Editorial

Vitamin D₃ Suppresses Immune Reactions in Atherosclerosis, Affecting Regulatory T Cells and Dendritic Cell Function

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Accumulated evidence indicates that 1,25-dihydroxyvitamin D₃ (vitamin D₃) plays important roles in bone and calcium metabolism and in immune processes.¹⁻⁴ Several autoimmune disorders have been linked to a deficiency in vitamin D₃.¹⁻⁴ Epidemiological data indicate that vitamin D₃ deficiency is associated with cardiovascular events.⁵⁻⁶

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Takeda et al⁷ report the results of a study undertaken to analyze the mechanisms by which vitamin D₃ might affect the development of atherosclerotic lesions. By using a mouse model, Takeda et al demonstrated that an orally administered active form of vitamin D₃ (calcitriol) led to a marked reduction in atherosclerotic lesion formation. The study revealed that a reduction in atherosclerotic lesion formation occurred by the suppression of immune reactions, with at least 2 cell types crucially involved in vitamin D₃ effects (ie, CD4⁺CD25⁺ Fork head box protein [Foxp] 3⁺ regulatory T cells [Tregs] and dendritic cells [DCs]).

Tregs exert functions in the induction and maintenance of immune tolerance.⁸⁻¹¹ The family of Tregs is represented by a heterogeneous cell population that includes adaptive and naturally occurring Tregs.⁸⁻¹¹ According to the current paradigm, adaptive Tregs develop from naïve T cells in the periphery and can produce interleukin 10 and transforming growth factor β, whereas naturally occurring Tregs originate in the thymus as CD4⁺CD25⁺ cells and perform their suppressive functions through cell-to-cell contacts and membrane-bound transforming growth factor β and cytotoxic T-lymphocyte antigen-4 (CTLA-4).⁵⁻¹¹ The transcription factor Foxp3 is necessary for the development of this subpopulation of CD25⁺ Tregs, being their characteristic marker.⁸⁻¹¹ Mouse model studies have demonstrated that Tregs play a protective role against atherosclerosis, igniting interest in this cell type as a potential cell target in combating atherosclerosis.¹² When analyzing atherosclerotic lesions of mice that received calcitriol orally, Takeda et al found that the lesions were characterized by a reduced accumulation of CD4⁺ cells and a significant increase in number of CD25⁺Foxp3⁺ Tregs (Figure). Neutralization of CD25 by injection of anti–CD25 antibody in mice indicated that the effects of vitamin D₃ were mainly Foxp3⁺ Treg dependent.⁷

In addition to Tregs, DCs have been involved in the initiation of immune reactions by stimulating differentiation of naïve T cells and maintaining tolerance to self-antigens.¹³⁻¹⁶ DCs populate atherosclerotic lesions in mice as in humans.¹⁷⁻¹⁹ Takeda et al⁷ undertook a comparative analysis of DC populations in atherosclerotic lesions in mice that received calcitrol and in control animals and found significant reductions in the number of CD86⁺ DCs in lesions.

The activation of effector T cells in atherosclerosis critically depends on the ability of T cells to receive antigen that is presented in complex with antigen-presenting molecules, such as major histocompatibility complex class II displayed on the surface of antigen-presenting cells.¹³⁻¹⁶ As in other anatomic locations,¹³⁻¹⁶ antigen presentation in arteries is provided by DCs,¹⁷⁻¹⁹ which are the most powerful of antigen-presenting cells.¹³⁻¹⁶ In addition to the development of atherosclerotic lesions, normal arteries of mice contain immature DCs that are thought to develop from circulating DC precursors originating from bone marrow (Figure).¹⁷⁻¹⁹ In the arterial wall, immature DCs consistently test the surrounding microenvironment for the presence of “danger” signals.¹⁷⁻¹⁹ After engulfing antigen, recognized by an immature DC as a danger signal, the DC matures, involving a reduction in endocytotic activity and an increase in the expression of antigen-presenting molecules. Some DCs that mature are thought to migrate via the lymphatic vessels to regional lymph nodes, where contact with T cells occurs and leads to T-cell activation (Figure).¹⁷ Apart from this “classical” migratory route, some DCs, activated by danger signals, can be retained within the arterial wall and mature locally before forming direct contacts with T cells in situ, which leads to the activation of T cells within the arterial vessels (Figure).¹⁷⁻¹⁹

The maturation of DCs is usually accompanied by the expression of costimulatory molecules (eg, CD40, CD80, and CD86) that are necessary for the activation of T cells in DC/T-cell contacts.¹³⁻¹⁹ However, in the absence of costimulation, T cells in DC/T-cell contacts undergo anergy or even apoptosis.¹⁴⁻¹⁸ Some immature (or semimature) DCs that lack expression of costimulatory molecules could become capable of forming contacts with T cells and, thus, these DCs acquire tolerogenic properties.¹⁴⁻¹⁶ A detailed analysis of atherosclerotic lesions in mice that received calcitriol orally allowed Takeda et al⁷ to conclude that these lesions contained increased numbers of immature DCs with tolerogenic functions.
Although a clear understanding of the interplay of Tregs and DCs is yet to be established, accumulating data indicate that continuous cross talk between these 2 cell types occurs\textsuperscript{20–22} and might lead to the induction of Tregs by immature DCs with an insufficient expression of costimulatory molecules.\textsuperscript{20,21} In their turn, Tregs play a crucial role in DC differentiation and maturation.\textsuperscript{20,21} Direct effects of vitamin D\textsubscript{3} on Tregs and DCs are recognized.\textsuperscript{23–25} Takeda et al \textsuperscript{7} also examined the numbers and characteristics of Tregs and DCs in the small intestine, mesenteric lymph nodes, and spleen; and showed that oral administration of calcitriol affected immune reactions in atherosclerosis locally (within the arterial wall) and systemically, further supporting the suggestion that immune reactions occurring in the arterial wall are just the “tip of the iceberg.”\textsuperscript{26} The findings allowed Takeda et al to proffer the novel concept in cardiology that intestinal and arterial immunity are interconnected; they suggest that the intestinal immune system might be a novel therapeutic target for treatment of atherosclerosis.

Accumulating knowledge has revealed that atherosclerosis is an autoimmune disease.\textsuperscript{27} The findings of the study by Takeda et al\textsuperscript{7} demonstrate a great similarity of immune mechanisms involved in atherosclerosis and other autoimmune disorders. As in the animal model examined by Takeda et al\textsuperscript{7} Tregs and DCs are the major players in immune reactions in autoimmune diseases, including multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, and osteoporosis.\textsuperscript{8–11,14–16} In these autoimmune diseases, vitamin D\textsubscript{3} supplementation may be beneficial or currently prescribed.\textsuperscript{1–4,23–25}

Despite the success from using statins, prevention of clinical events of atherosclerosis remains a major challenge.\textsuperscript{28} Immunization strategies directed against atherosclerosis-related antigens, such as epitopes within the low-density lipoprotein particle, develop rapidly\textsuperscript{29}; obviously, it would take time to eventuate their clinical use. The enhancement of inherent atheroprotective immunity by expansion of the use of Tregs may emerge as an alternative therapeutic strategy.\textsuperscript{12,28} The work of Takeda et al\textsuperscript{7} should further promote interest in the use of vitamin D\textsubscript{3} or vitamin D receptor agonists\textsuperscript{29} in the prevention and treatment of atherosclerosis.

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None.

**References**


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