

Correspondence

Reply

To the Editor:

We thank Thorp et al¹ for their reference to our letter to the editor, in which we show induction of cathelicidin in lesional skin of subjects with atopic dermatitis with oral vitamin D.² We read with interest their clinical study showing vitamin D levels to be significantly reduced in subjects with chronic urticaria compared with controls. As highlighted in these 2 observations, vitamin D appears to play a role in both innate and adaptive immunity and is associated with the development of autoimmune disease. Our study discovered a potential therapeutic role of vitamin D in the innate immune system of atopic subjects by increasing the production of the antimicrobial peptide cathelicidin in lesional skin after administration of 4000 IU of oral vitamin D3 for 3 weeks. Our study was based on previous findings that 1,25-dihydroxyvitamin D3 can increase the production of antimicrobial peptides in keratinocytes and monocytes. This phenomenon is caused in part by the action of a vitamin D response element in the cathelicidin promoter and the finding that pattern recognition molecules such as TLR2 and CD14 also increase after vitamin D stimulation.³⁻⁵ Importantly, keratinocytes and monocytes express both CYP27A1 and CYP27B1, enzymes that enable the active form of vitamin D (1,25-dihydroxyvitamin D3) to be rapidly produced from the stored precursor form after local skin injury. Thus by generating 1,25-dihydroxyvitamin D3 and subsequent binding of the vitamin D response element in the promoter region of the cathelicidin gene, cathelicidin expression was greatly increased. Presumably, by increasing nutritional stores of vitamin D, this enables atopics to compensate for an otherwise inadequate capacity to produce antimicrobial peptides in response to skin injury. Our data suggest that vitamin D induction of cathelicidin in the atopic scenario may be beneficial to the atopic subject, decreasing their susceptibility to infections.

Although the diagnosis of chronic urticaria still may not fall entirely in the autoimmune category, many believe that there is at least a subgroup with an autoimmune component, termed idiopathic urticaria with evidence of autoimmunity.⁶ The role of vitamin D in autoimmunity is thought to be primarily the profound effects on dendritic cells, because vitamin D inhibits maturation of dendritic cells and maintains the immature and tolerogenic phenotype while also inhibiting IL-12 and augmenting IL-10 production by dendritic cells, thus shifting toward a T_H2 phenotype.^{7,8} Furthermore, in the autoimmune disease psoriasis, the overabundance of cathelicidin enables plasmacytoid dendritic cells to be activated by self-DNA because of complexes formed by cathelicidin. Self-DNA–cathelicidin complexes signal

through TLR9 and result in IFN- α release by plasmacytoid dendritic cells and a T-cell response that leads to cutaneous inflammation.⁹ Similarly, cathelicidin can also complex with self-RNA to activate plasmacytoid dendritic cells through TLR7 and TLR8 signaling.¹⁰ These complexes of cathelicidin with self-DNA and RNA both drive the autoinflammatory response in psoriasis.

In their correspondence, Thorp et al¹ add to the list of diseases associated with vitamin D deficiency. This novel finding underscores the importance of monitoring vitamin D levels in subjects with chronic urticaria. Together our studies demonstrate the important role vitamin D appears to play in the balance of the innate and adaptive immune system by enhancing the protective innate immune response while maintaining self-tolerance.

Tissa Hata, MD

Richard Gallo, MD, PhD

From the Division of Dermatology, University of California San Diego. E-mail: rgallo@ucsd.edu.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

1. Thorp WA, Goldner W, Meza J, Poole JA. Reduced vitamin D levels in adult subjects with chronic urticaria. *J Allergy Clin Immunol* 2010;126:xxx-xx.
2. Hata TR, Kotol P, Jackson M, Nguyen M, Paik A, Udall D, et al. Administration of oral vitamin D induces cathelicidin production in atopic individuals. *J Allergy Clin Immunol* 2008;122:829-31.
3. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* 2004;173:2909-12.
4. Schaubert J, Dorschner RA, Coda AB, Büchler AS, Liu PT, Kiken D, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *J Clin Invest* 2007;117:803-11.
5. Liu P, Stenger S, Li H, Wenzel L, Tan B, Krutzik S, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;311:1770-3.
6. Fonacier LS, Dreskin SC, Leung DY. Allergic skin diseases. *J Allergy Clin Immunol* 2010;125(2 suppl. 2):S138-49.
7. Griffin MD, Lutz W, Phan VA, Bachman LA, McKean DJ, Kumar R. Dendritic cell modulation by 1 α ,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. *Proc Natl Acad Sci U S A* 2001;98:6800-5.
8. Széles L, Keresztes G, Töröcsik D, Balajthy Z, Krenács L, Pólska S, et al. 1,25-Dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. *J Immunol* 2009;182:2074-83.
9. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* 2007;449:564-9.
10. Ganguly D, Chamilos G, Lande R, Gregorio J, Meller S, Facchinetti V, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. *J Exp Med* 2009;206:1983-94.

doi:10.1016/j.jaci.2010.04.041