Vitamin D deficiency: protective against enteric infection?

Sylvia Christakos
Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey
Submitted 23 October 2012; accepted in final form 23 October 2012

Vitamin D is critical for calcium homeostasis (4). Recently, there is renewed interest in vitamin D because of experimental evidence indicating that 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], the hormonally active form of vitamin D, has numerous other functions, including immunomodulatory effects (6, 10). A role in immunity was suggested by early studies showing the presence of the vitamin D receptor (VDR) in activated T cells (3). In vitro studies have shown that 1,25(OH)₂D₃ impedes the transcription of pro-inflammatory cytokines such as IL-2, IL-17, and granulocyte-macrophage colony-stimulating factor (2, 18, 25), while promoting generation of Th2 cells (5). In addition, 1,25(OH)₂D₃ can inhibit the differentiation of dendritic cells (15, 23) and can regulate innate immunity by inducing the antimicrobial peptide cathelicidin (21). In vivo studies have shown that 1,25(OH)₂D₃ can at least partially protect against a number of experimental immune mediated diseases, including inflammatory bowel disease (IBD) (17). Evidence from mouse models [IL-10 knock out (-/-) mice, dextran sodium sulfate-treated mice and the CD45RBhigh transfer model] indicates that vitamin D and VDR deficiency enhance the severity of IBD (7, 12, 13).

In this issue of the American Journal of Physiology—Gastrointestinal and Liver Physiology, Ryz et al. (24) confirm that 1,25(OH)₂D₃ protects the GI tract during dextran sodium sulfate-induced colitis. However, they also report immunosuppressive actions of 1,25(OH)₂D₃ that impair host defenses against colitis induced by Citrobacter rodentium. 1,25(OH)₂D₃-treated mice infected with C. rodentium were shown to have increased pathogen burdens and exaggerated mucosal damage (24). 1,25(OH)₂D₃ suppressed colonic IFNγ, IL-17A, and IL-6, and it reduced expression of the antimicrobial peptide RegIIIγ (24). An important aspect of this study is the emphasis on the complexity of IL-17 biology and 1,25(OH)₂D₃ interaction. Although considerable literature indicates a pathological role of IL-17 in inflammatory diseases, this cytokine can also play a protective role against infections (14, 20). Thus, because of the seemingly paradoxical effects of IL-17, the authors demonstrate that inhibition of IL-17 by 1,25(OH)₂D₃ may not always be beneficial and can result in impaired host defense, at least in response to C. rodentium.

Previous studies have also suggested a protective role of IL-17 against C. rodentium in mucosal infection (17). Ishigame et al. (17), using IL-17A and IL-17F knockout (-/-) mice, showed that both IL-17A and IL-17F are required for protection of the colon against infection by C. rodentium (17). Expression of IL-17A and IL-17F was found to be essential for the induction of antimicrobial peptides β-defensins 1, 3, and 4. This study demonstrated differential cell-type-specific contributions of IL-17A and IL-17F in protection against C. rodentium infection (17). Although there was a trend for reduced expression of IL-17F, in the study of Ryz et al. (24), increased host susceptibility to C. rodentium was associated with a preferential suppression of IL-17A by 1,25(OH)₂D₃.

In addition to C. rodentium, IL-17 has been reported to mediate host defense against a number of other bacterial, fungal, and viral infections (20, 28, 29). For example, in response to the oral pathogen Porphyromonas gingivalis, IL-17RA-/- mice show enhanced periodontal bone destruction, reduced serum chemokine levels, and reduced neutrophil migration to bone (29). These findings suggest that the positive influence of IL-17 on neutrophil regulation outweighs the bone destructive action of IL-17. In a respiratory infection model using Klebsiella pneumoniae, IL-17R-/- mice had greater dissemination of K. pneumoniae in association with decreased neutrophil recruitment (28). It has been suggested that IL-17 can enhance host defense in lung epithelial cells by induction of chemokines and antimicrobial peptides, as well as by neutrophil regulation (19, 20, 28). It will be important to determine the effect of 1,25(OH)₂D₃ (which has antimicrobial activity, as well as suppressive effects on IL-17; see Refs. 16, 18, 21) in response to other infections. It is, indeed, possible that the response to 1,25(OH)₂D₃ will be dependent on the triggering stimuli and, at least in part, on whether the protective Th17 response outweighs the detrimental signals of IL-17.

In the study by Ryz et al. (24), the authors speculate that vitamin D insufficiency may put individuals at greater risk of immune mediated disease, while making them more resistant to enteric infection. It should be noted, however, that in experimental autoimmune diseases, as well as in response to infection, the role of vitamin D is quite complex, and the results of VDR deficiency are mixed. Although in mouse models of IBD, vitamin D and VDR deficiency enhances disease severity (7, 12, 13), in VDR-/- mice, experimental autoimmune encephalomyelitis (EAE) (a model of multiple sclerosis) is less severe and the onset is delayed (7, 22, 26). Thus, although 1,25(OH)₂D₃ suppresses EAE, studies in VDR-/- mice indicate that VDR is needed for development of immune elements involved in the induction of EAE. It should also be noted that in EAE, systemic lupus erythematosus, and IBD (IL-10-/- mouse model), dietary calcium is required for the suppressive effects of 1,25(OH)₂D₃ on autoimmune responses (8, 11). Dietary calcium, independent of 1,25(OH)₂D₃, can suppress EAE in the IL-10-/- mouse (9), and hypercalcemia itself has been suggested to be a mediator of the protective effect of 1,25(OH)₂D₃ in EAE (26). With regard to enteric infection, although the findings of Ryz et al. (24) suggest that vitamin D insufficiency results in protection against C. rodentium, this effect may not be observed with other infections. VDR deficiency in Salmonella infection, for example, results in more severe intestinal inflammation and VDR +/- mice are relatively more resistant than the VDR-/- mice (27).
Future studies need to address the specificity of the findings of Ryz et al. (24) for C. rodentium, as well as the response in VDR-/− mice and in vitamin D-deficient mice. Further studies related to host microbial interactions in the intestinal tract and the complex physiological consequences of modulation with 1,25(OH)2D3 and other factors that suppress proinflammatory cytokines are needed. These studies will potentially have important implications for identifying more effective therapies for mucosal inflammation.

GRANTS

S. Christakos receives funding from the National Institutes of Health (Grants AI-095055, AI-100379, and DK-38961).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.C. drafted manuscript; S.C. edited and revised manuscript; S.C. approved final version of manuscript.

REFERENCES