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Vitamin D, the immune system and asthma

Nancy E Lange, MD, MPH,
Channing Laboratory, Division of Pulmonary and Critical Care Medicine, Brigham & Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA Tel.: +1 617 525 0874 Fax: +1 617 525 0958 nlange@partners.org

Augusto Litonjua, MD, MPH,
Channing Laboratory, Division of Pulmonary and Critical Care Medicine, Brigham & Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA Tel.: +1 617 525 0874 Fax: +1 617 525 0958 reaal@channing.harvard.edu

Catherine M Hawrylowicz, PhD, and
King's College London, Department of Asthma Allergy and Respiratory Science, Guy's Hospital, London, SE1 9RT, UK Tel.: +44 020 7188 0598 Fax: +44 020 7403 8640 catherine.hawrylowicz@kcl.ac.uk

Scott Weiss, MD
Channing Laboratory, Division of Pulmonary and Critical Care Medicine, Brigham & Women's Hospital, 181 Longwood Avenue, Boston, MA 02115 USA Tel.: +1 617 525 0874 Fax: +1 617 525 0958 scott.weiss@channing.harvard.edu

Abstract

The effects of vitamin D on bone metabolism and calcium homeostasis have long been recognized. Emerging evidence has implicated vitamin D as a critical regulator of immunity, playing a role in both the innate and cell-mediated immune systems. Vitamin D deficiency has been found to be associated with several immune-mediated diseases, susceptibility to infection and cancer. Recently, there has been increasing interest in the possible link between vitamin D and asthma. Further elucidation of the role of vitamin D in lung development and immune system function may hold profound implications for the prevention and treatment of asthma.

Keywords

asthma; autoimmune disease; immune system regulation; T-regulatory cell; vitamin D; vitamin D deficiency

The role of vitamin D in the regulation of calcium and bone metabolism is well established. Recently, newer physiologic functions for vitamin D have been identified. Epidemiologic and genetic studies as well as research using animal models suggest vitamin D plays a vital and complex role in immune system function and regulation. Vitamin D insufficiency has been linked with susceptibility to infection, particularly respiratory infections [1–5], as well as to the development of a variety of cancers [6–11] and autoimmune diseases [12–16].

†Author for correspondence Channing Laboratory, Division of Pulmonary and Critical Care Medicine, Brigham & Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA Tel.: +1 617 525 0874 Fax: +1 617 525 0958 scott.weiss@channing.harvard.edu.

Asthma is one of the most common chronic diseases worldwide and has been increasing in prevalence over the last few decades [17,18]. Its exact cause remains unknown and likely has its origins in complex interactions among multiple genetic and environmental factors. Common risk factors for both asthma and vitamin D deficiency, such as an urbanized, westernized lifestyle [18–20], race/darker skin pigmentation [21–23] and obesity [24–26], along with increasing evidence of the immuno modulatory effects of vitamin D, have led to a hypo thesized link between the rising asthma prevalence and low vitamin D. This article will summarize some of the emerging evidence on the complex role of vitamin D in the immune system relevant to asthma, and provide an overview of investigations thus far linking vitamin D and asthma.

Vitamin D physiology

Vitamin D is an essential nutrient that humans obtain primarily through exposure to sunlight, and secondarily through diet and dietary supplements. Solar ultraviolet (UV) B (UVB) radiation converts 7-dehydrocholesterol in the skin to previtamin D_3 and subsequently to vitamin D_3. The ability to form this prohormone is influenced by skin pigmentation, sun protection, latitude, age, amount of UV radiation exposure and coverage by clothing, any of which may significantly affect vitamin D levels. In the diet, vitamin D is found mostly in oily fish (e.g., salmon and mackerel), and in fortified grain and dairy products. Vitamin D from the skin and diet is hydroxylated in the liver to 25-hydroxyvitamin D and stored. Under tight regulation by the parathyroid hormone, 25-hydroxyvitamin D is hydroxylated by 1-αhydroxylase in the kidney to the biologically active form, 1,25-dihydroxyvitamin D (1,25 $[OH]_2D_3$), to maintain calcium–phosphate homeostasis. More recently, hydroxylation to 1,25-dihydroxyvitamin D has also been noted to occur at extra-renal sites, including cells of the immune system [27]. The vitamin D receptor (VDR) is part of the steroid hormone nuclear receptor family and acts to regulate gene transcription.

A patient's vitamin D status is determined by measuring 25-hydroxyvitamin D, which is the major circulating form. It has a half-life of 2 weeks in the circulation, and levels correlate with secondary hyperparathyroidism, osteomalacia and rickets [28]. 1,25-dihydroxyvitamin D levels may be normal or even elevated in a vitamin D-deficient state, and are thus not reliable in determining a patient's vitamin D status [29]. Most experts define vitamin D deficiency as a 25-hydroxyvitamin D level (hereafter referred to as ‘vitamin D level’) below 20 ng/ml (50 nmol/l), although there is no consensus as to what level is ideal [30]. Many vitamin D experts would argue that levels of 30–40 ng/ml (75–100 nmol/l) [31,32] or even greater [33] are needed for nonskeletal outcomes, although further research is needed to confirm this.

Low vitamin D levels have been documented in many different populations around the world, including those in latitudes where sun exposure would be presumed to be adequate such as Saudi Arabia [34,35], India [36], Israel [37], Costa Rica [38] and areas of southern and southeastern USA [39,40], among others [28]. At higher latitudes (i.e., >35°), very little vitamin D is produced in the skin during the late fall and winter months due to minimal UVB radiation exposure at this time of year [28,41]. In one study in Boston (MA, USA; latitude 42°), 42% of African–American and Hispanic children had vitamin D levels less than 20 ng/ml [42]. Another study in Boston showed 57% of in-patients in a general medical ward to be vitamin D deficient (levels ≤15ng/ml) [43]. Increased time spent indoors [44], wider use of sunscreen and skin coverage with clothing are all factors contributing to low vitamin D levels. Diseases traditionally associated with vitamin D deficiency include rickets and osteomalacia. Increasing data associate low vitamin D levels with other diseases such as autoimmune diseases [12–16], many cancers [6–10] and asthma (Figure 1).

Vitamin D & the immune system

Increasing evidence implicates a complex role for vitamin D in the regulation of immune responses. Multiple immune cell types express VDRs, including activated T and B cells, macrophages [45] and dendritic cells [46]. Expression of 1α-hydroxylase, the enzyme that catalyzes the synthesis of active 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D, is expressed by cells at extra-renal sites, including epithelial cells, keratinocytes, activated macrophages and dendritic cells [27]. This not only highlights the capacity for extra-renal synthesis of the active form of vitamin D, but also the capacity to modulate innate [47] and adaptive [48] immune function at these sites.

Vitamin D inhibits the function of T lymphocytes both directly and via effects on antigen-presenting cells (APCs). It has potent antiproliferative effects on $CD4^+$ T cells [49]. Essentially all published studies using both human and murine models report inhibition of Th1-associated cytokine production [46,49–52]. More recently, vitamin D has been reported to inhibit IL-17 production [53,54]. IL-17 is an inflammatory cytokine important for defense against extracellular bacteria, but is also involved in autoimmune and allergic diseases, including asthma [55].

The effects of vitamin D on Th2 responses are more complex. Most reviews simply state that vitamin D promotes Th2 responses; however, a closer look at the literature reveals reports of both the inhibition and enhancement of Th2 responses. Th2 cells play a central role in the pathogenesis of asthma, producing cytokines such as IL-4, IL-5 and IL-13, and inducing the production of IgE by B cells, as well as the growth and differentiation of relevant effector cells, namely mast cells and eosinophils [56]. In experimental models, Th2 cells from animals primed with antigen can induce experimental asthma, including airway hyper-responsiveness and elevated eosinophils in naive animals [57]. In culture, vitamin D has been reported to enhance IL-4 and IL-13 synthesis by murine T cells in one study [58], but to inhibit IL-4 when added from the onset of differentiation in a second study [59]. Notably, both studies used naive T cells.

There is a general consensus that vitamin D alleviates autoimmune disease in animal models [46], which is associated with the inhibition of IFN-γ production. Variable effects on Th2 cytokine production are reported in these models [60,61]. In models of allergic airway disease, the data are also conflicting. In one study of murine asthma, the administration of 1,25-dihydroxyvitamin D was found to inhibit airway inflammation, decrease levels of IL-4 in bronchoalveolar lavage fluid and decrease T-cell migration, inhibiting the inflammatory response [62]. In another study, mice irradiated with a single erythemal dose of UVB light prior to sensitization with antigen, probably increasing vitamin D levels, had less airway hyper-responsiveness and inflammation than mice who were not [63]. However, in a different study, vitamin D enhanced Th2 responses (IL-4 and IL-13) when given early during immunization, but inhibited both IL-5 and airway eosinophilia when administered later [64]. Additional evidence comes from VDR knock-out mice, which do not develop experimental asthma [65]. Although these mice do have the ability to prime and activate immune cells and have elevated levels of circulating mediators associated with experimental asthma (e.g., IL-5, IL-13 and IgE), it appears that VDR expression is necessary for lung development and inflammation to occur [57]. In this same experiment, vitamin D-deficient mice did not have the same phenotype as the VDR knockout mice [57]. Such results point to the complexity of the role of vitamin D in the inflammatory responses involved in the pathogenesis of asthma, as well as the importance of the timing and dose of exposure.

In studies with human cells, vitamin D inhibits IFN-γ synthesis [52,66–68]. At least two reports describe the capacity of vitamin D to enhance [66,69] and to inhibit Th2 responses in culture;

of the latter, one was in blood from adults [68] and the second in cord blood [70]. The reason for these differences is unclear, but responsiveness to vitamin D has been suggested to differ according to the stage of differentiation and activation status of $CD4^+$ T cells [49]. Differential dose-dependent effects may also exist [66,68]. Importantly, studies looking at Th2 cytokines in peripheral blood post vitamin D supplementation [71] or calcitriol ingestion [68] show no evidence of Th2 enhancement, although the individuals were not challenged with antigen at the same time.

Several laboratories have described the capacity of vitamin D to promote regulatory T cells (Tregs) [72,73]. Tregs play an important role in the control of the immune response and inhibit Th2 responses, as well as airway inflammation and airway hyper-responsiveness [74,75], which may be the key to the potential role of vitamin D in asthma. Vitamin D acts on dendritic cells, which play a central role in the activation of T-cell-mediated immune responses to induce a tolerogenic phenotype associated with decreased expression of MHC class II and costimulatory ligands, decreased secretion of the immunostimulatory cytokine IL-12 [50] and increased IL-10, an anti-inflammatory cytokine with potent inhibitory effects on Th1 and Th2 responses [68]. Vitamin D also acts directly on T cells to promote an IL-10-secreting Treg phenotype either alone [68] or in concert with glucocorticoids [76]. In experimental models of allergic airway disease, IL-10 consistently shows anti-inflammatory properties [75,77,78] and in a number of studies also decreased airway hyper-responsiveness [79–84], although a few studies have reported the capacity of IL-10 to increase airway hyper-responsiveness [85,86], possibly via effects on airway smooth muscle [87]. The reasons for this discrepancy in effects on airway hyper-responsiveness (either increased or decreased) have not yet been clarified. In animal models, both oral [73] and topical [88] administration of vitamin D has been demonstrated to enhance Tregs. In an animal model of allergic experimental encephalomyelitis, IL-10 signaling was essential for 1,25-dihydroxyvitamin D-mediated inhibition of the disease [89]. Recently, 1,25-dihydroxyvitamin D was shown to potentiate the beneficial effects of allergen immunotherapy in a mouse model of allergic asthma, which was dependent on IL-10 and TGF-β [90]. Vitamin D also enhances IL-10 synthesis by dendritic cells [46] and B cells [91], while inhibiting antibody production, including IgE.

Human studies demonstrate that vitamin D supplementation is associated with increased serum levels of TGF-β1 [71]. TGF-β is a complex cytokine with a role in the peripheral induction of $Foxp3^+$ Treg immunosuppression, but also in wound healing and repair [92]. In addition, two studies demonstrate that vitamin D increases IL-10 synthesis. In one, calcitriol ingestion increased IL-10 gene expression by T cells assessed directly *ex vivo* pre- and postingestion [68], while a double-blind, randomized, placebo-controlled trial demonstrated that vitamin D supplementation in patients with congestive heart failure improved cytokine profiles by enhancing IL-10 and improving tumor necrosis factor:IL-10 ratios [93]. A recent study shows a nonlinear relationship between vitamin D levels and IgE, with both low (<25 nmol/l) and high (>135 nmol/l) vitamin D levels associated with elevated IgE [94]. Of note, only a small percentage of the total sampled population (58 subjects or ~0.8%) were in the group with the highest vitamin D level.

Vitamin D in fetal lung & immune system development

In the fetus, vitamin D appears to play a role in immune system and lung development. In early gestation, 1,25-dihydroxyvitamin D is synthesized by human decidual cells [95], and may exert autocrine or paracrine effects on the fetus' developing immune system. In addition, in human cord blood cells, vitamin D has been shown to decrease IFN-γ as well as IL-4 and IL-13 [70]. Although these effects seem contradictory to some described previously (i.e., that vitamin D increases IL-4), this re-emphasizes that the timing of vitamin D exposure in 'naive' versus mature T cells may determine the type of response and cytokine profile elicited.

Vitamin D receptors have been found in fetal type II alveolar pneumocytes of rats, and may play a role in lung development, pneumocyte differentiation and surfactant secretion [96–99]. Recent evidence suggests that type II alveolar pneumocytes may play a role in the induction of Tregs and self-tolerance [100]. Lung mechanics studied in rats showed decreased compliance in those born to mothers deprived of vitamin D [101]. The relationship between vitamin D and surfactant production appears to be more complex in studies of human fetal lung tissue [102,103].

Vitamin D in asthma & human disease

Multiple recent studies have noted the effects of vitamin D on the development of immune-related disorders and certain cancers. Epidemiologic studies have shown an association between low vitamin D levels and increased risk of, and/or higher mortality from, colon, breast and lung cancer [6–10]. Low vitamin D levels or intake have also been found to be associated with other immune-mediated diseases including Type I diabetes [13], multiple sclerosis [15, 16], rheumatoid arthritis [14] and inflammatory bowel disease [12]. These are primarily Th1-mediated diseases.

To date, studies that have investigated the link between vitamin D and asthma have been few and have had conflicting results. Initial evidence of a link was found in genetic association studies. The *VDR* maps to chromosome 12, a region of the genome previously found to be linked with asthma [104]. Two different family-based studies in North American subjects reported an association between *VDR* polymorphisms and asthma [104,105]; however, two German studies involving fewer subjects did not show this link [106,107]. Subsequent work by the same German group showed transmission disequilibrium in genes involved in vitamin D metabolism other than the *VDR* gene in children with asthma [108].

Two epidemiologic studies, one in a cohort in the Boston area and another in Aberdeen (Scotland, UK; latitude 57°), have demonstrated an association between pregnant women with lower vitamin D intake and a higher risk of wheeze in their children [109,110]. Each study involved over 1000 mothers and both showed that in mothers who had the highest vitamin D intake, there was a greater than 50% reduction in the risk of recurrent wheeze in their children. These studies assessed intake using food frequency questionnaires; vitamin D levels were not measured. A large cross-sectional study looking at over 14,000 subjects showed a strong correlation between higher serum vitamin D levels and better lung function in the Third National Health and Nutrition Examination Survey (NHANES III) data set [111].

Studies by other groups have shown conflicting data. One study from Finland showed an increased risk for asthma and atopy in adults who were supplemented with vitamin D during childhood [112]. However, this study did not assess vitamin D intake in mothers, or levels in either the subjects or their mothers. Another study from the UK showed an increased risk of eczema at 9 months of age, and asthma at 9 years of age in the children of women with higher vitamin D levels. This study had a large loss to follow-up, with only approximately 30% of the initial cohort retained at the time of analysis for asthma [113]. There continues to be a debate regarding the true relationship of vitamin D with asthma, with some authors believing that the increase in asthma prevalence is due to the fortification of foods with vitamin D [114]. In addition to the development of asthma, others have examined the relationship between vitamin D and asthma severity or response to treatment in those with existing asthma. After demonstrating that the administration of vitamin D in cell culture increases glucocorticoid-induced Treg secretion of the inhibitory cytokine IL-10, Xystrakis *et al*. administered vitamin D to steroid-resistant asthmatics and demonstrated a similar response *in vivo*, which may have treatment implications in this group [115]. Banerjee *et al*. showed that, in addition to immune system effects in asthmatics, vitamin D may also modulate chemokines secreted by airway

smooth muscle cells, an additional pathway by which airway reactivity may be modulated by vitamin D [116]. Similarly, another group looked at the VDR in bronchial smooth muscle cells and showed vitamin D to be a regulator of the expression of over 400 genes, some of which have been implicated in the pathogenesis of asthma [117]. This pathway may be involved in the airway remodeling seen in asthmatics. Our group analyzed a cohort of asthmatic children in Costa Rica and demonstrated that lower vitamin D levels correlated with markers of severity of asthma, including hospitalizations, the use of anti-inflammatory medications and airway hyper-responsiveness [38].

Infection, asthma & vitamin D

Infants who wheeze with viral respiratory infections are more likely to develop asthma. It is unclear whether the infection and/or specific viral agents may be causal. Some studies have shown a link between specific viruses and the subsequent development of asthma or allergy such as respiratory syncytial virus [118,119] or, more recently, rhinovirus [120]. A detailed discussion of the controversy surrounding the connection between early-life respiratory viral infections and wheeze or asthma is beyond the scope of this article but is covered elsewhere in detail [121]. Vitamin D may have an indirect link with the development of asthma through its association with susceptibility to infections [122].

It has been previously observed that children with rickets have an increased risk of respiratory infections [5,123–125]. Vitamin D increases the production of cathelicidin in macrophages [1], which enhances antimicrobial activity, especially in *Mycobacterium tuberculosis*, but also in other infections [126,127]. Airway epithelial cells have been found to express high levels of 1α-hydroxylase, converting 25-hydroxyvitamin D to its active form, leading to the increased production of both cathelicidin and the Toll-like receptor coreceptor CD14, important in the recognition of Gram-positive and -negative bacteria [128]. Vitamin D also enhances the differentiation and recruitment of macrophages, which may lead to an increased ability to fight infection [50]. Not all *in vitro* and animal models show a beneficial effect of vitamin D on the clearance of infections [129].

Low vitamin D levels have been found to be associated with respiratory infections in infants and adults [3–5]; higher levels may be associated with fewer influenza or other viral respiratory infections [130]. Ecological arguments have been made that seasonal vitamin D deficiency (worse in winter months) and influenza epidemics follow similar patterns [131–133]. Recent analysis of over 18,000 subjects in the NHANES III data set showed a strong independent association between low vitamin D levels and recent upper respiratory tract infections after adjusting for multiple demographic and clinical characteristics. This association was even stronger in individuals with asthma or chronic obstructive pulmonary disease [2]. However, a randomized, controlled trial of vitamin D supplementation in adults showed no difference in the incidence or severity of upper respiratory tract infections [134]. Mean 25-hydroxyvitamin D levels in the treatment arm were only 35 ng/ml (88.5 nmol/l), and it is unclear what level is adequate for optimal immune function. In addition, it may take up to 3 months to achieve steady-state levels [135], which was the duration of the study. In general, intervention studies are lacking and have been disappointing thus far [136,137]; more studies are needed to elucidate the clinical relevance of findings from *in vitro* studies of immune function. A recent review on vitamin D, asthma and infections covers this subject in greater detail [138].

Expert commentary & five-year view

The role of vitamin D in the pathogenesis of immune-mediated diseases such as asthma is only beginning to be understood. Several ongoing or planned human clinical trials are aimed at clarifying this link in the next 5 years. These include both prevention trials, such as one by our group of vitamin D supplementation in pregnant women for the prevention of allergy and

asthma in their children [201], as well as treatment in patients with known severe or steroid-resistant asthma [202]. In addition, studies of vitamin D supplementation in other disease states including TB, multiple sclerosis, lupus and cancer, along with ancillary laboratory investigations, for example of Treg cell function, will aid in our understanding of the role of vitamin D in the modulation of the immune system and its effects on disease. The elucidation of the precise roles of vitamin D in the immune system and in the pathogenesis of multiple diseases has the potential to have profound effects on our ability to prevent and treat these disorders.

Key issues

- Recent evidence points to vitamin D as an essential immune system regulator.
- Vitamin D deficiency and insufficiency are widespread, regardless of latitude.
- Low vitamin D levels have been linked with many immune-mediated diseases and cancers.
- Basic science and animal models demonstrate the multiplicative effects of vitamin D on cells of the immune system and cytokine profiles.
- Genetic and epidemiologic studies have shown an association between asthma and vitamin D.
- The rising prevalence of asthma may be linked to vitamin D deficiency.
- Further investigation is needed to fully understand the role of vitamin D in the development of allergy and asthma.

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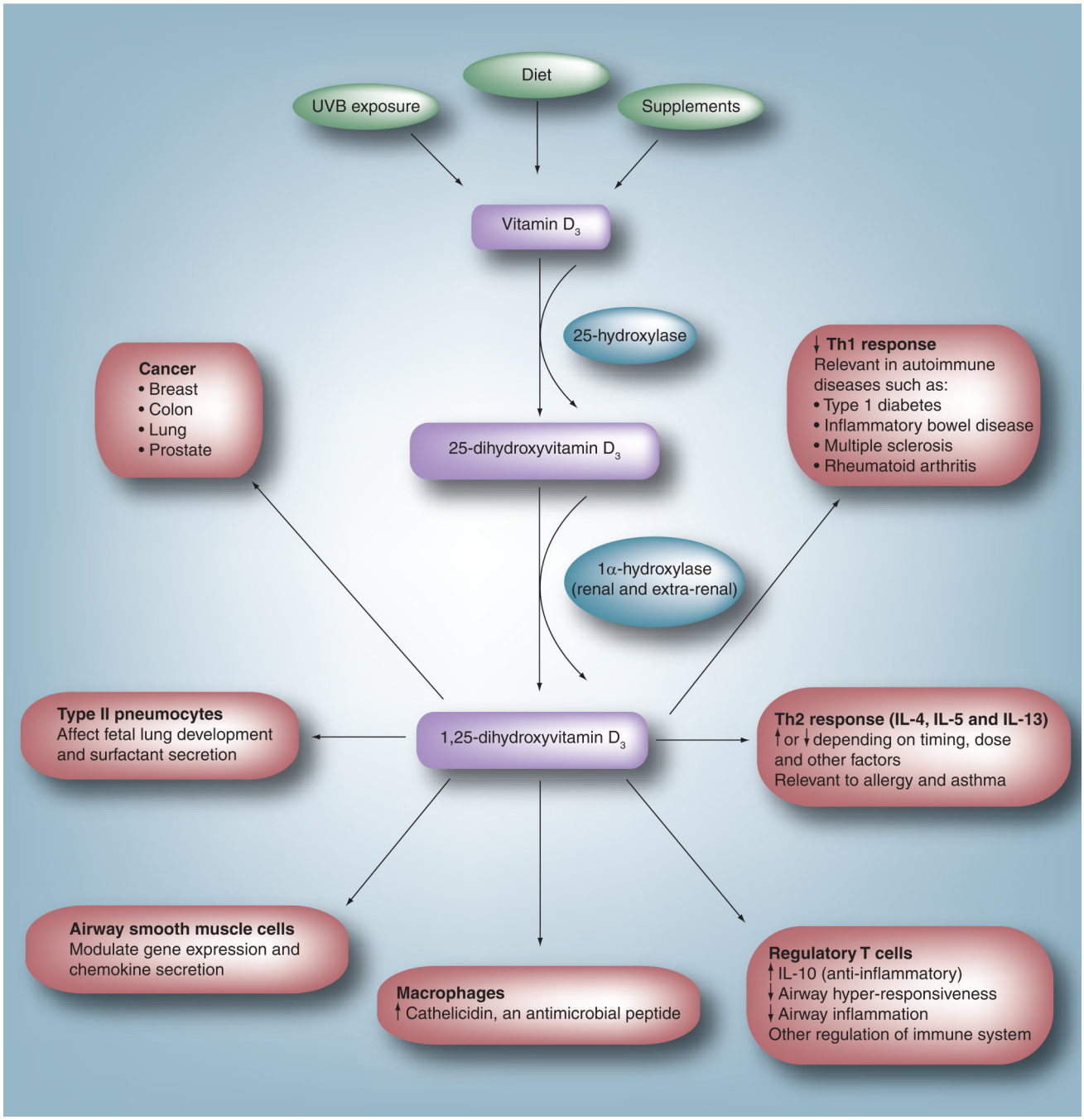

Figure 1. Extraskeletal effects of vitamin D

In humans, vitamin D is obtained through ultraviolet B exposure, diet and supplement intake. It is converted to 25-hydroxyvitamin D_3 by the liver. Circulating 25-hydroxyvitamin D_3 is converted to the active form, 1,25-dihydroxyvitamin D_3, in a variety of sites including the kidney and cells of the immune system. Experimental evidence suggests an effect of 1,25-dihydroxyvitamin D_3 on multiple different processes and cell types. In the immune system it leads to a decrease in the Th1 response, thought to be the mechanism involved in the association between low vitamin D levels and a variety of autoimmune diseases. It modulates the Th2 response affecting cytokines such as IL-4, IL-5 and IL-13. This is one possible link between vitamin D and allergy/asthma. It has been shown to upregulate T-regulatory cells, leading to

an increase in the synthesis of the anti-inflammatory cytokine IL-10. In macrophages, vitamin D upregulates synthesis of the antimicrobial peptide cathelicidin, which may enhance the ability to fight infections. In airway smooth muscle cells, it has been shown to modulate chemokine release. Vitamin D may play a role in fetal lung development and in the differentiation of type II pneumocytes and surfactant secretion. Vitamin D has also been associated with a lower incidence of and mortality from a variety of cancers.