

Commentary

Vitamin D and the immune system

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Recent studies have shown that the hormonal form of vitamin D, 1,25-dihydroxyvitamin D₃ (calcitriol), can affect both tissues and cells that are not directly involved in calcium homeostasis. In particular, a role for calcitriol as a regulator of immune cell differentiation and proliferation has been proposed. Specific high-affinity intracellular receptors for calcitriol (VDR) are detectable in activated T cells, and activated macrophages are able to synthesize calcitriol. A possible paracrine mechanism of action has been postulated. Vitamin D may therefore have a similar role to that of other immune regulatory molecules such as cytokines. The precise interaction of calcitriol with the cytokine network is not yet fully defined, but its ability to modulate immune cells *in vitro* and its association with inflammatory diseases are now well documented. These findings are outlined in this review with particular reference to effects on macrophages and lymphocytes.

Ectopic production of calcitriol

Initial evidence for the interaction of calcitriol with the immune system arose from studies of the disease sarcoidosis, a chronic granulomatous disorder often associated with hypercalcaemia and elevated circulating levels of calcitriol (Papapoulos, Clemens, Fraher *et al.* 1979). The latter have been attributed to ectopic synthesis of calcitriol by immune cells associated with sarcoidosis, such as alveolar macrophages (Adams, Sharma, Gacad & Singer, 1983). In contrast to endocrine synthesis of calcitriol (in the kidney), production of the hormone by sarcoid macrophages appears to be insensitive to feedback control by calcitriol itself, as well as other regulators such as calcium and parathyroid hormone (Reichel, Koeffler & Norman, 1990). The precise lesion which produces the abnormal regulation of calcitriol synthesis in sarcoid macrophages remains unclear, but may be due to defective feedback control of calcitriol production at the site of synthesis or in target cells for calcitriol such as lymphocytes. Normal macrophages have also been shown to synthesize calcitriol when activated by agents such as interferon- γ (Koeffler, Reichel, Bishop & Norman, 1985; Rook, Steele, Fraher *et al.* 1986) and lipopolysaccharide (Reichel, Koeffler,

Bishop & Norman, 1987). Production of the hormone may thus act as part of the normal immune response and induction of calcitriol synthesis in response to infection may stimulate the synthesis of other inflammatory mediators such as interleukin-1 (IL-1), which will in turn affect the level of lymphocyte activity.

Calcitriol and monocyte function

The secretory role of macrophages is central to the production of localized concentrations of calcitriol within immune microenvironments. However, macrophages perform other functions which can also be modulated by calcitriol. The hormone has been shown to stimulate both phagocytic and antibody-dependent macrophage cytotoxicity. Rook *et al.* (1986) reported that calcitriol enhances the ability of macrophages to inhibit proliferation of *Mycobacterium tuberculosis in vitro*. Other studies have shown that the hormone increases Fc receptor expression on mononuclear cells (Abe, Shiina, Miyaura *et al.* 1984), and can aid their protection in inflammatory environments by inducing expression of the heat shock protein (Polla, Healy, Amento & Krane, 1986). Cells such as macrophages which are involved in presenting antigen are known as accessory cells. Another important group of accessory cells are dendritic cells which express abundant VDR, further emphasizing a possible role for the hormone in antigen presentation (Brennan, Katz, Nunn *et al.* 1987).

Macrophages are derived from less mature myeloid stem cells which originally have a common pleuripotent cell origin and many groups including ours have examined the effect of vitamin D on stem cell development, in particular the mononuclear phagocyte system (Hewison, Barker, Brennan *et al.* 1989). These studies have been greatly facilitated by the development of leukaemic cell lines from myeloid precursor cells. It is not yet clear at which point in the stem cell pathway VDR induction occurs, but more mature cell lines such as HL 60 and U937 express these receptors and are responsive to calcitriol which stimulates differentiation towards macrophage-like cells (Karmali, Bhalla, Farrow *et al.* 1989). In this

respect the antiproliferative effects of calcitriol are similar to those observed with agents such as retinoic acid, dimethyl sulphoxide and phorbol esters. More importantly, calcitriol is effective at concentrations which are physiological (10^{-10} – 10^{-8} mol/l) and which correspond to the accepted affinity values for its receptor.

Calcitriol and lymphocyte function

Calcitriol has also been shown to act upon T and B cells, and is thereby able to modulate both the cytotoxic and antibody-producing functions of lymphocytes. Studies *in vitro* have suggested that the main effect of calcitriol is to inhibit the proliferation of activated T cells which, unlike resting T cells, express VDR. This appears to be dependent on a threshold of VDR expression (Karmali, Hewison, Rayment *et al.* 1991) and is, in part, mediated through inhibition of T-cell secretion of the lymphokine IL-2. Calcitriol also inhibits interferon- γ synthesis by T cells (Rigby, Denome & Fanger, 1987), and this may act as part of the control of calcitriol synthesis by macrophages which produce the hormone when stimulated with interferon- γ . T-cell development takes place in the thymus with VDR being expressed in medullary cells, but not in the less mature cortical cells. However, the precise role of calcitriol in T-lymphocyte development is unclear as VDR expression is lost after the cells leave the thymus. Recent studies have also shown that VDR are present in T-cell-related natural killer cells (Fagan, Beeker, Adams & Lemire, 1991), indicating that calcitriol may have a role in modulating the immune response to viral and neoplastic infection. The interaction of vitamin D with B cells is less clear than its effects on T cells, and although calcitriol inhibits immunoglobulin production by B cells this appears to be due to indirect suppression of the antibody-stimulating activity of T-helper cells or macrophages (Lemire, Adams, Kermani-Arab *et al.* 1985).

Clinical aspects

There is a close relationship between ectopic production of calcitriol by immune cells and the hypercalcaemia observed with inflammatory diseases such as sarcoidosis and tuberculosis. However, the immune modulatory effects of vitamin D may have a much wider clinical impact. Indeed, the paracrine, and possible autocrine functions of vitamin D with the immune system might not be entirely distinct from the endocrine activity of calcitriol in mineral homeostasis. Vitamin D deficiency has been shown to be associated with impaired immune responses such as decreased leukocyte chemotaxis (Bar-Shavit, Noff, Edelstein *et al.* 1981), and has also been reported to increase

susceptibility to infection (Stroder & Kasal, 1970). The contribution of immune effects of calcitriol on mineral homeostasis have yet to be studied in detail, but may have a significant effect on calcium mobilization. Calcitriol stimulates monocyte secretion of IL-1 and prostaglandin E₂, both of which induce bone resorption but inhibit lymphocyte production of interferon- γ , a suppressor of calcium mobilization.

A potentially important clinical application of the antiproliferative effect of calcitriol on monocytes has been in the development of antileukaemic agents. The use of vitamin D in myeloproliferative disorders *in vivo* has, so far, been less successful than related agents such as retinoic acid. However, a wide range of new vitamin D analogues are currently being investigated with the aim of retaining the sensitive differentiating properties of calcitriol whilst minimizing the possible dangerous hypercalcaemic effects of the hormone (Abe, Takita, Nakano *et al.* 1989). Recent studies have also shown that calcitriol inhibits both CD4 expression and HIV infection of human monocytes (Connor & Rigby, 1991), and this offers another possible exciting application in the development of new vitamin D metabolites for the treatment of immunodeficiency.

In summary, there is now increasing evidence for the contribution of endocrine systems to the immune response, and calcitriol may have a particularly versatile role in this interaction. Localized production of the hormone can benefit the immune environment in several ways. First, by stimulating phagocytic and antibody presenting actions, calcitriol may help to promote initial immune responses. This would include the recruitment of additional monocytes by promotion of stem cell differentiation, but may also involve activation of T cells via antigen presentation and cytokine secretion. These stimulatory effects are counterbalanced by the ability of the hormone to inhibit T-cell proliferation and thereby act as part of the feedback control of the immune response. Vitamin D may be seen as an addition to the long list of cytokines which have been reported in recent years. However, its close association with immune disorders and potential therapeutic applications have made a particularly exciting contribution to these studies.

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