dependent on keratinocyte-derived TGF- β . Therefore under homeostatic conditions, active VitD3 metabolite produced by keratinocytes might synergistically act with TGF- β on LCs and enhance the capacity of this DC subset to generate FOXP3⁺ Treg cells through a mechanism that depends on LC-derived TGF- β , thus maintaining skin homeostasis. Under inflammatory conditions, active VitD3 metabolite might also reach dermal layers of the skin. There VitD3 would instruct DDCs to induce IL-10⁺FOXP3⁻ T_R1 cells that might help to avoid harmful excessive immune responses for the host. In the context of psoriasis or atopic dermatitis, topical treatment with VitD3 might restore normal immune responses by acting on both skin DC subsets, thus inducing different molecular responses with complementary effects that promote immune regulation.

The *in vivo* relevance of these findings needs to be further evaluated, particularly in the allergic microenvironment, where additional factors, such as cytokines, might influence the effect of VitD3 on LCs or DDCs.¹³ In addition, the potential biological reasons for differential effects of a specific metabolite on DCs within

From ^athe Swiss Institute of Allergy and Asthma Research (SIAF), Davos, University of Zurich, Davos Platz, Davos, and ^bthe Department of Biochemistry and Molecular Biology, Chemistry School, Complutense University of Madrid.

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Reprint requests: Cezmi A. Akdis, MD, Swiss Institute of Allergy and Asthma Research (SIAF), Obere Str. 22, CH-7270, Davos Platz, Switzerland. E-mail: akdisac@siaf.uzh.ch.

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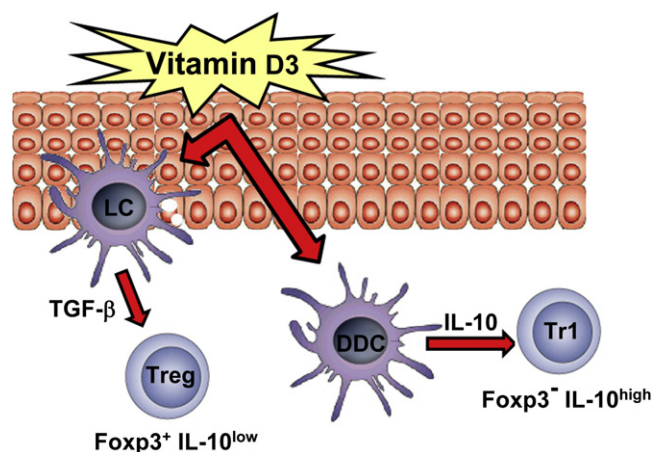


FIG 1. Vitamin D3 targets skin DC subsets to promote the development of distinct Treg cell populations. Vitamin D3-activated epidermal LCs generate Foxp3⁺IL-10^{low} Treg cells in a TGF-β-dependent fashion, whereas vitamin D3-activated DDCs promote Foxp3⁺IL-10^{high} Tr1 cell development through a mechanism that requires IL-10.

different environments are largely unknown, and it is likely that a better understanding of these unique tissue-specific effects will be of great significance for the maintenance of appropriate immune responses in the context of skin inflammation.

It is also important to mention that this study contributes to the concept that specific metabolites have a profound effect on the modulation of DC activity, leading to different subsets of effector or Treg cells. Direct influence on Treg cell differentiation through activation of transcription factors, such as the Runt-related transcription factors RUNX1 and RUNX3, should also be considered.¹⁴ Active metabolites, such as those derived from vitamin A or tryptophan, are crucial for the modulation of DC functional properties, especially those related to their tolerogenic capacity.^{15,16} Considering that DCs are important sentinels monitoring microbial activity within tissues, particularly those in close contact with the external environment, it is reasonable to speculate that they should also be equipped with sensors that allow them to detect the nutrient status of bystander cells. Under certain circumstances, the release and accumulation of specific metabolites might represent very important signals that surrounding DCs must properly interpret so that they can mount adequate immune responses to maintain tissue integrity and homeostasis or to develop controlled inflammatory responses to clear pathogens.

In conclusion, the present study contributes to our current knowledge on the potential mechanisms by which VitD3 exerts its immunosuppressive function on skin inflammatory diseases. In

particular, this work supports the existence of functional DC subsets associated with functional Treg cell subsets. This study also raises new interesting questions. For example, what are the molecular checkpoints that determine the DC's decision to secrete IL-10 or TGF-β in response to a single metabolite? The identification of novel pathways that are required for the generation of Treg cell populations, as well as the discovery of molecules that modulate the tolerogenic capacity of specific DC subsets in specific tissues, will be of great importance in the design of novel therapeutic approaches for the treatment of diseases related to a breakdown in immunologic tolerance.

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