The Role of Vitamin D in Regulating Immune Responses

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Interest in vitamin D seems to be surging due to the increased number of studies suggesting that it could prevent a variety of chronic diseases. Many national surveys have demonstrated a growing proportion of the population presenting with serum concentrations below the lower limit of 10 ng/ml, whereas less than 5% reached 30 ng/ml, a level generally recommended for avoiding vitamin D insufficiency [1-3].

Vitamin D receptor has been found on many immune cells, such as macrophages, dendritic cells, T and B cells, mainly after activation. The engagement of VDR on DCs was shown to shape DC phenotype and function, enhancing their tolerogenicity in adaptive immune responses. Tolerogenic DCs induced by a short treatment with VDR agonists promote CD4+CD25+FoxP3+ T regulatory cells, which are able to mediate transplantation tolerance and arrest the development of autoimmune diseases [4]. In addition, it has been shown that vitamin D inhibits pro-inflammatory processes by suppressing the over-activity of CD4+ Th1, Th2 and Th17 cells and the production of their related cytokines such as interleukin-2, interferon-gamma and tumor necrosis factor-alpha [5,6].

The receptor for the biologically active metabolite of vitamin D appears to be a key player in these associations, as a mediator not only of the biological effects of vitamin D, but of the regulation of vitamin D metabolism itself, as well [7].

The possible involvement of vitamin D deficiency in the development of autoimmune diseases has recently gained interest. Epidemiological studies present evidence linking vitamin D deficiency with autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus [8-10]. Prospective studies on the involvement of vitamin D in SLE are limited, but most of the existing cross-sectional studies show an inverse relationship between levels of vitamin D and disease activity [11,12]. When vitamin D was added *in vitro*, many immunological abnormalities characteristic of SLE were reversed, suggesting that vitamin deficiency skews the immunological response towards the loss of tolerance [13]. In another study, although vitamin D deficiency was common among SLE patients and was found to be associated with both sun avoidance and extreme fatigue, this had no relation to SLE severity. Here, the authors were able to show that along with its beneficial effect in SLE, hydroxychloroquine therapy prevented vitamin D deficiency [14].

When immunomodulatory mechanisms of vitamin D are discussed, many studies point to their ability to enhance the anti-inflammatory loop, namely, their ability to modulate T regulatory cell function. In this issue of *IMAJ*, Prietl et al. [15] question whether vitamin D supplementation increases Treg cell frequency (% Tregs) of circulating CD4+ T cells in apparently healthy individuals. Following a supplementation of 140,000 U at baseline, volunteers were assessed 4 weeks (visit 1) and 8 weeks after baseline (visit 2). The authors demonstrated that in 46 study participants who completed the trial, 25(OH) D levels increased from 23.9 ± 12.9 ng/ml at baseline to 45.9 ± 14.0 ng/ml at visit 1 and 58.0 ± 15.1 ng/ml at visit 2. Compared to baseline levels of %Tregs (4.8 ± 1.4), vitamin D supplementation induced a significant %Tregs increase at study visit 1 and visit 2 (5.8 ± 1.7, $P < 0.001$; and 5.6 ± 1.6, $P < 0.001$) respectively.

RECENT STUDIES LINKING VITAMIN D AND TREG CELLS

Allergen-specific immunotherapy was shown to suppress allergen-induced airway manifestations in a mouse model of allergic asthma. Moreover, allergen immunotherapy induced IL-10-dependent longlasting tolerance of ovalbumin-induced asthma manifestations, pointing to a role for Treg cells. Since immature tolerogenic DCs play a critical role in Treg cell generation and peripheral tolerance, it was intriguing to explore whether allergen immunotherapy could be improved by adding vitamin D, inhibiting the DC maturation. In this regard Taher and colleagues [16] were able to demonstrate that 1.25(OH)2 D3 potentiates the efficacy of immunotherapy and that the regulatory cytokines IL-10 and transforming growth factor-beta play a crucial role in the effector phase of this mouse model.

Human IL-10-secreting Tregs (IL-10-Tregs), which express low levels of

VDR = vitamin D receptor
DCs = dendritic cells

SLE = systemic lupus erythematosus
Tregs = regulatory T cells

IL = interleukin

CD4+CD25+ Treg-associated transcription factor FoxP3, can be induced following activation, through either polyclonal stimuli or a specific antigen presentation, in the presence of the glucocorticoid dexamethazone and the active form of vitamin D (1α,25-dihydroxyvitamin D3; 1α,25VitD3). In a very recent study the stimulation of 1α,25VitD3-induced IL-10-secreting Tregs with toll-like receptor-9 agonists, CpG oligonucleotides, resulted in decreased IL-10 and IFNγ synthesis and a concurrent loss of regulatory function. This suggests that TLR-9 could be used to monitor and potentially modulate the function of 1α,25VitD3-induced IL-10-secreting Tregs *in vivo*, and that this has implications in cancer therapy and vaccine design [17].

It is noteworthy that in addition to its systemic effect, topical vitamin D analogs such as calcipotrol were found to affect cutaneous immune responses. In this respect it was demonstrated that exposure of the skin to calcipotriol before transcutaneous immunization with OVA protein and CpG adjuvant prevents Ag-specific CD8+ T cell priming coincident with Langerhans cell depletion in the skin. Immunization through calcipotriol-treated skin induces CD4+CD25+ Treg cells that prevent subsequent Ag-specific CD8+ T cell proliferation and IFNγ production. In addition, it is suggested that ultraviolet B-induced tolerance is induced via a vitamin D receptor-dependent mechanism since vitamin D receptor knockout mice failed to increase FoxP3+ Tregs in their peripheral draining lymph node following irradiation [18].

In conclusion, the impact of the vitamin D pathway on immune function, including its therapeutic effects on IL-10, Tregs, and toll-like receptors with respect to its influence on both autoimmune diseases and cancer should be further elucidated.

IFNγ = interferon-gamma
TLR = toll-like receptor
OVA = ovalbumin

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