1,25-Dihydroxyvitamin D_3 and the Immune System (42915)

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The recent discovery of receptors for 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) in cells of the immune system along with evidence for a multifaceted influence of this hormone on monocytes and lymphocytes have raised the possibility that 1,25-$(OH)_2D_3$ is an immunoregulatory agent. The mechanism(s) underlying the involvement of 1,25-$(OH)_2D_3$ in immunoregulation and the importance of such an involvement for physiology, pathophysiology, and therapeutics, however, remain unclear.

The following is an interpretive update of the evidence for the interactions between 1,25-$(OH)_2D_3$ and the immune system.

Receptors for 1,25-$(OH)_2D_3$ in cells of the immune system

It has been well established during the last few years that cells of the hematolymphopoietic tissue are targets for the actions of 1,25-$(OH)_2D_3$. Indeed, transformed cell lines of the myelomonocytic and the lymphocytic cell lineage, as well as peripheral normal human blood monocytes and tissue macrophages possess proteins, that, similar to the receptor protein in the classical target tissues of 1,25-$(OH)_2D_3$, bind the ligand with high affinity ($K_d \simeq 10^{-10}$ M) and specificity and are capable of DNA interactions (1–3). Unlike peripheral blood monocytes, that express this protein constitutively, normal resting T and B lymphocytes do not exhibit detectable binding to radioactive 1,25-$(OH)_2D_3$. Nevertheless, activation of peripheral blood T lymphocytes *in vitro* with mitogenic lectins, phorbol esters, or antigens leads to the expression of the receptor protein (1, 2, 4). The two major subpopulations of T lymphocytes, namely, the helper/inducer and suppressor/cytotoxic cells possess similar concentrations of the 1,25-$(OH)_2D_3$ receptor protein upon activation with mitogens (5). 1,25-$(OH)_2D_3$ receptor binding is also present in peripheral blood B lymphocytes activated with the Epstein-Barr virus as well as in myeloma cells (3, 6). The expression of the 1,25-$(OH)_2D_3$ receptor in lymphocytes coincides with the cell entry into the $G1_\alpha$ phase of the cell cycle, and the concentration of the receptor protein reaches a peak at $G1_\beta$ and declines during the S phase (5, 7).

In addition to *in vitro* activated cells, *in vivo* expression of 1,25-$(OH)_2D_3$ receptors has been shown in the peripheral blood lymphocytes of rheumatoid arthritis patients (8). Lymphocytes in the peripheral blood of such patients also express surface markers of activation. Furthermore, 1,25-$(OH)_2D_3$ receptors have been detected in specimens of human thymus and tonsils (9). In both tissues, a positive correlation between 1,25-$(OH)_2D_3$ binding and the activation phase of lymphocytes was detected. It is worth noting that patients with vitamin D-resistant rickets, a syndrome characterized by defective 1,25-$(OH)_2D_3$ receptor binding to DNA in classical target tissues of the hormone, exhibit defective 1,25-$(OH)_2D_3$ binding in their peripheral blood lymphocytes as well (10, 11).

Lymphocytes of the T cell lineage undergo functional maturation within the thymus gland before they are released into the blood stream. One subset of the T lymphocytes that reside in the thymus express the 1,25-$(OH)_2D_3$ receptor protein constitutively (12, 13). These 1,25-$(OH)_2D_3$ receptor-bearing cells belong to the peanut agglutinin (PNA)-negative subset of thymocytes that are localized in the medulla of the gland and exhibit a more functionally mature phenotype (14). In contrast to the PNA-negative cells, the less mature PNA-positive cells that are localized in the cortex of the thymus do not express the 1,25-$(OH)_2D_3$ receptor. Interestingly enough it is the latter but not the former cells that express the receptor protein for glucocorticoids, another class of immunoregulatory hormones (14). PNA-positive and PNA-negative thymocytes are thought to represent a single lineage of T lymphocytes in two subsequent stages of intrathymic maturation. This would suggest that as T lymphocytes differentiate within the thymus gland, they switch off expression of the GC receptor gene and turn on expression of the 1,25-$(OH)_2D_3$ receptor gene. The fact that the 1,25-$(OH)_2D_3$ receptor protein is expressed in PNA-negative cells is by itself intriguing since the PNA-negative cells are the closest, in terms of phenotypic characteristics, to the T lymphocytes in peripheral blood. Nevertheless, as it was

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discussed above, peripheral blood lymphocytes do not express 1,25-$(OH)_2D_3$ receptors; but the receptor appears only when resting lymphocytes become activated.

Although not shown directly, the dramatic increase of the 1,25-$(OH)_2D_3$ receptor protein following *in vitro* activation of resting peripheral blood lymphocytes is consistent with enhanced transcription of the 1,25-$(OH)_2D_3$ receptor gene. Because of similarities in the state of activation, the time kinetics, and the pathologic situations associated with the expression of the *myc* oncogene and the 1,25-$(OH)_2D_3$ receptor protein in lymphocytes, we have searched for and found an intriguing association between the expression of c-*myc* and the expression of the 1,25-$(OH)_2D_3$ receptor protein in mammalian cells at large (15). Whether the *myc* oncogene is a *cis*- or *trans*-activating element for the 1,25-$(OH)_2D_3$ gene and thus responsible for the up-regulation of the 1,25-$(OH)_2D_3$ receptor in activated lymphocytes remains only a matter of conjecture. We have also noted recently that the concentration of the 1,25-$(OH)_2D_3$ receptor protein in *in vitro*-activated lymphocytes can differ depending upon the nature of the activation signal (Xiao-peng Yu, unpublished observations and reference (5)). This quantitative difference is not related to the rate of DNA synthesis, and thus it is possible that certain second messengers generated upon lymphocyte activation may act to modulate expression of the receptor gene.

Influence of 1,25-$(OH)_2D_3$ on Cells of the Immune System

Lymphocyte Proliferation, Interleukin 2 and Interleukin 1. Following the demonstration of 1,25-$(OH)_2D_3$ receptors in cells of the immune system, a substantial amount of *in vitro* evidence has accumulated to suggest that 1,25-$(OH)_2D_3$ exerts a potent and widespread influence on immune phenomena (16, 17). The cellular requirements and the mechanistic events accounting for the effects of this hormone are, however, poorly understood.

1,25-$(OH)_2D_3$ acts on mixed cultures of human peripheral blood mononuclear cells (PBMC) activated with the mitogen phytohemagglutinin (PHA) to decrease interleukin 2 (IL-2) production and to inhibit the proliferative response of lymphocytes to PHA (18, 19). This effect occurs at low concentrations of the hormone (1×10^{-12}–1×10^{-11} *M*); the relative potency of other analogs of 1,25-$(OH)_2D_3$ corresponds closely with their relative affinity for the receptor protein, suggesting a receptor-mediated effect. Cell cycle analysis of PHA-activated lymphocytes demonstrates that 1,25-$(OH)_2D_3$ inhibits proliferation by arresting the cells at the $G1_\alpha$–$G1_\beta$ border of the cell cycle (7, 20). The antiproliferative effect of 1,25-$(OH)_2D_3$ does not seem to be caused by interference with the initial activation process nor with the expression of activation-related molecules (7). Moreover, this effect is not influenced by the concentration of extracellular calcium (7). Based on the observations described above, it has been suggested that 1,25-$(OH)_2D_3$ exerts its antiproliferative effects by direct actions on lymphocytes. However, monocytes are also targets for 1,25-$(OH)_2D_3$ actions. Because monocytes are necessary for activation of T cells by antigens or mitogens such as PHA, one cannot exclude the possibility that the 1,25-$(OH)_2D_3$-induced inhibition of T cell proliferation is secondary to effects of the hormone on monocytes.

Interleukin 1 (IL-1) production by monocytes provides a necessary early activation signal for mitogen stimulation of T cells leading to expression of the IL-2 receptor and IL-2 production. The requirement for monocytes in T cell activation, however, can be replaced *in vitro* by phorbol myristic acetate or by the addition of exogenous IL-2. To explore the possibility that 1,25-$(OH)_2D_3$ might affect T cell proliferation via monocytes, we examined the effect of the hormone on highly purified normal T cell populations activated with PHA, either in the presence of homologous monocytes or in the presence of phorbol myristic acetate (21). 1,25-$(OH)_2D_3$ caused a significant dose-dependent inhibition of both proliferation and IL-2 production in the presence of monocytes. In contrast, 1,25-$(OH)_2D_3$ failed to inhibit either proliferation or IL-2 production when phorbol myristic acetate was used instead of monocytes. To assess more directly the involvement of monocytes in the hormone-mediated inhibition of T cell proliferation, we pretreated monocyte-enriched cultures with 1,25-$(OH)_2D_3$ for various periods of time. Pretreatment of monocytes with 1,25-$(OH)_2D_3$ caused inhibition of the subsequent T cell proliferation. The magnitude of inhibition was dependent on the length of the exposure of monocytes to the hormone. Monocyte production of prostaglandins, known inhibitors of T cell proliferation, may also be a factor in the 1,25-$(OH)_2D_3$-induced effects on lymphocyte proliferation. We therefore used indomethacin, a prostaglandin synthetase inhibitor, to examine the possibility that the 1,25-$(OH)_2D_3$-mediated inhibition of T cell proliferation via monocytes could be due to prostaglandin release. Indomethacin had no significant effect on the hormone-mediated inhibition, suggesting that prostaglandins do not play a significant role. Other reports, however, suggest a minor role of prostaglandins in the inhibitory effects of 1,25-$(OH)_2D_3$ (22, 23).

We have also examined whether 1,25-$(OH)_2D_3$ influences IL-1 production by monocytes using specific radioimmunoassays. The effect of 1,25-$(OH)_2D_3$ on IL-1 production has been examined earlier by others using bioassays, but the results of these studies have been contradictory (24–27). Utilizing two specific radioimmunoassays (one for IL-1α and the other for IL-1β), we have been able to demonstrate that 1,25-$(OH)_2D_3$ suppresses both forms of the monokine. 1,25-$(OH)_2D_3$ reduced IL-1α and IL-1β levels in monocyte culture

supernatants as well as in the cell extracts, suggesting that the hormone inhibits the production of IL-1. Addition of soluble IL-1 to these cultures, nevertheless, did not overcome the 1,25-$(OH)_2D_3$-mediated inhibition of T cell proliferation; an observation previously reported by Rigby *et al.* (20). It has been suggested that the soluble form of the monokine may not be critical in lymphocyte activation and that a different form, i.e., cell-associated IL-1 may be more important (28). To determine the role of membrane-associated IL-1 in the 1,25-$(OH)_2D_3$-induced inhibition of lymphocyte proliferation, we examined cell-associated IL-1 activity in 1,25-$(OH)_2D_3$-treated monocytes that were subsequently fixed with paraformaldehyde; we found that 1,25-$(OH)_2D_3$ inhibited this activity in a dose-dependent manner (21).

The finding that 1,25-$(OH)_2D_3$ inhibits IL-1 production suggests that 1,25-$(OH)_2D_3$-induced inhibition of IL-2 production and T cell proliferation in PHA-activated PBMC is secondary to a direct effect of 1,25-$(OH)_2D_3$ on the accessory monocytes. The evidence that pretreatment of monocytes with 1,25-$(OH)_2D_3$ inhibits the subsequent ability of these cells to induce T cell proliferation in this system is consistent with this hypothesis. IL-1 promotes the transmission of the mitogenic signal mainly in the T4 subset of lymphocytes. This evidence in combination with the findings that 1,25-$(OH)_2D_3$ inhibits the proliferation of T4 cells only adds further support to the hypothesis that 1,25-$(OH)_2D_3$ inhibition of T cell proliferation is mediated via IL-1 (5, 29).

Although considerable evidence exists demonstrating the ability of 1,25-$(OH)_2D_3$ to suppress lymphocyte proliferation in PBMC activated with PHA, there are other studies to suggest that 1,25-$(OH)_2D_3$ is not a universal inhibitor of lymphocyte proliferation. Instead, 1,25-$(OH)_2D_3$ may inhibit T cell proliferation only when specific pathways of activation and specific cell interactive mechanisms are involved. Lacey *et al.* (30) have shown that 1,25-$(OH)_2D_3$ has no effect on the proliferation of the murine T helper cell clone D10; yet in combination with concanavalin A (Con A), the hormone produces up to a 50-fold increase in the proliferation rate of the cells. Similarly, 1,25-$(OH)_2D_3$ acts to enhance Con A-induced normal bovine lymphocyte proliferation and, at low concentrations, stimulates interleukin 2 production by a T cell lymphoma line (31, 32). Furthermore, 1,25-$(OH)_2D_3$ inhibits proliferation of human lymphotropic virus type 1-infected cell lines but does not inhibit the proliferation of immature lymphoblastic T and B cells or B cells derived from adult T cell leukemia (33).

We have recently compared the effect of 1,25-$(OH)_2D_3$ on the proliferation of normal human lymphocytes using either PHA or the anti-T3 monoclonal antibody (OKT3). The OKT3 antibody induces activation via the T cell antigen receptor (Ti)/T3 complex and resembles more closely the physiologic activation pathway of lymphocytes. For these studies we utilized either PBMC (monocytes and lymphocytes) or highly purified T cells. Because pure T cells do not proliferate in response to OKT3 in the absence of monocytes, recombinant IL-2 was added simultaneously with the OKT3 antibody in the latter cell preparations. In contrast to the PHA activation system, in both the mixed cultures and the pure T cells, the OKT3-induced proliferation of normal human lymphocytes was unaffected by the presence of 1,25-$(OH)_2D_3$ (21).

A summary of the evidence for the influence of 1,25-$(OH)_2D_3$ on lymphocyte proliferation *in vitro* is shown in Table I.

Other Lymphokine Synthesis. 1,25-$(OH)_2D_3$ affects other cytokine production in addition to IL-1 and IL-2. Both γ-interferon (IFN-γ and granulocyte/monocyte-colony-stimulating factor (GM-CSF) production by PHA-activated human lymphocytes is decreased in the presence of 1,25-$(OH)_2D_3$ (34, 35). These effects appear to be the result of 1,25-$(OH)_2D_3$ actions directly on T cells since IFN-γ and GM-CSF are inhibited at the protein and mRNA levels (34–37). It has been demonstrated that 1,25-$(OH)_2D_3$ does not affect the rate of transcription of the GM-CSF gene but regulates GM-CSF posttranscriptionally by influencing the stability of GM-CSF mRNA (38).

In agreement with the earlier reports, we have observed a dose-dependent inhibition of IFN-γ by 1,25-$(OH)_2D_3$ (10^{-10}–10^{-8} *M*) in PBMC activated with PHA. Nevertheless, both in PBMC activated with OKT3 and in pure T cells activated with the combination of OKT3 and recombinant IL-2 we observed a biphasic effect of 1,25-$(OH)_2D_3$ on IFN-γ. Significant stimulation of IFN-γ occurred at lower concentrations of the hormone (10^{-12}–10^{-10} *M*) and inhibition was evident only at supraphysiologic concentrations (10^{-8} *M*) (21).

These observations suggest that the mode of activation of lymphocytes is critical for the influence of 1,25-$(OH)_2D_3$ on lymphokine production as it is for the influence of the hormone on lymphocyte proliferation. Although it can be argued that antigen-induced activation is theoretically more relevant to the *in vivo* situation than the mitogen-induced activation, it is difficult to extrapolate from the *in vitro* studies whether the physiologically relevant effect of the hormone is stimulation rather than inhibition of IFN-γ. A stimulatory effect of 1,25-$(OH)_2D_3$ on IFN-γ, however, would be consistent with the possibility of synergism between these two compounds as suggested by the evidence that 1,25-$(OH)_2D_3$ enhances the ability of IFN-γ to induce the expression of Ia molecules and that in concert with this lymphokine acts to promote the differentiation of monocytic cells (39, 40). Moreover, it would be in line with the *in vivo* evidence that administration of 1α-$(OH)D_3$ to elderly humans causes a significant elevation of the circulating levels of α-interferon (41).

Table I. Effects of $1,25\text{-}(OH)_2D_3$ on Lymphocyte Proliferation *In Vitro*

Cell type	Species	Activator	$1,25\text{-}(OH)_2D_3$ Effect	Reference
PBMC	Human	PHA	↓[a]	(7, 18, 19, 20, 27, 42)
PBMC	Human	OKT3	→	(21)
PBMC	Human	PWM	↓	(42)
PBMC	Human	Dermatophyton-0	↓	(42)
PBMC	Bovine	PHA	↓	(74)
PBMC	Bovine	PWM	↓	(74)
PBMC	Bovine	Con A	↑↓	(31)
Pure T cells	Human	OKT3	→	(21)
Pure T cells	Human	PHA + PMA	→	(21)
T4 lymphocytes	Human	PHA	↓	(5, 42, 75)
T8 lymphocytes	Human	PHA	→↓	(5, 42, 75)
B lymphocytes	Human	*Staphylococcus aureus*	↓	(77)
B lymphocytes	Human	PWM	↓	(77)
Thymocytes	Murine	IL-1	↓	(43)
Thymocytes	Murine	IL-2	↓	(43)
Thymocytes	Murine	Con A	→	(78)
T helper clone (D10.G4.1)	Murine	Con A	↑	(30)
		Con A + IL-1	↑↓	
T cell hybridoma	Murine	PHA	→	(78)
T cell hybridoma	Murine	Con A	→	(78)
T cell hybridoma	Murine	Anti-Thy-1 Ab	→	(78)
T cell hybridoma	Murine	Ia-bearing cells	↓	(78)
Spleen cells	Murine	Con A	→	(78)
Primed lymph node cells	Murine	KLH	↓	(78)

[a] ↑ = increased, ↓ = decreased, → = no effect.

B Lymphocytes. In addition to its potent effects on T lymphocytes, $1,25\text{-}(OH)_2D_3$ can inhibit immunoglobulin production induced by pokeweed mitogen (PWM) and by the Epstein-Barr virus (6, 42). Evidence that the PWM-driven antibody synthesis is T cell dependent and that $1,25\text{-}(OH)_2D_3$ inhibits the Epstein-Barr virus-induced antibody production (a T cell-independent response) suggests that the hormone can affect immunoglobulin production via direct actions on both T and B cells.

Thymocytes. The demonstration of $1,25\text{-}(OH)_2D_3$ receptors in thymocytes has prompted investigations on the effects of $1,25\text{-}(OH)_2D_3$ on these cells as well. In primary cultures of rat and mouse thymocytes, $1,25\text{-}(OH)_2D_3$ exerts a protective effect against the spontaneous lysis of the PNA-negative subpopulation of thymocytes, but has no effect on the $1,25\text{-}(OH)_2D_3$ receptor negative (PNA-positive) cells (13, 14). This effect is distinct from that observed for glucocorticoids, which enhance the lysis of the PNA-positive cells, suggesting that these two steroid hormones play different regulatory roles in the biology of the thymus (14). Furthermore, primary cultures of rat and human thymocytes maintained in the presence of $1,25\text{-}(OH)_2D_3$ exhibit a substantial increase in the percentage of cells expressing the helper marker, suggesting that $1,25\text{-}(OH)_2D_3$ may play a role in the intrathymic differentiation of lymphocytes (14). In addition to its effect on resting thymocytes, $1,25\text{-}(OH)_2D_3$ inhibits the proliferation of mouse thymocytes activated *in vitro* with PHA and IL-2 (13, 43).

Monocytes/Macrophages. Beyond the evidence for the influence of $1,25\text{-}(OH)_2D_3$ on the proliferation and function of lymphocytes there is a series of observations to suggest that the hormone affects other phases of the immune response. It is well established that $1,25\text{-}(OH)_2D_3$ promotes the differentiation of leukemic, normal myeloid stem cells, and peripheral blood monocytes toward the macrophage phenotype (44–48). $1,25\text{-}(OH)_2D_3$ also acts on monocytes and macrophages to influence their immune functions. Specifically, $1,25\text{-}(OH)_2D_3$ enhances IFN-γ-induced expression of the class II major histocompatibility complex antigens (Ia molecules) in the murine line WEHI-3 and increases the ability of these cells to stimulate antigen-specific Ia-restricted T cell activation (39). Similarly, $1,25\text{-}(OH)_2D_3$ alone augments antigen presentation by $H\text{-}2^k$-matched spleen-derived murine macrophages (49). $1,25\text{-}(OH)_2D_3$ also enhances the cytotoxic function of monocytes/macrophages, and $1,25\text{-}(OH)_2D_3$-treated human monocytes exhibit enhanced phagocytosis and killing of mycobacteria (50). $1,25\text{-}(OH)_2D_3$ treatment of peripheral blood monocytes also increases the production of hydrogen peroxide and the expression of heat shock protein (51, 52). Consistent with these *in vitro* observations is the evidence that vitamin D deficiency in humans and animals is associated with decreased ability of monocytes/macrophages to react to

nonspecific inflammatory stimuli and impaired capacity for phagocytosis. These defects can be corrected *in vitro* by incubating macrophages with 1,25-$(OH)_2D_3$ (53).

The Role of 1,25-$(OH)_2D_3$ in Immunity

The *in vitro* evidence for the regulation of immune cell functions by 1,25-$(OH)_2D_3$, along with the presence of receptors for the hormone *in vivo* in cells of the immune system, suggest a role of 1,25-$(OH)_2D_3$ in the regulation of immune phenomena in the whole organism. Clinical information and results from *in vivo* experiments with 1,25-$(OH)_2D_3$ support this suggestion. At this stage, however, it is difficult to reconcile the whole spectrum of the *in vitro* observations with *in vivo* data. Unlike earlier suggestions that 1,25-$(OH)_2D_3$ might be an immunosuppressive agent, it is becoming increasingly apparent that 1,25-$(OH)_2D_3$ may be capable of both stimulating immune responses in certain circumstances and suppressing them in others. The available clinical information and the *in vivo* experimentation are consistent with an immunostimulating role of 1,25-$(OH)_2D_3$. Thus, vitamin D deficiency states are associated with defective rather than enhanced immunity, and cellular immunity is impaired in end stage renal disease where production of 1,25-$(OH)_2D_3$ by the kidney has virtually ceased (54). This situation appears to have important clinical implications in the case of tuberculosis where a link between vitamin D deficiency and impaired host defense to mycobacterium exists (55). Long-held views that vitamin D was beneficial in the treatment of tuberculosis are supported by recent epidemiologic and clinical studies indicating an association between vitamin D status and the incidence of the disease. The discovery of a potent antituberculosis activity of 1,25-$(OH)_2D_3$ *in vitro* provides clues for the mechanistic basis of this phenomenon (50). Additional support for the immunostimulating capability of 1,25-$(OH)_2D_3$ is provided by evidence that administration of 1α-$(OH)D_3$ to hemodialyzed patients with renal failure leads to near normalization of lymphoproliferative responses and enhances the primary response against sheep red blood cells in rats with renal osteodystrophy (56–58). Furthermore, administration of 1α-$(OH)D_3$ to elderly normal individuals enhances tuberculin reaction and causes a significant elevation of the circulating levels of α-interferon (41, 59).

Whether the role of 1,25-$(OH)_2D_3$ in immunobiology is exerted through systemic or localized actions remains unclear at this stage. The fact that there is neither a major nor clinically apparent systemic defect of the immune defense in vitamin D deficiency argues against a systemic role for circulating 1,25-$(OH)_2D_3$; yet it does not exclude the possibility that 1,25-$(OH)_2D_3$ could be a permissive factor in generalized immunity. On the other hand, evidence that exogenous administration of 1,25-$(OH)_2D_3$ can alter the function of blood lymphocytes raises the possibility that circulating 1,25-$(OH)_2D_3$ could have at least pharmacologic systemic effects. Several synthetic analogs of 1,25-$(OH)_2D_3$ with equal or greater potency on cells of the immune system and lesser hypercalcemic properties than the natural hormone have been recently developed (60–65). Evaluation of the effectiveness of these new compounds on immunomodulation *in vivo* should resolve this issue in the near future. Instead of (or in addition to) being a systemic immunomodulator 1,25-$(OH)_2D_3$ may be a local mediator of macrophage-lymphocyte interactions. This latter hypothesis is well supported by evidence that macrophages, transformed lymphocytes, as well as granulomata and multinucleated giant cells synthesize 1,25-$(OH)_2D_3$ locally (66–70). Thus, 1,25-$(OH)_2D_3$ may act in a paracrine fashion as a local modulator of interactions between cells of the immune system. Appreciation of the fact that *in situ* production of 1,25-$(OH)_2D_3$ by sarcoid tissues plays a major role in the pathophysiology of this disease and is responsible for the sarcoidosis-associated hypercalcemia underlines the clinical significance of the local production of 1,25-$(OH)_2D_3$ by cells of the immune system (71–73).

Summary

There is substantial evidence that lymphocytes and monocytes are targets for the actions of the hormonal form of vitamin D, 1,25-$(OH)_2D_3$ and that 1,25-$(OH)_2D_3$ acts to modulate the proliferation, differentiation, and immune functions of these cells. The effects of the hormone on lymphocytes are mediated directly as well as indirectly via the accessory monocytes. Depending upon the presence or absence of monocytes and the mode of lymphocyte activation, 1,25-$(OH)_2D_3$ can either stimulate or suppress lymphocytes. This evidence as well as clinical information and *in vivo* studies support a role of 1,25-$(OH)_2D_3$ in immunobiology. The physiologic, pathophysiologic, and pharmacologic implications of the immunomodulating properties of 1,25-$(OH)_2D_3$ however have not been well established.

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