Impact of Vitamin D in the Treatment of Tuberculosis

Khanh vinh quoc Luong, MD and Lan Thi Hoang Nguyen, MD

Abstract: Tuberculosis (TB) is a major global health problem and often coincides with nutritional deficiency. In fact, vitamin D deficiency has been reported among TB patients, and vitamin D receptor polymorphisms are associated with susceptibility to *Mycobacterium tuberculosis*. High doses of vitamin D were widely used to treat TB patients in the preantibiotic era. This approach was successful: vitamin D can suppress intracellular growth of *M tuberculosis in vitro*. Vitamin D also induced the expression of cathelicidin, which is involved in the first line of defense in TB patients. Thus, vitamin D may have a role in TB treatment, and further investigation is needed.

Key Indexing Terms: Vitamin D; Calcitriol; Tuberculosis. **[Am J Med Sci 2011;341(6):493–498.]**

Vitamin D is essential for both normal bone structure and serum calcium maintenance through the regulation of calcium absorption in the gut and reabsorption in the kidney, mediated by the vitamin D receptor (VDR). Many reports have described other nontraditional roles of vitamin D, including roles in experimental autoimmune encephalomyelitis,[1] multiple sclerosis,[2] collagen-induced arthritis,[3] diabetes mellitus,[4] cardiovascular disease[5] and cancer.[6] Vitamin D metabolites are important immunomodulatory hormones that activate monocytes and suppress lymphocyte proliferation, immunoglobulin production and cytokine synthesis. The presence of VDR in peripheral blood monocytes and activated T cells[7,8] suggests a relationship between vitamin D and the immune system. Studies have shown defective macrophage functions; such as impaired chemotaxis, phagocytosis and increased production of proinflammatory cytokines with vitamin D deficiency.[9] An association between low serum 25-hydroxyvitamin D_3 ($25OHD_3$) levels and acute respiratory infections has also been shown in young army recruits.[10] Cell-mediated immunity is crucial to the host response to infection with *Mycobacterium tuberculosis*.[11,12] Malnutrition is known to suppress immunity,[13] and a possible link between vitamin D deficiency and impaired host defense against *M tuberculosis* has been suggested.[14] In 2007, a meta-analysis of randomized controlled trials suggested that vitamin D supplements were associated with a decreased risk of mortality due to any cause.[15] In this article, we will review the role of vitamin D in tuberculosis (TB).

VITAMIN D POLYMORPHISM AND TB

Genetic studies provide excellent opportunities to link molecular variations with epidemiological data. DNA sequences variations, as polymorphisms, have modest and subtle but true biological effects. Receptors play a crucial role in the regulation of cellular function, and small changes in their structure might influence various intracellular signal-transduction pathways. 1,25-Dihydroxyvitamin D_3 ($1,25OHD_3$) binds to a nuclear receptor, VDR, which is associated with specific recognition sequences called vitamin D-responsive elements. The commonly occurring linked single nucleotide genetic markers (polymorphisms) at the 3′ end of VDRs are restriction fragment length polymorphism of *Bsm*I, *Apa*I and *Taq*I and the exon 2 splice site *Fok* polymorphism.

Polymorphisms in the *VDR* gene have been reported to be associated with susceptibility to *M tuberculosis*. In fact, a *Taq*I polymorphism in *VDR* gene has been shown to be associated with resistance to TB and might provide protection against TB in West Africa and native Paraguayans.[16,17] However, no evidence for this association exists in the Tibetan population.[18] An increased probability of culture conversion during TB treatment has been independently associated with the *Taq*I Tt genotype.[19] *M tuberculosis*-infected monocytes secrete matrix metalloproteinase (MMP)-9,[20] which is correlated with the severity of TB.[21] Interestingly, the *Taq*I T allele has been associated with decreased production of an antiproteinase (tissue inhibitor of metalloproteinase 1) that is a natural inhibitor of MMP-9.[22] Calcitriol also modulates tissue MMP expression under experimental conditions.[23] Selvaraj et al[24,25] found a higher frequency of the tt genotype in female TB patients, whereas the Bb and FF genotypes were more frequent in male TB patients. A *Fok*I polymorphism in *VDR* has been linked to an increased risk of clinical TB in Tibetan patients and has been associated with low serum vitamin D levels among Indian immigrants in England; however, this polymorphism is protected against active TB diseases in native Paraguayans.[17,26] Babb et al[26] reported that smoking status and VDR genotype contribute independently to smear conversion time and that the *Apa*I AA genotype and *Taq*I T-containing genotypes predictive of a faster response to TB chemotherapy. However, that case–control study did not identify an association between *VDR* genotype and TB. Polymorphisms in the *VDR* gene and *NRAMP1* gene (natural resistance-associated macrophage protein 1, now renamed *SLC11a1*—solute carrier family 11a member 1) have been statistically associated with TB susceptibility in Han Chinese and Iranian populations.[27,28] The *NRAMP1* gene has been shown to regulate the concentration of divalent cations in the phagosomes of macrophage.[29] Furthermore, an association between TB resistance and *NRAMP1* gene variants has been shown in a Cambodian population.[30] However, no association has been found between *NRAMP1* gene polymorphisms and TB in various other racial groups (Denmark, Taiwan and Morocco).[31–33] A polymorphism in Toll-like receptor (TLR) 2 can result in predisposition to the development of TB in humans.[34] Genetic variants in interleukin (IL)-1β, VDR *Fok*1 and TLR2 have also been found to be associated with an increased risk of extra pulmonary TB.[35] Lewis et al[36] conducted a meta-analysis of VDR polymorphisms and TB risk using studies of different ethnic populations studies published before August 2004. They found that the results of these studies were inconclusive and that the studies themselves were underpowered. VDR genotype might affect the severity of TB, but no association was found between TB and VDR polymorphisms in a South African population.[37]

From the Vietnamese American Research Foundation, Westminster, California.

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Correspondence: Khanh vinh quoc Luong, MD, 14971 Brookhurst Street, Westminster, CA 92683 (E-mail: Lng2687765@aol.com).

In a family-based study, the transmission-disequilibrium test analysis showed a significant global association of the single-nucleotide polymorphism combinations *Fok*I-*Bsm*L-*Taq*I and *Fok*I-*Apa*I with TB greater than that of individual single-nucleotide polymorphism.[37] Recently, Gao et al[38] reviewed 23 studies with regard to the relationship between *VDR* polymorphisms and TB. They noted that the *Fok*I ff genotype showed a pronounced positive association with TB. On the other hand, a significant inverse correlation with TB was identified for the *Bsm*I bb genotype, and marginally significant associations with TB were also found for the *Taq*I and *Apa*I polymorphisms. VDR gene variants may regulate cytotoxic T-cell responses via $1,25OHD_3$-mediated suppression of granzyme A expression in TB.[39] A Gc gene variant of the vitamin D binding protein has been shown to be related to decreased circulating levels of $25OHD_3$, $1,25OHD_3$ and vitamin D binding protein[40,41] and was found to be strongly associated with susceptibility to active TB among Gujarati Asians living in London.[41] The relationship between allelic variations in VDR and TB has been summarized in Table 1.

TABLE 1. Relationship between allelic variations in vitamin D receptor (*VDR*) gene and tuberculosis (TB)

	Linked to
Polymorphism in the *VDR* gene	
*Taq*I	Resistance to TB in West Africa and native Paraguayans
	No TB Association in the Tibetan population
Tt allele	Increased culture conversion during TB treatment
T allele	Decreased tissue inhibitor of metalloproteinase (TIMP)-1
tt genotype	Higher frequency in female TB patients
Bb and FF genotype	Higher frequency in male TB patients
*Fok*I	Increased risk TB in Tibetan patients
	Decreased vitamin D levels in Indian immigrants in England
	Against active TB in native Paraguayans
	Increased risk of extra pulmonary TB
ff genotype	Positive association with TB
*Apa*I AA genotype	Predictive of a faster response to TB chemotherapy
*Bsm*I bb genotype	Significant associations with TB
VDR gene variants	May regulate cytotoxic T-cell response by suppression granzyme A in TB
	No TB association in a South African population
Vitamin D binding protein (DBP)	
Gc gene variant	Decreased levels of $25OHD_3$, $1,25OHD_3$ and DBP
	Associated with susceptibility to active TB among Gujarati Asians in London

$25OHD_3$, 25-hydroxyvitamin D_3; $1,25OHD_3$, 1,25-dihydroxyvitamin D_3.

ROLE OF VITAMIN D IN TB

High doses of vitamin D were widely used to treat active TB in the preantibiotic era. In 1847, Charpy and Dowling[42] discussed the role of vitamin D in cutaneous TB. Vitamin D was used to treat TB of the bone and offered some improvement.[43] Williams[44] then reported the beneficial effects of fish liver oil in TB patients. In addition, the importance of sunlight has been observed throughout the history of TB treatment. In 1854, Hermann Brehmer, a Silesian botany student who was suffering from TB, traveled to the Himalayan mountains to pursue his botanical studies and cured his TB.[45] Ultraviolet (UV) light B exposure is sufficient to double the circulating $25OHD_3$ levels, but no significant change has been observed in antimycobacterial immunity.[46] Association between vitamin D deficiency and TB has been reported in a number of studies. A vegetarian diet, which is associated with a low plasma vitamin D level, is an independent risk factor for active TB among Asian immigrants living in south London.[47] TB patients also have significantly lower mean concentrations of serum $25OHD_3$ compared with healthy subjects.[48,49] A correlation between serum levels of vitamin D and risk for latent TB infection has been noted among African immigrants living in Australia.[50] Furthermore, low vitamin D levels have been associated with a 5-fold increased risk for progression to TB.[51] Patients with chronic renal failure are also at an increased risk for developing TB,[52] because certain uremic toxins can suppress $1,25OHD_3$ synthesis and its biological activity.[53] To study the association between low vitamin D serum levels and the risk of active TB in humans, Nnoaham and Clarke[54] conducted a systematic review and meta-analysis of observational studies published between 1980 and July 2006. They found that low vitamin D serum levels were associated with higher risk of active TB.

Vitamin D is known to suppress the intracellular growth of *M tuberculosis in vitro*.[55] Crowle et al[56] demonstrated that a concentration of 4 μg/mL of $1,25OHD_3$ *in vivo* could inhibit the multiplication of virulent tubercle bacilli in cultured human macrophages. In 1969, Brincourt[57] reported that vitamin D supplements were able to dissolve cavities in TB patients. Furthermore, in a random trial, multivitamin supplements (including vitamin D) reduced mortality by 50% among human immunodeficiency virus-infected TB patients.[58] Morcos et al[59] treated 24 cases of TB in children and noted clinical and radiological improvement after vitamin D treatment. In another study, vitamin D supplements resulted in more rapid sputum clearance of acid-fast bacilli and radiological improvement among Indonesian TB patients.[60] Anti-TB therapy and correction of a vitamin D deficiency have also resulted in clinical and microbiologic improvements in a refractory drug-susceptible TB patient.[61] On the other hand, Wejse et al[62] reported that vitamin D did not improve the clinical outcomes of TB patients as their trial demonstrated no overall effect on mortality in TB patients. However, this finding may have been due to a suboptimal dosage.

MECHANISM OF VITAMIN D IN TB

The gene encoding for the tryptophan-aspartate-containing coat proteins has been recognized to play a crucial role in the *M tuberculosis* survival within human macrophages.[63] The combination of vitamin D and retinoic acid has been reported to down-regulate tryptophan-aspartate-containing coat proteins

transcription in a dose-dependent manner[64] and inhibits *M tuberculosis* entry into and survival within macrophages.[65] $1,25OHD_3$ reduces the viability of *M tuberculosis* by enhancing the fusion of phagosomes and lysosomes in the infected macrophages.[66]

The role of $1,25OHD_3$ is important in normal innate immune responses. TLRs are a part of the innate immune system and detect foreign invaders. TLR2 activation leads to direct antimicrobial activity against intracellular *M tuberculosis* infection in human and murine macrophages.[67] TLR activation results in the expression of VDR and 1α-vitamin D hydroxylase in human monocytes.[68] $1,25OHD_3$ can cause vitamin D-induced expression of cathelicidin in bronchial epithelial cells[69] and may also enhance the production of leucine-leucine-37 (LL-37), an antimicrobial peptide of the cathelicidin, which acts as a first line of defense in TB prevention.[70] Liu et al[68,71] demonstrated that poor vitamin intake may increase susceptibility to *M tuberculosis* infection by inefficiently supporting the induction of cathelicidin mRNA expression in monocytes. The addition of a VDR antagonist inhibited this induction of cathelicidin mRNA by more than 80%; consequently, the antimicrobial activity was reduced by approximately 70%.[68] $1,25OHD_3$ can directly induce antimicrobial gene expression and activity through vitamin D-responsive elements located in the promoters of cathelicidin and defensin.[72] Furthermore, knockdown of either defensin or cathelicidin in primary monocytes results in a loss of TLR-mediated antimicrobial activity against intracellular mycobacteria.[73] $1,25OHD_3$ also induces autophagy in human monocytes via cathelicidin and leads to the localization of mycobacterial phagosomes with autophagosomes in human macrophages in a cathelicidin-dependent manner.[74] African Americans seem to be more susceptible to *M tuberculosis* infection in rural communities of southeastern America.[75] Crowle and Elkins[76] reported that the tubercle bacilli grew significantly faster in infected macrophages from African Americans and $1,25OHD_3$ gave less protection against bacilli-infected macrophages from African Americans than from white donors. Furthermore, vitamin D insufficiency is more prevalent among African Americans than other Americans in North American.[77] African Americans may have an intestinal resistance to the actions of $1,25OHD_3$.[78,79]

MMP enzymes can degrade all components of the pulmonary extracellular matrix. *M tuberculosis* induces MMP expression in infected human macrophages,[80,81] and these enzymes have been implicated in the pulmonary cavitation observed in TB patients. In terms of treatment, $1,25OHD_3$ has been reported to inhibit MMP secretion by human monocytes[82–84] and enhances the level of its inhibitors (tissue inhibitor of metalloproteinase-1) in TB.[84]

Vitamin D-induced monocyte resistance to *M tuberculosis* is regulated by PI 3-K (class I phosphatidylinositol 3-kinase) and is mediated by NADPH-dependent phagocyte oxidase.[85] PI 3-K is a multifunctional signaling molecule that has been implicated in a wide range of cellular processes.[86]

In vitamin D-deficient mice, macrophages function abnormally, but these defects can be corrected by $1,25OHD_3$ restoration *in vitro* and *in vivo*.[87] *In vitro*, $1,25OHD_3$ stimulates macrophage differentiation and hydrogen peroxide (H_2O_2) production[88–92] and inhibits bacterial growth in macrophages infected with *M tuberculosis*.[91,92] $1,25OHD_3$ enhances mycobacterial killing by increasing nitric oxide production, a potent antimicrobial mechanism in activated macrophages. Furthermore, $1,25OHD_3$ may limit host damage by decreasing *M bovis*-induced gamma interferon (IFN-γ) production.[93] TB-infected mice deficient in nitric oxide synthetase 2 develop severe necrotizing pyogranulomatous inflammation of the lungs with heavy TB bacilli colonization and systematic dissemination.[94] $1,25OHD_3$ reduces the growth of *M tuberculosis* in cultured human peripheral blood mononuclear cells by 75%.[95] Furthermore, lymphocyte apoptosis is diminished by the addition of $1,25OHD_3$ to cultured TB-infected mononuclear cells.[93] *In vitro* and *in vivo*, IFN-γ is a potent enhancer of mononuclear phagocyte H_2O_2 secretion in murine cells; however, no additive or synergistic effects of $1,25OHD_3$ and IFN-γ have been shown with regard to H_2O_2 production.[96]

The presence of the VDR in peripheral blood monocytes and activated T cells[7–97] provides evidence for relationship between vitamin D and the immune system. Vitamin D has a significant role in TB, along with its associated immune-regulatory activities. $1,25OHD_3$ up-regulates innate immunity via phagocytosis by monocyte/macrophage populations and down-regulates acquired immunity by inhibiting major histocompatibility complex class II antigen expression by antigen-presenting cells.[98] In mice, TB-infected lungs have been shown to produce high levels of tumor necrosis factor α, IFN-γ and IL-6 mRNA.[99] $1,25OHD_3$ differentially modulates the production of cytokines in response to *M tuberculosis* antigens predominantly by suppressing the production of IL-12 and IFN-γ.[100] IL-12 is a key cytokine required for T_H1 development,[101] a prominent feature in TB lesions.[102]

Pyrazinamide (PZA) is an important TB drug and plays a key role in shortening TB therapy from 9 to 12 months to 6 months.[103] Wade and Yang reported that UV light enhanced the activity of PZA against *M tuberculosis in vitro*[103] and suggested that UV light can generate free radicals that cause damage to macromolecules—such as DNA—and affect membrane integrity. $1,25OHD_3$ has been reported to have a synergistic effect with PZA to kill tubercle bacilli in cultured human macrophages.[104]

A modest but significant abnormality in the regulation of circulating $1,25OHD_3$ has been observed in normocalcemic TB patients.[105] Increased $1,25OHD_3$ levels have been reported in TB patients, and, consequently, hypercalcemia has also been observed in TB patients, which could lead to down-regulation of VDR expression.[105,106] This $1,25OHD_3$ level is produced by bronchoalveolar macrophages and T lymphocytes in the blood in TB patients.[107] Selvaraj et al[108] suggested that high plasma $1,25OHD_3$ levels in TB patients might be because of up-regulated expression of *CYP27b*, which is involved in the conversion of $25OHD_3$ to $1,25OHD_3$. Previous studies have reported that *M tuberculosis* lipopeptides stimulate the up-regulation of *CYP27b1* through dendritic cells and monocytes.[70] Adams et al[109] suggested that diminished availability of the $25OHD_3$ substrate, available for *CYP27b1* compromises host's responses to *M tuberculosis*. The addition of $1,25OHD_3$ can lead to increased serum $25OHD_3$ levels, normal serum calcium levels[108] and increased expression of cathelicidin, which may enhance immunity against TB.[108] On the other hand, $1,25OHD_3$ does not result in a concomitant increase in 24-hydroxylase enzyme activity.[110] Chloroquine has been used to control hypercalcemia in granulomatous patients,[111] and chloroquine therapy has been associated with a significant reduction in the serum levels of $1,25OHD_3$ and urinary calcium, perhaps via inhibition of the conversion of $25OHD_3$ to $1,25OH_2D_3$. However, a combination of three drugs (chloroquine, $1,25OHD_3$ and PZA) kills TB faster than the combination of $1,25OHD_3$ and PZA in cultured human macrophages.[112]

Ketoconazole has been reported to decrease the serum levels of ionized calcium and $1,25OHD_3$ in TB-associated hypercalcemia[113] and has also been shown to act against *M tuberculosis in vitro* and in a mouse model.[114]

CONCLUSION

The relationship between vitamin D and TB has been discussed previously, and vitamin D may have a role in TB treatment. Vitamin D supplementation may be beneficial to individuals with insufficient vitamin D levels. Additional studies into the role of vitamin D in TB treatment are warranted.

REFERENCES

1. **Lemire JM, Archer DC.** 1,25-Dihydroxyvitamin D_3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. J Clin Invest 1991;87:1103–7.
2. **Hayes CE, Cantorna MT, DeLuca HF.** Vitamin D and multiple sclerosis. Proc Soc Exp Biol Med 1997;216:21–7.
3. **Cantorna MT, Hayes CE, DeLuca HF.** 1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. J Nutr 1998;128:68–72.
4. **Luong K, Nguyen LT, Nguyen DN.** The role of vitamin in protecting type 1 diabetes mellitus. Diabetes Metab Res Rev 2005;21:338–46.
5. **Luong KV, Nguyen LT.** Vitamin D and cardiovascular disease. Curr Med Chem 2006;13:2443–7.
6. **Luong K, Nguyen LT.** The beneficial role of vitamin D and its analogs in cancer treatment and prevention. Crit Rev Oncol Hematol 2010;73:192–201.
7. **Bhalla AK, Amento EP, Clemens TL, et al.** Specific high-affinity receptors for 1,25-dihydroxyvitamin D_3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J Clin Endocrinol Metab 1983;57:1308–10.
8. **Provvedini DM, Tsoukas CD, Deftos LJ, et al.** 1,25-dihydroxyvitamin D_3 receptors in human leukocytes. Science 1983;221:1181–3.
9. **Overbergh L, Decallonne B, Valckx D, et al.** Identification and immune regulation of 25-hydroxyvitamin D-1-α-hydroxylase in murine macrophages. Clin Exp Immunol 2000;120:139–46.
10. **Laaksi I, Ruohola JP, Tuohimaa P, et al.** An association of serum vitamin D concentrations $<$40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr 2007;86:714–7.
11. **Rook GA.** Role of activated macrophages in the immunopathology of tuberculosis. Br Med Bull 1988;44:611–23.
12. **Lowrie DB, Andrew PW.** Macrophage antimycobacterial mechanisms. Br Med Bull 1988;44:624–34.
13. **Good RA.** Nutrition and immunity. J Clin Immunol 1981;1:3–11.
14. **Davies PD.** A possible link between vitamin D deficiency and impaired host defence to *Mycobacterium tuberculosis*. Tubercle 1985;66:301–6.
15. **Autier P, Gandini S.** Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007;167:1730–7.
16. **Bellamy R, Ruwende C, Corrah T, et al.** Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the Vitamin D receptor gene. J Infect Dis 1999;179:721–4.
17. **Wilbur AK, Kubatko LS, Hurtado AM, et al.** Vitamin D receptor gene polymorphisms and susceptibility *M. tuberculosis* in native Paraguayans. Tuberculosis 2007;13:396–7.
18. **Chen XR, Feng YL, Ma Y, et al.** Study on the association of two polymorphisms of the vitamin D receptor (*VDR*) gene with the susceptibility to pulmonary tuberculosis (PTB) in Chinese Tibetans. [Article in Chinese.] Sichuan Da Xue Xue Bao Yi Xue Ban 2006;37:847–51.
19. **Roth DE, Soto G, Arenas F, et al.** Association between vitamin D receptor gene polymorphisms and response to treatment of pulmonary tuberculosis. J Infect Dis 2004;190:920–7.
20. **Friedland JS, Shaw TC, Price NM, et al.** Differential regulation of MMP-1/9 and TIMP-1 secretion in human monocytic cells in response to *Mycobacterium tuberculosis*. Matrix Biol 2002;21:103–10.
21. **Timms PM, Mannan N, Hitman GA, et al.** Circulating MMP9, vitamin D and variation in the TIMP-1 response with *VDR* genotype: mechanisms for inflammatory damage in chronic disorders? QJM 2002;95:787–96.
22. **Dean DD, Schwartz Z, Schmitz J, et al.** Vitamin D regulation of metalloproteinase activity in matrix vesicles. Connect Tissue Res 1996;35:331–6.
23. **Wilkinson RJ, Llewelyn M, Toossi Z, et al.** Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet 2000;355:618–21.
24. **Selvaraj P, Chandra G, Kurian SM, et al.** Association of vitamin D receptor gene variants of BsmI, ApaI and Fok1 polymorphisms with susceptibility or resistance to pulmonary tuberculosis. Curr Sci 2003;84:1564–8.
25. **Selvaraj P, Narayanan PR, Reetha AM.** Association of vitamin D receptor genotype with susceptibility to pulmonary tuberculosis in female patients & resistance in female contacts. Indian J Med Res 2000;111:172–9.
26. **Babb C, van der Merwe L, Beyers N, et al.** Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients. Tuberculosis (Edinb) 2007;87:295–302.
27. **Liu W, Cao WC, Zhang CY, et al.** VDR and NRAMP1 gene polymorphisms in susceptibility to pulmonary tuberculosis among the Chinese Han population: a case-control study. Int J Tuberc Lung Dis 2004;8:428–34.
28. **Merza M, Farnia P, Anoosheh S, et al.** The NRAMPI, VDR and TNF-alpha gene polymorphisms in Iranian tuberculosis patients: the study on host susceptibility. Braz J Infect Dis 2009;13:252–6.
29. **Forbes JR, Gros P.** Divalent-metal transport by NRAMP proteins at the interface of host-pathogen interactions. Trends Microbiol 2001;9:397–403.
30. **Delgado JC, Baena A, Thim S, et al.** Ethnic-specific genetic associations with pulmonary tuberculosis. J Infect Dis 2002;186:1463–8.
31. **Søborg C, Andersen AB, Madsen HO, et al.** Natural resistance-associated macrophage protein 1 polymorphisms are associated with microscopy-positive tuberculosis. J Infect Dis 2002;186:517–21.
32. **Liaw YS, Tsai-Wu JJ, Wu CH, et al.** Variations in the NRAMP1 gene and susceptibility of tuberculosis in Taiwanese. Int J Tuberc Lung Dis 2002;6:454–60.
33. **El Baghdadi J, Remus N, Benslimane A, et al.** Variants of the human NRAMP1 gene and susceptibility to tuberculosis in Morocco. Int J Tuberc Lung Dis 2003;7:599–602.
34. **Ben-Ali M, Barbouche MR, Bousnina S, et al.** Toll-like receptor 2 Arg677Trp polymorphism is associated with susceptibility to tuberculosis in Tunisian patients. Clin Diagn Lab Immunol 2004;11:625–6.
35. **Motsinger-Reif AA, Antas PR, Oki NO, et al.** Polymorphisms in IL-1beta, vitamin D receptor Fok1, and Toll-like receptor 2 are associated with extrapulmonary tuberculosis. BMC Med Genet 2010;11:37.
36. **Lewis SJ, Baker G, Davey Smith G.** Meta-analysis of vitamin D receptor polymorphisms and pulmonary tuberculosis risk. Int J Tuberc Lung Dis 2005;9:1174–7.
37. **Bornman L, Campbell SJ, Fielding K, et al.** Vitamin D receptor polymorphisms and susceptibility to tuberculosis in West Africa: a case-control and family study. J Infect Dis 2004;190:1631–41.
38. **Gao L, Tao Y, Zhang L, et al.** Vitamin D receptor genetic polymor-

phisms and tuberculosis: updated systematic review and meta-analysis. Int J Tuberc Lung Dis 2010;14:15–23.

39. **Vidyarani M, Selvaraj P, Raghavan S, et al.** Regulatory role of 1, 25-dihydroxyvitamin D_3 and vitamin D receptor gene variants on intracellular granzyme A expression in pulmonary tuberculosis. Exp Mol Pathol 2009;86:69–73.
40. **Lauridsen AL, Vestergaard P, Hermann AP, et al.** Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. Calcif Tissue Int 2005;77:15–22.
41. **Abbas S, Linseisen J, Slanger T, et al.** The Gc2 allele of the vitamin D binding protein is associated with a decreased postmenopausal breast cancer risk, independent of the vitamin D status. Cancer Epidemiol Biomarkers Prev 2008;17:1339–43.
42. **Charpy J, Dowling GB.** Vitamin D in cutaneous tuberculosis. Lancet 1947;13:2:398.
43. **Pattison CE.** Vitamin D and the calcification of bone in tuberculosis. British Med J 1929:419–20.
44. **Williams CJB.** Cod liver oil in phthisis. London J Med 1949;1:1–18.
45. **Warren P.** The evolution of the sanatorium: the first half-century, 1854–1904. Can Bull Med Hist 2006;23:457–76.
46. **Yesudian PD, Berry JL, Wiles S, et al.** The effect of ultraviolet B-induced vitamin D levels on host resistance to *Mycobacterium tuberculosis*: a pilot study in immigrant Asian adults living in the United Kingdom. Photodermatol Photoimmunol Photomed 2008;24: 97–8.
47. **Strachan DP, Powell KJ, Thaker A, et al.** Vegetarian diet as a risk factor for tuberculosis in immigrant south London Asians. Thorax 1995;50:175–80.
48. **Davies PDO, Brown RC, Woodhead JS.** Serum concentrations of vitamin D metabolites in untreated tuberculosis. Thorax 1985;40: 187–90.
49. **Sita-Lumsden, Lapthorn G, Swaminathan R, et al.** Reactivation of tuberculosis and vitamin D deficiency: the contribution of diet and exposure to sunlight. Thorax 2009;62:1003–7.
50. **Gibney KB, MacGregor L, Leder K, et al.** Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. Clin Infect Dis 2008;46:443–6.
51. **Talat N, Perry S, Parsonnet J, et al.** Vitamin d deficiency and tuberculosis progression. Emerg Infect Dis 2010;16:853–5.
52. **Cuss FM, Carmichael DJ, Linington A, et al.** Tuberculosis in renal failure: a high incidence in patients born in the Third World. Clin Nephrol 1986;25:129–33.
53. **Hsu CH, Patel SR.** Uremic toxins and vitamin D metabolism. Kidney Int Suppl 1997;62:S65–8.
54. **Nnoaham KE, Clarke A.** Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol 2008; 37:113–9.
55. **Rockett KA, Brookes R, Udalova I, et al.** 1,25-dihydroxyvitamin D_3 induces nitric oxide synthase and suppresses growth of *Mycobacterium tuberculosis* in a human macrophage-like cell line. Infect Immun 1998;66:5314–21.
56. **Crowle AJ, Ross EJ, May MH.** Inhibition by $1,25(OH)_2$-vitamin D_3 of the multiplication of virulent tubercle bacilli in cultured human macrophages. Infect Immun 1987;55:2945–50.
57. **Brincourt J.** Liquefying effect on suppurations of an oral dose of calciferol. [Article in French.] Presse Med 1969;77:467–70.
58. **Range N, Changalucha J, Krarup H, et al.** The effect of multivitamin/mineral supplementation on mortality during treatment of pulmonary tuberculosis: a randomised two-by-two factorial trial in Mwanza, Tanzania. Br J Nutr 2006;95:762–70.
59. **Morcos MM, Gabr AA, Samuel S, et al.** Vitamin D administration to tuberculous children and its value. Boll Chim Farm 1998; 137:157–64.
60. **Nursyam EW, Amin Z, Rumende CM.** The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. Acta Med Indones 2006;38:3–5.
61. **Yamshchikov AV, Oladele A, Leonard MK Jr, et al.** Vitamin D as adjunctive therapy in refractory pulmonary tuberculosis: a case report. South Med J 2009;102:649–52.
62. **Wejse C, Gomes VF, Rabna P, et al.** Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2009;179:843–50.
63. **Ferrari G, Langen H, Naito M, et al.** A Coat protein on phagosomes involved in the intracellular survival of mycobacteria. Cell 199;97: 435–47.
64. **Anand PK, Kaul D.** Vitamin D_3-dependent pathway regulates TACO gene transcription. Biochem Biophys Res Commun 2003;310:876–7.
65. **Anand PK, Kaul D, Sharma M.** Synergistic action of vitamin D and retinoic acid restricts invasion of macrophages by pathogenic mycobacteria. J Microbiol Immunol Infect 2008;41:17–25.
66. **Hmama Z, Sendide K, Talal A, et al.** Quantitative analysis of phagolysosome fusion in intact cells: inhibition by mycobacterial lipoarabinomannan and rescue by an 1α,25-dihydroxyvitamin D_3-phosphoinositide 3-kinase pathway. J Cell Sci 200;117:2131–40.
67. **Thoma-Uszynski S, Stenger S, Takeuchi O, et al.** Induction of direct antimicrobial activity through mammalian toll-like receptors. Science 2001;291:1544–7.
68. **Liu PT, Stenger S, Li H, et al.** Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311: 1770–3.
69. **Yim S, Dhawan P, Ragunath C, et al.** Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D_3. J Cyst Fibros 2007;6:403–10.
70. **Rivas-Santiago B, Hernandez-Pando R, Carranza C, et al.** Expression of cathelicidin LL-37 during *Mycobacterium tuberculosis* infection in human alveolar macrophages, monocytes, neutrophils, and epithelial cells. Infect Immun 2008;76:935–41.
71. **Liu PT, Stenger S, Tang DH, et al.** Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. J Immunol 2007;179: 2060–3.
72. **Wang TT, Nestel FP, Bourdeau V, et al.** Cutting edge: 1,25-dihydroxyvitamin D_3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004;173:2909–12.
73. **Liu PT, Schenk M, Walker VP, et al.** Convergence of IL-1beta and VDR activation pathways in human TLR2/1-induced antimicrobial responses. PLoS One 2009;4:e5810.
74. **Yuk JM, Shin DM, Lee HM, et al.** Vitamin D_3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe 2009;6:231–43.
75. **O'Donnell MR, Chamblee S, von Reyn CF, et al.** Racial disparities in primary and reactivation tuberculosis in a rural community in the southeastern United States. Int J Tuberc Lung Dis 2010;14:733–40.
76. **Crowle AJ, Elkins N.** Relative permissiveness of macrophages from black and white people for virulent tubercle bacilli. Infect Immun 1990;58:632–8.
77. **Harris SS.** Vitamin D and African Americans. J Nutr 2006;136: 1129–9.
78. **Dawson-Hughes B, Harris S, Kramich C, et al.** Calcium retention and hormone levels in black and white women on high- and low-calcium diets. J Bone Miner Res 1993;8:779–87.
79. **Dawson-Hughes B, Harris S, Finneran S, et al.** Calcium absorption

responses to calcitriol in black and white premenopausal women. J Clin Endocrinol Metab 1995;80:3068–72.

80. **Elkington PT, Nuttall RK, Boyle JJ, et al.** *Mycobacterium tuberculosis*, but not vaccine BCG, specifically upregulates matrix metalloproteinase-1. Am J Respir Crit Care Med 2005;172:1596–604.
81. **Chang JC, Wysocki A, Tchou-Wong KM, et al.** Effect of *Mycobacterium tuberculosis* and its components on macrophages and the release of matrix metalloproteinases. Thorax 1996;51:306–11.
82. **Elkington PT, Emerson JE, Lopez-Pascua LD, et al.** *Mycobacterium tuberculosis* up-regulates matrix metalloproteinase-1 secretion from human airway epithelial cells via a p38 MAPK switch. J Immunol 2005;175:5333–40.
83. **Coussens A, Timms PM, Boucher BJ, et al.** 1alpha,25-dihydroxyvitamin D_3 inhibits matrix metalloproteinases induced by *Mycobacterium tuberculosis* infection. Immunology 2009;127:539–48.
84. **Anand SP, Selvaraj P.** Effect of 1,25 dihydroxyvitamin D_3 on matrix metalloproteinases MMP-7, MMP-9 and the inhibitor TIMP-1in pulmonary tuberculosis. Clin Immunol 2009;133:126–31.
85. **Sly LM, Lopez M, Nauseef WM, et al.** 1α,25-Dihydroxyvitamin D_3-induced monocyte antimycobacterial activity is regulated by phosphatidylinositol 3-kinase and mediated by the NADPH-dependent phagocyte oxidase. J Biol Chem 2001;276:35482–93.
86. **Fry MJ.** Structure, regulation and function of phosphoinositide 3-kinases. Biochim Biophys Acta 1994;1226:237–68.
87. **Bar-Shavit ZD, Noff D, Edelstein S, et al.** 1,25-dihydroxyvitamin D_3 and the regulation of macrophage function. Cacif Tissue Int 1981;33:673–6.
88. **Abe E, Shiina Y, Miyaura C, et al.** Activation and fusion induced by 1 alpha, 25-dihydroxyvitamin D_3 and their relation in alveolar macrophages. Proc Natl Acad Sci U S A 1984;81:7112–6.
89. **Amento EP, Bhalla AK, Kurnick JT, et al.** 1 alpha,25-dihydroxyvitamin D_3 induces maturation of the human monocyte cell line U937, and, in association with a factor from human T lymphocytes, augments production of the monokine, mononuclear cell factor. J Clin Invest 1984;73:731–9.
90. **Cohen MS, Mesler DE, Snipes RG, et al.** 1,25-Dihydroxyvitamin D_3 activates secretion of hydrogen peroxide by human monocytes. J Immunol 1986;136:1049–53.
91. **Gluck WL, Weinberg JB.** 1α,25 Dihydroxyvitamin D_3 and mononuclear phagocytes: enhancement of mouse macrophage and human monocyte hydrogen peroxide production without alteration of tumor cytolysis. J Leukoc Biol 1987;42:498–503.
92. **Rook GA, Steele J, Fraher L, et al.** Vitamin D_3, gamma interferon, and control of proliferation of *Mycobacterium tuberculosis* by human monocytes. Immunology 1986;57:159–63.
93. **Crowle AJ, Ross EJ.** Inhibition by retinoic acid of multiplication of virulent tubercle bacilli in cultured human macrophages. Infect Immun 1989;57:840–4.
94. **Waters WR, Palmer MV, Nonnecke BJ, et al.** Mycobacterium bovis infection of vitamin D-deficient NOS2-/- mice. Microb Pathog 2004;36:11–7.
95. **Waters WR, Nonnecke BJ, Rahner TE, et al.** Modulation of Mycobacterium bovis-specific responses of bovine peripheral blood mononuclear cells by 1,25-dihydroxyvitamin D_3. Clin Diagn Lab Immunol 2001;8:1204–12.
96. **Martineau AR, Wilkinson KA, Newton SM, et al.** IFN-gamma- and TNF-independent vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. J Immunol 2007;178:7190–8.
97. **Murray HW, Spitalny GL, Nathan CF.** Activation of mouse peritoneal macrophages in vitro and in vivo by interferon-gamma. J Immunol 1985;134:1619–22.
98. **Tokuda N, Levy RB.** 1,25-dihydroxyvitamin D_3 stimulates phagocytosis but suppresses HLA-DR and CD13 antigen expression in human mononuclear phagocytes. Proc Soc Exp Biol Med 1996;211:244–50.
99. **Chacón-Salinas R, Serafín-López J, Ramos-Payán R, et al.** Differential pattern of cytokine expression by macrophages infected in vitro with different *Mycobacterium tuberculosis* genotypes. Clin Exp Immunol 2005;140:443–9.
100. **Vidyarani M, Selvaraj P, Jawahar MS, et al.** 1, 25 Dihydroxyvitamin D_3 modulated cytokine response in pulmonary tuberculosis. Cytokine 2007;40:128–34.
101. **O'Garra A.** Cytokines induce the development of functionally heterogeneous T helper cell subsets. Immunity 1998;8:275–83.
102. **Lin Y, Zhang M, Hofman FM, et al.** Absence of a prominent Th2 cytokine response in human tuberculosis. Infect Immun 1996;64:1351–6.
103. **Wade MM, Zhang Y.** Effects of weak acids, UV and proton motive force inhibitors on pyrazinamide activity against *Mycobacterium tuberculosis* in vitro. J Antimicrob Chemother 2006;58:936–41.
104. **Crowle AJ, Salfinger M, May MH.** 1,25$(OH)_2$-vitamin D_3 synergizes with pyrazinamide to kill tubercle bacilli in cultured human macrophages. Am Rev Respir Dis 1989;139:549–52.
105. **Sharma OP.** Hypercalcemia in granulomatous disorders: a clinical review. Curr Opin Pulm Med 2000;6:442–7.
106. **Cadranel J, Garabedian M, Milleron B, et al.** 1,25$(OH)_2D_3$ production by T lymphocytes and alveolar macrophages recovered by lavage from normocalcemic patients with tuberculosis. J Clin Invest 1990;85:1588–93.
107. **Epstein S, Stern PH, Bell NH, et al.** Evidence for abnormal regulation of circulating 1 alpha, 25-dihydroxyvitamin D_3 in patients with pulmonary tuberculosis and normal calcium metabolism. Calcif Tissue Int 1984;36:541–4.
108. **Selvaraj P, Prabhu Anand S, Harishankar M, et al.** Plasma 1,25 dihydroxy vitamin D_3 level and expression of vitamin d receptor and cathelicidin in pulmonary tuberculosis. J Clin Immunol 2009;29:470–8.
109. **Adams JS, Chen H, Chun R, et al.** Substrate and enzyme trafficking as a means of regulating 1,25-dihydroxyvitamin D synthesis and action: the human innate immune response. J Bone Miner Res 2007;22(suppl 2):V20–4.
110. **Ren S, Nguyen L, Wu S, et al.** Alternative splicing of vitamin D-24-hydroxylase: a novel mechanism for the regulation of extrarenal 1,25-dihydroxyvitamin D synthesis. J Biol Chem 2005;280:20604–11.
111. **O'Leary TJ, Jones G, Yip A, et al.** The effects of chloroquine on serum 1,25-dihydroxyvitamin D_3 and calcium metabolism in sarcoidosis. N Engl J Med 1986;315:727–30.
112. **Crowle AJ, May MH.** Inhibition of tubercle bacilli in cultured human macrophages by chloroquine used alone and in combination with streptomycin, isoniazid, pyrazinamide, and two metabolites of vitamin D_3. Antimicrob Agents Chemother 1990;34:2217–22.
113. **Saggese G, Bertelloni S, Baroncelli GI, et al.** Ketoconazole decreases the serum ionized calcium and 1,25-dihydroxyvitamin D levels in tuberculosis-associated hypercalcemia. Am J Dis Child 1993;147:270–3.
114. **Byrne ST, Denkin SM, Gu P, et al.** Activity of ketoconazole against *Mycobacterium tuberculosis* in vitro and in the mouse model. J Med Microbiol 2007;56(Pt 8):1047–51.