Available online at www.sciencedirect.com
SCIENCE DIRECT®
Cellular Immunology 233 (2005) 115–124
Cellular Immunology
www.elsevier.com/locate/ycimm

Review

Intervention in autoimmunity: The potential of vitamin D receptor agonists

Luciano Adorini *

BioXell, Via Olgettina 58, I-20132 Milan, Italy

Received 21 April 2005; accepted 21 April 2005
Available online 3 June 2005

Abstract

Vitamin D receptor (VDR) agonists are well known for their capacity to control calcium metabolism and to regulate growth and differentiation of many cell types. More recently, it has become clear that VDR agonists possess immunoregulatory properties and, in particular, pronounced pro-tolerogenic activities. VDR agonists can act directly on T cells, but DCs appear to be their primary targets. The capacity of VDR agonists to modulate DC and T cell functions is mediated by VDR expression in both cell types and by the presence of common targets in their signal transduction pathways, such as the nuclear factor NF-κB that is downregulated by VDR agonists in APCs and in T cells. A potentially very important activity of VDR agonists is their capacity to induce in vitro and in vivo tolerogenic DCs able to enhance $CD4^+CD25^+$ suppressor T cells that, in turn, inhibit Th1 cell responses. These mechanisms of action can explain some of the immunoregulatory properties of VDR agonists in the treatment of Th1-mediated autoimmune diseases, but may also represent a physiologic element in the VDR-mediated regulation of innate and adaptive immune responses.

Keywords: Tolerogenic dendritic cells; Vitamin D analogs; Immunomodulation; Autoimmune diseases

1. Introduction

Failure of tolerance mechanisms may lead to autoreactive T cell activation and to induction of autoimmune diseases. To selectively interfere with the activation of pathogenic T cells involved in autoimmune diseses, immune intervention can be primarily directed to three cellular targets: antigen-presenting cells (APCs), autoreactive T cells, and suppressor/regulatory T cells. The common goal of these approaches is to selectively inhibit the activation of pathogenic MHC class II-restricted $CD4^+$ T cells [1].

Different forms of immunointervention have been successfully used to prevent and sometimes treat experimental autoimmune diseases, including modulation of antigen recognition, costimulation blockade, induction of regulatory T cells, deviation to non-pathogenic or protective responses, neutralization of proinflammatory cytokines, induction or administration of anti-inflammatory cytokines, and modulation of leukocyte trafficking. Several of these approaches target DCs, aiming at inducing or enhancing tolerogenic properties in this APC type critically involved in modulating T cell responses. A variety of agents, both biologic and pharmacologic, have been shown to promote the intrinsic tolerogenic capacity of DCs [2,3]. Biological agents include costimulation-blocking agents, such as anti-CD40L and CD152-Ig, and anti-inflammatory cytokines like IL-10 and TGF-β. Pharmacological agents include immunosuppressive molecules such as mycophenolate mofetil, sirolimus, desoxyspergualin, corticosteroids, and VDR agonists.

VDR agonists have been shown to be effective in several models of autoimmune diseases and are the most used topical agents in the treatment of psoriasis, an autoimmune disease of the skin, indicating their

* Fax: +39 02 2153203.
E-mail address: Luciano.Adorini@bioxell.com.

0008-8749/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.cellimm.2005.04.013

potential applicability in the treatment of a variety of autoimmune diseases.

2. Vitamin D receptor agonists as immunoregulatory agents

$1,25(OH)_2D_3$, the activated form of vitamin D, is a secosteroid hormone that has, in addition to its central function in calcium and bone metabolism, important effects on the growth and differentiation of many cell types, and pronounced immunoregulatory properties [4–8]. The biological effects of $1,25(OH)_2D_3$ are mediated by the vitamin D receptor (VDR), a member of the superfamily of nuclear hormone receptors [9,10]. Agonist binding induces conformational changes in the VDR, which promote heterodimerization with the retinoid X receptor (RXR) and recruitment of a number of corepressor and coactivator proteins, including steroid receptor coactivator family members and a multimember coactivator complex, the D receptor interacting proteins. These coactivators induce chromatin remodeling through intrinsic histone-modifying activities and direct recruitment of key transcription initiation components at regulated promoters. Thus, the VDR functions as a agonist-activated transcription factor that binds to specific DNA sequence elements in vitamin D responsive genes and ultimately influences the rate of RNA polymerase II-mediated gene transcription [11].

The discovery of VDR expression in most cell types of the immune system, in particular in APCs such as macrophages and DCs, as well as in both $CD4^+$ and $CD8^+$ T lymphocytes, prompted a number of studies investigating the capacity of VDR agonists to modulate T cell responses (Table 1). Following the pioneering work of Glimcher and co-workers [12], VDR agonists were subsequently found to be selective inhibitors of Th1 cell development [13,14], and to inhibit directly Th1-type cytokines such as IL-2 and IFN-γ [15–17]. $1,25(OH)_2D_3$ has been also shown, in some cases, to enhance the development of Th2 cells via a direct effect on naïve $CD4^+$ cells [18]. Collectively, direct T cell targeting by VDR agonists (Table 1) could contribute to account for their beneficial effects in the treatment of autoimmune diseases (Fig. 1).

Table 1
Effects of VDR agonists on T cells

Effect	References
Inhibition of T cell proliferation	[12]
Induction of hyporesponsiveness to allo and self-antigens	[19–23]
Inhibition of IL-2 production	[15,16]
Inhibition of IFN-γ production	[17,105]
Inhibition of Th1 cell development	[13,14]
Variable effects on IL-4 production and deviation to Th2	[14,18,75,105–107]
Increased production of IL-10	[80]
Increased expression of CD152	[19,43]
Downregulation of CD95 expression	[108]
Enhanced frequency of regulatory T cells	[41,43,80]

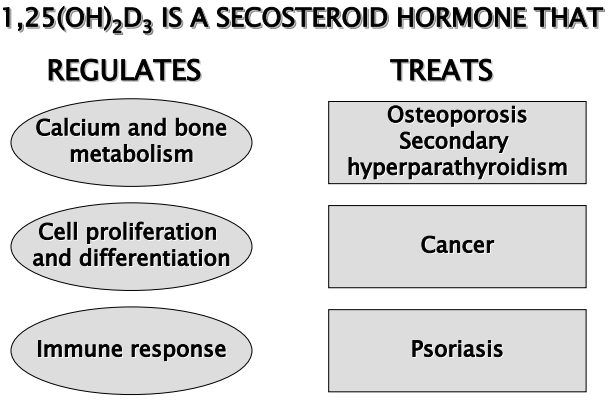

Fig. 1. Clinically relevant effects of VDR agonists and proven therapeutic applications.

Data accumulated in the past few years clearly demonstrate that, in addition to exerting direct effects on T cell activation, VDR agonists markedly modulate the phenotype and function of APCs, and in particular of DCs (Table 2). In vitro and in vivo experiments have shown that VDR agonists induce DCs to acquire tolerogenic properties that favor the induction of regulatory rather than effector T cells [3]. VDR agonists arrest the differentiation and maturation of DCs, maintaining them in an immature state, as shown by decreased expression of maturation markers and increased antigen uptake [19–24]. Collectively, studies performed either on monocyte-derived DCs from human peripheral blood or on bone-marrow derived mouse DCs have consistently shown that in vitro treatment of DCs with VDR agonists leads to downregulated expression of the costimulatory molecules CD40, CD80, CD86, and to markedly decreased IL-12 and enhanced IL-10 production, resulting in inhibition of T-cell activation. The near abrogation of IL-12 production and the strongly enhanced production of IL-10 highlight the important functional effects of $1,25(OH)_2D_3$ and its analogs on DCs and are, at least in part, responsible for the induction of DCs with tolerogenic properties.

These intriguing actions of VDR agonists have been demonstrated in several experimental models and could be exploited, in principle, to treat a variety of human autoimmune diseases [4–6,25]. In addition, it is conceivable that $1,25(OH)_2D_3$, which is produced by macrophages [26–28], DCs [29], and T cells [27], could physiologically contribute to regulate innate and adaptive immune responses. This appealing concept, still speculative, is so far mostly based on epidemiological data, but it is supported by the observation that VDR deficient, compared to wild-type mice, show hypertrophy of subcutaneous lymph nodes with an increase in mature DCs [30].

Table 2
Phenotypic and functional modifications induced by VDR agonists in human myeloid dendritic cells

Phenotype	Effect
Maturation marker expression	
CD83	Decreased
DC-LAMP	Decreased
Antigen uptake	
Mannose receptor expression	Increased
Costimulatory molecule expression	
CD40	Decreased
CD80	Decreased
CD86	Decreased
Inhibitory molecule expression	
ILT3	Increased
ILT4	Unmodified
B7-H1	Unmodified
Chemokine receptor expression	
CCR7	Decreased
Function	**Effect**
Cytokine production	
IL-10	Increased
IL-12	Decreased
Chemokine production	
CCL2	Increased
CCL17	Decreased
CCL18	Increased
CCL20	Decreased
CCL22	Increased
Apoptosis	
Maturation-induced	Increased
T-cell activation	
Response to alloantigens	Decreased

Compiled from [19,109] and from the author's unpublished data.

3. Immunomodulatory effects of VDR agonists in autoimmune disease models

The immunoregulatory properties of VDR agonists have been studied in different models of autoimmune diseases (Table 3). Notably, $1,25(OH)_2D_3$ and its analogues can prevent systemic lupus erythematosus in $MRL^{lpr/lpr}$ mice [31–33], experimental allergic encephalomyelitis (EAE) [14,34,35], collagen-induced arthritis [36,37], Lyme arthritis [37], inflammatory bowel disease [38], and autoimmune diabetes in non-obese diabetic (NOD) mice [39–41]. $1,25(OH)_2D_3$ analogs are able not only to prevent but also to treat ongoing autoimmune diseases, as demonstrated by their ability to inhibit type 1 diabetes development in adult NOD mice [41] and the recurrence of autoimmune disease after islet transplantation in the NOD mouse [42], or to ameliorate significantly the chronic-relapsing EAE induced in Biozzi mice by spinal cord homogenate [14].

An important property of $1,25(OH)_2D_3$ and its analogs is their capacity to modulate both APCs and T cells. The induction of tolerogenic DCs, which leads to an enhanced number of $CD4^+CD25^+$ regulatory T cells [41,43] renders them appealing for clinical use, especially for the prevention and treatment of autoimmune diseases and grsft rejection. In addition, additive and even synergistic effects have been observed between VDR agonists and immunosuppressive agents, such as CsA and sirolimus, in autoimmune diabetes and EAE models [44,45].

Distinct regulatory mechanisms may predominate in different autoimmune disease models, although a common pattern, characterized by inhibition of Th1 cell development, has been frequently observed.

3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an immune-mediated disease, with a prominent involvement of Th1 cells [46], characterized by articular inflammation and subsequent tissue damage leading to severe disability and increased mortality. Among the different animal models of RA, two have been used to test the effects of VDR agonists on the course of the disease, namely Lyme arthritis and collagen-induced arthritis in the mouse. Infection of mice with *Borrelia burgdorferi*, the causative agent of human Lyme arthritis, produces acute arthritic lesions with footpad and ankle swelling. Supplementation with $1,25(OH)_2D_3$ of an adequate diet fed to mice infected with *B. burgdorferi* minimized or prevented these symptoms [37]. The same treatment could also prevent collagen-induced arthritis, and when given to mice with

Table 3
Effects of VDR agonist treatment in animal models of autoimmune diseases

Experimental models	Main effects	References
Arthritis	Decreased incidence and severity of collagen-induced or Lyme arthritis, also when given at disease onset	[36,37]
Autoimmune diabetes	Inhibition of insulitis and reduction of diabetes, even when given after islet infiltration	[39,40,44,110]
Experimental allergic encephalomyelitis	Prevention and treatment of disease, inhibition of relapses	[14,34,74,107]
Inflammatory bowel disease	Significant amelioration of symptoms, block of of disease progression	[38]
Psoriasis	Inhibition of leukocyte activation and amelioration of histological and clinical sign of disease in human psoriatic skin grafts transplanted to SCID mice	[103]
Systemic lupus erythematosus	Inhibition of proteinuria, prevention of skin lesions	[31,33]

early symptoms prevented the progression to severe arthritis, compared with untreated controls [37]. In a separate study, VDR agonists displayed a similar capacity to prevent and to suppress already established collagen-induced arthritis without inducing hypercalcemia [36].

VDR expression by human articular chondrocytes in osteoarthritic cartilage has been found often associated with sites where matrix metalloproteinases (MMPs) expression was prevalent, in contrast to their virtual absence in normal age-matched cartilage [47]. Together with in vitro studies [48], the data suggests that $1,25(OH)_2D_3$ contributes to the regulation of MMPs and PGE_2 production by human articular chondrocytes in osteoarthritic cartilage. Coupled to the evidence obtained in animal models, these results suggest that VDR agonists may be able to control, at least in part, RA development.

3.2. Type 1 diabetes

The nonobese diabetic (NOD) mouse, that spontaneously develops type 1 diabetes with a pathogenesis similar to the human disease, represents a useful model for the study of autoimmune diabetes [49]. Several effector mechanisms leading to specific islet β-cell destruction have been identified, including cytotoxic $CD8^+$ lymphocytes and macrophages [50], both of which are regulated by IL-12-dependent T helper 1 (Th1) cells [51]. The activation of Th1 cells specific for β-cell autoantigens could reflect defective elimination of autoreactive T-cell clones [52], inefficient mechanisms of peripheral tolerance [53], enhanced IL-12 production [54] or impaired suppressive mechanisms [55].

Agents like $1,25(OH)_2D_3$ and its analogs, able to inhibit in vivo IL-12 production and Th1 development [14], and to enhance $CD4^+CD25^+$ regulatory T cells [43] may therefore be beneficial in the treatment of type 1 diabetes. $1,25(OH)_2D_3$ itself reduces the incidence of insulitis [56] and prevents type 1 diabetes development [39], but only when administered to NOD mice starting from three weeks of age, before the onset of insulitis. $1,25(OH)_2D_3$ was found ineffective in preventing progression of diabetes in NOD mice when given from 8 weeks of age, when NOD mice present a well established insulitis [57]. However, a combined treatment of 8-week-old NOD mice with the $1,25(OH)_2D_3$ analog MC 1288 and cyclosporine A reduced the incidence of disease, although neither treatment alone was effective [44]. In contrast, we have identified the $1,25(OH)_2D_3$ analog 1,25-dihydroxy-16,23*Z*-diene-26,27-hexafluoro-19-nor vitamin D_3 (BXL-219) that is able, as a monotherapy, to treat the ongoing type 1 diabetes in the adult NOD mouse, effectively blocking the disease course [41]. This property is likely due, at least in part, to the increased metabolic stability of this analog against the inactivating C-24 and C-26 hydroxylations, and the C-3 epimerization [58], resulting in a 100-fold more potent immunosuppressive activity compared to $1,25(OH)_2D_3$. A short treatment with non-hypercalcemic doses of BXL-219 inhibits IL-12 production and pancreatic infiltration of Th1 cells while increasing the frequency of $CD4^+CD25^+$ regulatory T cells in pancreatic lymph nodes, arresting the immunological progression and preventing the clinical onset of type 1 diabetes in the NOD mouse [41].

Protection from type 1 diabetes was found associated with a selective decrease of Th1 cells in the pancreatic lymph nodes and in the pancreas, without a marked deviation to the Th2 phenotype. The frequency of $CD4^+CD25^+$ cells in the pancreatic lymph nodes of VDR agonist-treated NOD mice was twofold higher compared to untreated 8-week-old and to age-matched vehicle-treated controls. These cells were anergic, as demonstrated by their impaired capacity to proliferate and secrete IFN-γ in response to TCR ligation, inhibited the T cell response to the pancreatic autoantigen IA-2, and delayed disease transfer by pathogenic $CD4^+CD25^-$ cells [41].

Immature DCs have been shown to induce $CD4^+$ cells with regulatory properties [59], and arrest of DCs at the immature stage induced by BXL-219 treatment could account for the enhanced frequency of $CD4^+CD25^+$ cells. $CD4^+CD25^+$ regulatory T cells appear to play an important role in controlling the progression of type 1 diabetes in NOD mice, because a low level of $CD4^+CD25^+$ T cells correlates with exacerbation and acceleration of the disease [55]. It is likely that this cell population is more relevant than Th2 cells in disease control, although both could contribute to protection. Indeed, $1,25(OH)_2D_3$ can induce regulatory cells with disease-suppressive activity in the NOD mouse [39] and a disease-preventing VDR agonist could deviate pancreas-infiltrating cells to the Th2 phenotype [44]. In addition, the pro-apoptotic activity of $1,25(OH)_2D_3$ and its analogs can restore the defective sensitivity to apoptosis of NOD lymphocytes [60], leading to a more efficient elimination of potentially dangerous autoimmune effector cells. Sensitization of inflammatory cells to apoptotic signals has also been implicated in the inhibition of EAE by $1,25(OH)_2D_3$ [61]. The increased apoptosis induced by $1,25(OH)_2D_3$ and its analogs in DCs [19] and T cells [60] has been observed after different apoptosis-inducing signals, and could help to explain why short-term treatments with these agents afford long-term protection and promote tolerance induction.

In both islet transplantation and type 1 diabetes models, treatment with VDR agonists has a profound effect on the migration of effector T cells, preventing their entry into the pancreatic islets [43,62]. Thus, VDR agonist-induced downregulation of chemokine production by islet cells could represent an important mechanism of action leading to inhibition of T1D development. We have found that transcripts encoding all Toll-like receptors (TLRs) are expressed by mouse and human islet cells and they are functional, as demonstrated by the

marked upregulation of chemokine production following TLR engagement by specific agonists [63], suggesting that TLR-mediated upregulation of proinflammatory chemokine production like CXCL10, CCL2, and CCL5 by islet cells plays an important role in the early events leading to leukocyte infiltration into the pancreatic islets. The constitutive and inducible production by mouse and human islet cells of CXCL10, an agonist for CXCR3 expressed by Th1 cells [64], was most prominent. CXCL10 has been implicated in human T1D, as elevated serum levels have been observed in diabetes patients and in autoantibody-positive subjects at risk of developing the disease [65,66]. In addition, our results show that CCL5, the agonist for CCR5, another chemokine receptor expressed by Th1 cells [64], is also constitutively produced by islet cells and is markedly upregulated following TLR ligation. Mouse islet cells produce, besides CCL5, the CCL2 and CCL3 agonists able to recruit $CCR1^+$ and $CCR2^+$ macrophages [63]. CCL2 has been shown to be produced also by human islet cells, and it appears to play an important role in the clinical outcome of islet transplantation in T1D patients [67]. Islet-produced CXCL10, CCL5, CCL2, and CCL3 could also recruit immature dendritic cells [64]. Thus, pancreatic β cells, as well as other islet cell types, produce chemokines potentially able to attract the pathogenic cells ultimately responsible for β cell death.

The VDR agonist BXL-219 significantly downregulates in vitro and in vivo proinflammatory chemokine production by islet cells, inhibiting T cell recruitment into the pancreatic islets and T1D development [63]. The inhibition of CXCL10 may be particularly relevant, consistent with the decreased recruitment of Th1 cells into sites of inflammation by treatment with an anti-CXCR3 antibody [68], and with the substantial delay of T1D development observed in CXCR3-deficient mice [69]. The inhibition of islet chemokine production by BXL-219 treatment in vivo persists after restimulation with TLR agonists and is associated with upregulation of IκBα transcription, an inhibitor of nuclear factor κB (NF-κB), and with arrest of NF-κB p65 nuclear translocation [63], highlighting a novel mechanism of action exerted by VDR agonists potentially relevant for the treatment of T1D and other autoimmune diseases. These observations expand the known mechanisms of action exerted by vitamin D analogs in the treatment of T1D and other autoimmune diseases, that include arrest of DC maturation, inhibition of Th1 cell responsiveness, and enhancement of regulatory T cells [5,6,25]. In addition to modulating chemokine production in target tissues such as pancreatic islets, it is also possible that VDR agonists can affect the migration of $CD25^+$ T regulatory cells by regulating their chemokine receptor expression, a hypothesis that we are currently testing.

The observation that ongoing type 1 diabetes in the adult NOD mouse can be arrested by a relatively short course of treatment with a VDR agonist suggests that a similar treatment may also inhibit disease progression in prediabetic or newly diagnosed type 1 diabetes patients. Polymorphisms of the vitamin D receptor gene have been associated with type 1 diabetes in different populations [70] and epidemiological studies have shown a higher incidence of the disease in northern than in southern latitudes [71], suggesting a possible involvement of a $1,25(OH)_2D_3$ deficiency in the pathogenesis of type 1 diabetes. This is further supported by a large population-based case-control study [72] and by a birth-cohort study [73] showing that the dietary vitamin D supplementation contributes to a significantly decreased risk of type 1 diabetes development.

3.3. Experimental allergic encephalomyelitis

Experimental allergic encephalomyelitis (EAE) is considered as a model for multiple sclerosis (MS), and in both diseases Th1-type cells specific for myelin antigens appear to play a pathogenic role [1]. $1,25(OH)_2D_3$ and the non-hypercalcaemic analogue (5*Z*,7*E*,23*E*,24a*E*)-(1*S*,3*R*)-24a,24b-dihomo-9,10-seco-cholesta-5,7,10(19),23,24a pentaene-1,3,25-triol (Ro 63–2023) have been shown to be selective and potent inhibitors of Th1 development in vitro and in vivo without inducing a deviation to the Th2 phenotype [14]. Administration of $1,25(OH)_2D_3$ or its analogue could prevent chronic-relapsing experimental allergic encephalomyelitis (CR-EAE) induced by the MOG peptide 35–55 in Biozzi AB/H mice, and this was associated with a profound reduction of $MOG_{35–55}$-specific proliferation and Th1 cell development. Importantly, the non-hypercalcaemic analogue Ro 63–2023 also provided long-term protection from EAE relapses induced by immunization with spinal cord homogenate when administered for a short time either at symptom onset or even after the first peak of disease. Neuropathological analysis showed a significant reduction of inflammatory infiltrates, demyelinated areas and axonal loss in brains and spinal cords of treated mice. Thus, inhibition of IL-12-dependent Th1 cell development is associated with effective treatment of CR-EAE, further suggesting the feasibility of this approach in the treatment of multiple sclerosis [1].

These results demonstrate a correlation between the capacity of $1,25(OH)_2D_3$ and the less calcemic analog Ro 63–2023 to inhibit IL-12-dependent Th1 development and to treat EAE, a correlation that was not established by previous studies [34,35,74,75]. Conversely, a systemic increase in the transcripts for TGF-β1 and IL-4 was suggested to be responsible for the capacity of $1,25(OH)_2D_3$ to inhibit EAE [75], in contrast with the results of Mattner et al. [14], demonstrating that $1,25(OH)_2D_3$ is a potent inhibitor of Th1 development and EAE without deviating the response to the Th2 pathway, as well as with the preferential inhibition of Th1 responses by $1,25(OH)_2D_3$ observed by Lemire et al. [13]. The reasons

for this discrepancy are not clear, although the different EAE models analyzed could play a role. TGF-β1 [76] and IL-4 [77,78] have been reported to be beneficial in EAE but this activity has been ascribed to indirect inhibition of encephalitogenic Th1 cells. IL-10 also appears to be critical in the control of pathogenic Th1 responses in EAE [79], and $1,25(OH)_2D_3$ has been shown in vitro to strongly enhance IL-10 production by human DCs [19] and to favour the induction of IL-10-producing regulatory T cells [80].

$1,25(OH)_2D_3$ can cross the intact blood–brain barrier [81] and could therefore directly inhibit CNS APCs, like microglia, that regulate intracerebral T cell responses [82], or target infiltrating T cells as well as recruited APCs. $1,25(OH)_2D_3$ administration inhibits the expression of inducible nitric oxide synthase in macrophages, activated microglia and astrocytes during EAE [83], and this could also contribute to amelioration of the disease. Alternatively, the immunomodulatory effects of VDR agonists could be mainly exerted in peripheral lymphoid organs leading to inhibition of encephalitogenic T cell development.

3.4. Inflammatory bowel disease

Inflammatory bowel diseases (IBDs) are immune-mediated diseases of unknown aetiology affecting the gastrointestinal tract. At least two distinct forms of IBDs have been defined, ulcerative colitis, and Crohn's disease. These are chronic recurring illnesses most commonly involving inflammation of the terminal ileum and colon, although they can also affect many sites throughout the alimentary tract. In addition to genetic factors, including also VDR gene polymorphisms [84], the environment contributes to IBD development, and vitamin D may be an important environmental component in this respect. Lower amounts of $1,25(OH)_2D_3$ are synthesized from sunlight exposure in areas in which IBDs occur most often, such as North America and Northern Europe [85], a situation common to other autoimmune diseases [86], in particular type 1 diabetes [71], and multiple sclerosis [87]. Dietary intake of vitamin D is problematic because few foods are naturally rich in vitamin D and weight loss, with consequently reduced vitamin D intake, occurs in the majority of IBD patients.

In IBD models, the immune-mediated attack against the gastro-intestinal tract has been shown to be mediated by Th1 cells [88], and the production of Th1-type cytokines has also been found associated with human IBDs [89]. Animal models have been developed in which IBD symptoms occur spontaneously, and a well-studied one is the IL-10 knock-out (KO) mouse [90]. In conventional animal facilities, IL-10 KO mice develop enterocolitis within 5–8 weeks of life, and approximately 30% of these mice die of severe anemia and weight loss [90]. The enterocolitis that develops in IL-10 KO mice is due to an uncontrolled immune response to conventional microflora, because germfree IL-10 KO mice do not develop disease, and mice raised in specific pathogen-free facilities develop a milder disease [90]. IL-10 KO mice were made vitamin D deficient, vitamin D sufficient or supplemented with $1,25(OH)_2D_3$ [38]. Vitamin D-deficient, in contrast to vitamin D-sufficient IL-10 KO mice, rapidly developed diarrhea and a severe wasting disease. The essential role of VDR-mediated signaling in the control of IBD has been confirmed by the accelerated and enhanced disease observed in VDR/IL-10 double-deficient mice [91].

Administration of $1,25(OH)_2D_3$ significantly ameliorated IBD symptoms in IL-10 KO mice and treatment for as little as 2 weeks blocked the progression and ameliorated symptoms in mice with already established IBD [38]. This would be consistent with the observation that patients with Crohn's disease have depressed IL-10 production and respond positively to IL-10 administration [92]. Interestingly, VDR agonists inhibit the proliferation of rectal epithelial cells [93] and of T cells [94] in active ulcerative colitis patients, further suggesting their possible use in the treatment of IBDs.

3.5. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a T-cell dependent antibody-mediated autoimmune disease and the mouse strain $MRL^{lpr/lpr}$ spontaneously develops a SLE-like syndrome sharing many immunological features with human SLE. Administration of VDR agonists significantly prolonged the average life span of $MRL^{lpr/lpr}$ mice and induced a significant reduction in proteinuria, renal arteritis, granuloma formation, and knee joint arthritis [31–33]. In addition, dermatological lesions, like alopecia, necrosis of the ear, and scab formation, were also completely inhibited by $1,25(OH)_2D_3$ therapy [33].

These data suggest a beneficial role of VDR agonists in the treatment of human SLE. Indeed, VDR agonists can significantly reduce cell proliferation and IgG production, both polyclonal and anti-dsDNA, while enhancing B cell apoptosis in lymphocytes from SLE patients [95]. However, it has also been shown that in (NZBxW)F1 mice, prone to developing SLE, treatment with $1,25(OH)_2D_3$ worsens the disease, possibly explaining how sunlight could be a factor aggravating the course of SLE [96]. These results could be reconciled by the observation that $MRL^{lpr/lpr}$ mice receiving $1,25(OH)_2D_3$ and a diet with a normal/high calcium content (0.87%) showed reduced SLE, whereas the same treatment in $MRL^{lpr/lpr}$ mice on a very low calcium content diet (0.02%) led to accelerated and more severe SLE [4], a situation already noted in EAE [97].

3.6. Psoriasis

Psoriasis is a chronic inflammatory skin disease that affects about 2% of the population. Although the pathogenesis of psoriasis is still incompletely understood, it appears to be primarily a Th1-mediated autoimmune disease involving hyperproliferation of keratinocytes [98]. Given the capacity of VDR agonists to modulate both cell types, their success in treating psoriasis is perhaps not surprising. VDR agonists are currently the mainstay treatment in mild and moderate psoriasis, accounting for about 50% of all drugs used to treat this disease. At present, VDR agonists are used only topically, because a safe analog for systemic use has not yet been developed. In addition to topical calcitriol, calcipotriol, and tacalcitol have shown efficacy and safety in extensive controlled studies [99].

Mechanistically, the beneficial effects of VDR agonists in psoriasis could reflect inhibition of proliferation and cytokine production by skin-infiltrating T cells [100]. VDR agonists have been shown to increase IL-10 production in psoriatic lesions [101] and to decrease IL-6 and IL-8 secretion by keratinocytes [102]. In addition, $1,25(OH)_2D_3$ but not IL-10 could prevent leukocyte activation and reduce the histological and clinical scores in human psoriatic skin transplanted onto SCID mice [103]. The apoptotic process in psoriatic lesions has been suggested to be in part regulated by Bcl-xL, and decreasing the expression of Bcl-xL by treatment with VDR agonists might ameliorate psoriatic lesions by contributing to the completion of the apoptotic process [104].

4. Conclusions

The vitamin D endocrine system is involved in a variety of biological processes able to modulate immune responses, and the tolerogenic properties of VDR agonists render this class of compounds particularly suitable for the treatment of autoimmune diseases. However, topical treatment of psoriasis is the only clinical application so far established for VDR agonists in the therapy of autoimmune diseases. The calcemic liability of VDR agonists has certainly contributed to hamper progress towards clinical applications, a situation that may be corrected by the ongoing development of several more potent and less calcemic analogs. A challenge for the future will be the development of safe VDR agonists for the systemic treatment of psoriasis, and the translation to the clinic of orally active VDR agonists that have been shown to effectively treat a given experimental autoimmune disease. The accumulating evidence for the multiple immunomodulatory mechanisms regulated by VDR agonists should indeed prompt further exploration of their potential in the development of therapies for several autoimmune disorders.

References

[1] L. Adorini, Selective immunointervention in autoimmune diseases: lessons from multiple sclerosis, J. Chemother. 13 (2001) 219–234.

[2] P.T. Coates, B.L. Colvin, K. Kaneko, T. Taner, A.W. Thomson, Pharmacologic, biologic, and genetic engineering approaches to potentiation of donor-derived dendritic cell tolerogenicity, Transplantation 75 (2003) 32S–36S.

[3] L. Adorini, N. Giarratana, G. Penna, Pharmacological induction of tolerogenic dendritic cells and regulatory T cells, Semin. Immunol. 16 (2004) 127–134.

[4] H.F. Deluca, M.T. Cantorna, Vitamin D: its role and uses in immunology, FASEB J. 15 (2001) 2579–2585.

[5] C. Mathieu, L. Adorini, The coming of age of 1,25-dihydroxyvitamin D(3) analogs as immunomodulatory agents, Trends Mol. Med. 8 (2002) 174–179.

[6] M.D. Griffin, N. Xing, R. Kumar, Vitamin D and its analogs as regulators of immune activation and antigen presentation, Annu. Rev. Nutr. (2003).

[7] K.V. Pinette, Y.K. Yee, B.Y. Amegadzie, S. Nagpal, Vitamin D receptor as a drug discovery target, Mini. Rev. Med. Chem. 3 (2003) 193–204.

[8] A.W. Norman, M.T. Mizwicki, W.H. Okamura, Ligand structure–function relationships in the vitamin D endocrine system from the perspective of drug development (including cancer treatment), Recent Results Cancer Res. 164 (2003) 55–82.

[9] M.R. Haussler, G.K. Whitfield, C.A. Haussler, J.C. Hsieh, P.D. Thompson, S.H. Selznick, C.E. Dominguez, P.W. Jurutka, The nuclear vitamin D receptor: biological and molecular regulatory properties revealed, J. Bone Miner. Res. 13 (1998) 325–349.

[10] A.W. Norman, S. Ishizuka, W.H. Okamura, Ligands for the vitamin D endocrine system: different shapes function as agonists and antagonists for genomic and rapid response receptors or as a ligand for the plasma vitamin D binding protein, J. Steroid Biochem. Mol. Biol. 76 (2001) 49–59.

[11] C. Carlberg, P. Polly, Gene regulation by vitamin D3, Crit. Rev. Eukaryot. Gene Expr. 8 (1998) 19–42.

[12] A.K. Bhalla, E.P. Amento, B. Serog, L.H. Glimcher, 1,25-Dihydroxyvitamin D3 inhibits antigen-induced T cell activation, J. Immunol. 133 (1984) 1748–1754.

[13] J.M. Lemire, D.C. Archer, L. Beck, H.L. Spiegelberg, Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions, J. Nutr. 125 (1995) 1704S–1708S.

[14] F. Mattner, S. Smiroldo, F. Galbiati, M. Muller, P. Di Lucia, P.L. Poliani, G. Martino, P. Panina-Bordignon, L. Adorini, Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D_3, Eur. J. Immunol. 30 (2000) 498–508.

[15] I. Alroy, T. Towers, L. Freedman, Transcriptional repression of the interleukin-2 gene by vitamin D_3: direct inhibition NFATp/AP-1 complex formation by a nuclear hormone receptor, Mol. Cell. Biol. 15 (1995) 5789–5799.

[16] A. Takeuchi, G. Reddy, T. Kobayashi, T. Okano, J. Park, S. Sharma, Nuclear factor of activated T cells (NFAT) as a molecular target for 1a,25-dihydroxyvitamin D_3-mediated effects, J. Immunol. 160 (1998) 209–218.

[17] M. Cippitelli, A. Santoni, Vitamin D3: a transcriptional modulator of the interferon-gamma gene, Eur. J. Immunol. 28 (1998) 3017–3030.

[18] A. Boonstra, F.J. Barrat, C. Crain, V.L. Heath, H.F. Savelkoul, A. O'Garra, 1alpha,25-Dihydroxyvitamin D3 has a direct effect on naive $CD4^+$ T cells to enhance the development of Th2 cells, J. Immunol. 167 (2001) 4974–4980.

[19] G. Penna, L. Adorini, 1,25-Dihydroxyvitamin D3 inhibits differentiation, maturation, activation and survival of dendritic cells leading to impaired alloreactive T cell activation, J. Immunol. 164 (2000) 2405–2411.

[20] L. Piemonti, P. Monti, M. Sironi, P. Fraticelli, B.E. Leone, E. Dal Cin, P. Allavena, V. Di Carlo, Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells, J. Immunol. 164 (2000) 4443–4451.
[21] M.D. Griffin, W.H. Lutz, V.A. Phan, L.A. Bachman, D.J. McKean, R. Kumar, Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs, Biochem. Biophys. Res. Commun. 270 (2000) 701–708.
[22] A. Berer, J. Stockl, O. Majdic, T. Wagner, M. Kollars, K. Lechner, K. Geissler, L. Oehler, 1,25-Dihydroxyvitamin D(3) inhibits dendritic cell differentiation and maturation in vitro, Exp. Hematol. 28 (2000) 575–583.
[23] M.O. Canning, K. Grotenhuis, H. de Wit, C. Ruwhof, H.A. Drexhage, 1-alpha,25-Dihydroxyvitamin D3 (1,25(OH)(2)D(3)) hampers the maturation of fully active immature dendritic cells from monocytes, Eur. J. Endocrinol. 145 (2001) 351–357.
[24] A.G. van Halteren, E. van Etten, E.C. de Jong, R. Bouillon, B.O. Roep, C. Mathieu, Redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D(3), Diabetes 51 (2002) 2119–2125.
[25] L. Adorini, Immunomodulatory effects of vitamin D receptor ligands in autoimmune diseases, Int. Immunopharmacol. 2 (2002) 1017–1028.
[26] P.F. Barnes, R.L. Modlin, D.D. Bikle, J.S. Adams, Transpleural gradient of 1,25-dihydroxyvitamin D in tuberculous pleuritis, J. Clin. Invest. 83 (1989) 1527–1532.
[27] J. Cadranel, M. Garabedian, B. Milleron, H. Guillozo, G. Akoun, A.J. Hance, 1,25(OH)2D2 production by T lymphocytes and alveolar macrophages recovered by lavage from normocalcemic patients with tuberculosis, J. Clin. Invest. 85 (1990) 1588–1593.
[28] L. Overbergh, B. Decallonne, D. Valckx, A. Verstuyf, J. Depovere, J. Laureys, O. Rutgeerts, R. Saint-Arnaud, R. Bouillon, C. Mathieu, Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages, Clin. Exp. Immunol. 120 (2000) 139–146.
[29] M. Hewison, L. Freeman, S.V. Hughes, K.N. Evans, R. Bland, A.G. Eliopoulos, M.D. Kilby, P.A. Moss, R. Chakraverty, Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells, J. Immunol. 170 (2003) 5382–5390.
[30] M.D. Griffin, W. Lutz, V.A. Phan, L.A. Bachman, D.J. McKean, R. Kumar, Dendritic cell modulation by 1alpha,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo, Proc. Natl. Acad. Sci. USA 98 (2001) 6800–6805.
[31] T. Koizumi, Y. Nakao, T. Matsui, T. Nakagawa, S. Matsuda, K. Komoriya, Y. Kanai, T. Fujita, Effects of corticosteroid and 1,24*R*-dihydroxy-vitamin D3 administration on lymphoproliferation and autoimmune disease in MRL/MP-lpr/lpr mice, Int. Arch. Allergy Appl. Immunol. 77 (1985) 396–404.
[32] J. Abe, K. Nakamura, Y. Takita, T. Nakano, H. Irie, Y. Nishii, Prevention of immunological disorders in MRL/l mice by a new synthetic analogue of vitamin D3: 22-oxa-1 alpha,25-dihydroxyvitamin D3, J. Nutr. Sci. Vitaminol. (Tokyo) 36 (1990) 21–31.
[33] J.M. Lemire, A. Ince, M. Takashima, 1,25-Dihydroxyvitamin D3 attenuates the expression of experimental murine lupus of MRL/l mice, Autoimmunity 12 (1992) 143–148.
[34] J.M. Lemire, D.C. Archer, 1,25-Dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis, J. Clin. Invest. 87 (1991) 1103–1107.
[35] M.T. Cantorna, C.E. Hayes, H.F. DeLuca, 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis, Proc. Natl. Acad. Sci. USA 93 (1996) 7861–7864.
[36] P. Larsson, L. Mattsson, L. Klareskog, C. Johnsson, A vitamin D analogue (MC 1288) has immunomodulatory properties and suppresses collagen-induced arthritis (CIA) without causing hypercalcaemia, Clin. Exp. Immunol. 114 (1998) 277–283.
[37] M.T. Cantorna, C.E. Hayes, H.F. DeLuca, 1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis, J. Nutr. 128 (1998) 68–72.
[38] M.T. Cantorna, C. Munsick, C. Bemiss, B.D. Mahon, 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease, J. Nutr. 130 (2000) 2648–2652.
[39] C. Mathieu, M. Waer, J. Laureys, O. Rutgeerts, R. Bouillon, Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3, Diabetologia 37 (1994) 552–558.
[40] C. Mathieu, M. Waer, K. Casteels, J. Laureys, R. Bouillon, Prevention of type I diabetes in NOD mice by nonhypercalcemic doses of a new structural analog of 1,25-dihydroxyvitamin D3, KH1060, Endocrinology 136 (1995) 866–872.
[41] G. Gregori, N. Giarratana, S. Smiroldo, M. Uskokovic, L. Adorini, A 1a,25-Dihydroxyvitamin D_3 analog enhances regulatory T cells and arrests autoimmune diabetes in NOD mice, Diabetes 51 (2002) 1374–1376.
[42] K. Casteels, M. Waer, J. Laureys, D. Valckx, J. Depovere, R. Bouillon, C. Mathieu, Prevention of autoimmune destruction of syngeneic islet grafts in spontaneously diabetic nonobese diabetic mice by a combination of a vitamin D3 analog and cyclosporine, Transplantation 65 (1998) 1225–1232.
[43] S. Gregori, M. Casorati, S. Amuchastegui, S. Smiroldo, A.M. Davalli, L. Adorini, Regulatory T cells induced by 1a,25-Dihydroxyvitamin D_3 and mycophenolate mofetil treatment mediate transplantation tolerance, J. Immunol. 167 (2001) 1945–1953.
[44] K.M. Casteels, C. Mathieu, M. Waer, D. Valckx, L. Overbergh, J.M. Laureys, R. Bouillon, Prevention of type I diabetes in nonobese diabetic mice by late intervention with nonhypercalcemic analogs of 1,25-dihydroxyvitamin D3 in combination with a short induction course of cyclosporin A, Endocrinology 139 (1998) 95–102.
[45] E. van Etten, D.D. Branisteanu, A. Verstuyf, M. Waer, R. Bouillon, C. Mathieu, Analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants, Transplantation 69 (2000) 1932–1942.
[46] H. Schulze-Koops, J.R. Kalden, The balance of Th1/Th2 cytokines in rheumatoid arthritis, Best Pract. Res. Clin. Rheumatol. 15 (2001) 677–691.
[47] L.C. Tetlow, D.E. Woolley, Expression of vitamin D receptors and matrix metalloproteinases in osteoarthritic cartilage and human articular chondrocytes in vitro, Osteoarthritis Cartilage 9 (2001) 423–431.
[48] L.C. Tetlow, D.E. Woolley, The effects of 1 alpha,25-dihydroxyvitamin D(3) on matrix metalloproteinase and prostaglandin E(2) production by cells of the rheumatoid lesion, Arthritis Res. 1 (1999) 63–70.
[49] M.A. Atkinson, E.H. Leiter, The NOD mouse model of type 1 diabetes: as good as it gets?, Nat. Med. 5 (1999) 601–604.
[50] C. Benoist, D. Mathis, Cell death mediators in autoimmune diabetes—no shortage of suspects, Cell 89 (1997) 1–3.
[51] S. Trembleau, G. Penna, E. Bosi, A. Mortara, M.K. Gately, L. Adorini, IL-12 administration induces Th1 cells and accelerates autoimmune diabetes in NOD mice, J. Exp. Med. 181 (1995) 817–821.
[52] W.M. Ridgway, M. Fasso, A. Lanctot, C. Garvey, C.G. Fathman, Breaking self-tolerance in nonobese diabetic mice, J. Exp. Med. 183 (1996) 1657–1662.
[53] T.L. Delovitch, B. Singh, The non-obese diabetic mouse as a model of autoimmune diabetes: immune dysregulation gets the NOD, Immunity 7 (1997) 727–738.
[54] L. Adorini, Interleukin 12 and autoimmune diabetes, Nat. Genet. 27 (2001) 131–132.

[55] B. Salomon, D.J. Lenschow, L. Rhee, N. Ashourian, B. Singh, A. Sharpe, J.A. Bluestone, B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes, Immunity 12 (2000) 431–440.
[56] C. Mathieu, J. Laureys, H. Sobis, M. Vandeputte, M. Waer, R. Bouillon, 1,25-Dihydroxyvitamin D3 prevents insulitis in NOD mice, Diabetes 41 (1992) 1491–1495.
[57] C. Mathieu, K. Casteels, R. Boullion, Vitamin D and Diabetes, Academic Press, New York, 1997.
[58] M.R. Uskokovic, A.W. Norman, P.S. Manchand, G.P. Studzinski, M.J. Campbell, H.P. Koeffler, A. Takeuchi, M. Siu-Caldera, D.S. Rao, G.S. Reddy, Highly active analogs of 1alpha,25-dihydroxyvitamin D(3) that resist metabolism through C-24 oxidation and C-3 epimerization pathways, Steroids 66 (2001) 463–471.
[59] H. Jonuleit, E. Schmitt, G. Schuler, J. Knop, A.H. Enk, Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells, J. Exp. Med. 192 (2000) 1213–1222.
[60] K.M. Casteels, C.A. Gysemans, M. Waer, R. Bouillon, J.M. Laureys, J. Depovere, C. Mathieu, Sex difference in resistance to dexamethasone-induced apoptosis in NOD mice: treatment with 1,25(OH)2D3 restores defect, Diabetes 47 (1998) 1033–1037.
[61] K.M. Spach, L.B. Pedersen, F.E. Nashold, T. Kayo, B.S. Yandell, T.A. Prolla, C.E. Hayes, Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis, Physiol. Genomics 18 (2004) 141–151.
[62] L. Adorini, S. Gregori, L.C. Harrison, Understanding autoimmune diabetes: insights from mouse models, Trends Mol. Med. 8 (2002) 31–38.
[63] N. Giarratana, G. Penna, S. Amuchastegui, R. Mariani, K.C. Daniel, L. Adorini, A vitamin D analog downregulates proinflammatory chemokine production by pancreatic islets inhibiting T cell recruitment and type 1 diabetes development, J. Immunol. 173 (2004) 2280–2287.
[64] D. Rossi, A. Zlotnik, The biology of chemokines and their receptors, Annu. Rev. Immunol. 18 (2000) 217–242.
[65] A. Shimada, J. Morimoto, K. Kodama, R. Suzuki, Y. Oikawa, O. Funae, A. Kasuga, T. Saruta, S. Narumi, Elevated serum IP-10 levels observed in type 1 diabetes, Diabetes Care 24 (2001) 510–515.
[66] F. Nicoletti, I. Conget, M. Di Mauro, R. Di Marco, M.C. Mazzarino, K. Bendtzen, A. Messina, R. Gomis, Serum concentrations of the interferon-gamma-inducible chemokine IP-10/CXCL10 are augmented in both newly diagnosed Type I diabetes mellitus patients and subjects at risk of developing the disease, Diabetologia 45 (2002) 1107–1110.
[67] L. Piemonti, B.E. Leone, R. Nano, A. Saccani, P. Monti, P. Maffi, G. Bianchi, A. Sica, G. Peri, R. Melzi, L. Aldrighetti, A. Secchi, V. Di Carlo, P. Allavena, F. Bertuzzi, Human pancreatic islets produce and secrete MCP-1/CCL2: relevance in human islet transplantation, Diabetes 51 (2002) 55–65.
[68] J.H. Xie, N. Nomura, M. Lu, S.L. Chen, G.E. Koch, Y. Weng, R. Rosa, J. Di Salvo, J. Mudgett, L.B. Peterson, L.S. Wicker, J.A. DeMartino, Antibody-mediated blockade of the CXCR3 chemokine receptor results in diminished recruitment of T helper 1 cells into sites of inflammation, J. Leukoc. Biol. 73 (2003) 771–780.
[69] S. Frigerio, T. Junt, B. Lu, C. Gerard, U. Zumsteg, G.A. Hollander, L. Piali, Beta cells are responsible for CXCR3-mediated T-cell infiltration in insulitis, Nat. Med. 8 (2002) 1414–1420.
[70] A.G. Uitterlinden, Y. Fang, J.B. Van Meurs, H.A. Pols, J.P. Van Leeuwen, Genetics and biology of vitamin D receptor polymorphisms, Gene 338 (2004) 143–156.
[71] A. Green, E.A. Gale, C.C. Patterson, Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study, Lancet 339 (1992) 905–909.
[72] Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group, Diabetologia 42 (1999) 51–54.
[73] E. Hypponen, E. Laara, A. Reunanen, M.R. Jarvelin, S.M. Virtanen, Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study, Lancet 358 (2001) 1500–1503.
[74] D. Branisteanu, M. Waer, H. Sobis, S. Marcelis, M. Vandeputte, R. Boullion, Prevention of murine experimental allergic encephalomyelitis: cooperative effects of cyclosporine and 1 a,25-$(OH)_2D_3$, J. Neuroimmunol. 61 (1995) 151–160.
[75] M. Cantorna, W. Woodward, C. Hayes, H. DeLuca, 1,25-Dihydroxyvitamin D_3 is a positive regulator for the two anti-encephalitogenic cytokines TGF-b1 and IL-4, J. Immunol. 160 (1998) 5314–5319.
[76] M. Racke, S. Dhib-Jalbut, B. Cannella, P. Alert, C. Raine, D. McFarlin, Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-b1, J. Immunol. 146 (1991) 3012–3019.
[77] M.K. Racke, A. Bonomo, D.E. Scott, B. Cannella, A. Levine, C.S. Raine, E.M. Shevach, M. Roecken, Cytokine-induced immune deviation as a therapy for inflammatory autoimmune disease, J. Exp. Med. 180 (1994) 1961–1966.
[78] R. Furlan, P.L. Poliani, F. Galbiati, A. Bergami, L. Grimaldi, G. Comi, L. Adorini, G. Martino, Central nervous system delivery of interleukin 4 by a nonreplicative herpes simplex type 1 viral vector ameliorates autoimmune demyelination, Hum. Gene Ther. 9 (1998) 2605–2617.
[79] E. Bettelli, M. Prabhu Das, E.D. Howard, H.L. Weiner, R.A. Sobel, V.K. Kuchroo, IL-10 is critical in the regulation of autoimmune encephalomyelitis as demonstrated by studies of IL-10- and IL-4-deficient and transgenic mice, J. Immunol. 161 (1998) 3299–3306.
[80] F.J. Barrat, D.J. Cua, A. Boonstra, D.F. Richards, C. Crain, H.F. Savelkoul, R. de Waal-Malefyt, R.L. Coffman, C.M. Hawrylowicz, A. O'Garra, In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines, J. Exp. Med. 195 (2002) 603–616.
[81] M. Gascon-Barre, P. Huet, Apparent [^{3}H]1,25-dihydroxyvitamin D3 uptake by canine and rodent brain, Am. J. Physiol. 244 (1983) 266–271.
[82] F. Aloisi, F. Ria, L. Adorini, Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes, Immunol. Today 21 (2000) 141–147.
[83] E. Garcion, S. Nataf, A. Berod, F. Darcy, P. Brachet, 1,25-Dihydroxyvitamin D3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis, Brain Res. 45 (1997) 255–267.
[84] J.D. Simmons, C. Mullighan, K.I. Welsh, D.P. Jewell, Vitamin D receptor gene polymorphism: association with Crohn's disease susceptibility, Gut 47 (2000) 211–214.
[85] B.A. Hendrickson, R. Gokhale, J.H. Cho, Clinical aspects and pathophysiology of inflammatory bowel disease, Clin. Microbiol. Rev. 15 (2002) 79–94.
[86] M.T. Cantorna, Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence?, Proc. Soc. Exp. Biol. Med. 223 (2000) 230–233.
[87] C.E. Hayes, Vitamin D: a natural inhibitor of multiple sclerosis, Proc. Nutr. Soc. 59 (2000) 531–535.
[88] S. Bregenholt, M.H. Claesson, Increased intracellular Th1 cytokines in scid mice with inflammatory bowel disease, Eur. J. Immunol. 28 (1998) 379–389.
[89] M. Niessner, B.A. Volk, Altered Th1/Th2 cytokine profiles in the intestinal mucosa of patients with inflammatory bowel disease as assessed by quantitative reversed transcribed polymerase chain reaction (RT-PCR, Clin. Exp. Immunol. 101 (1995) 428–435.

[90] R. Kuhn, J. Lohler, D. Rennick, K. Rajewsky, W. Muller, Interleukin-10-deficient mice develop chronic enterocolitis, Cell 75 (1993) 263–274.
[91] M. Froicu, V. Weaver, T.A. Wynn, M.A. McDowell, J.E. Welsh, M.T. Cantorna, A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases, Mol. Endocrinol. 17 (2003) 2386–2392.
[92] K. Asadullah, W. Sterry, H.D. Volk, Interleukin-10 therapy—review of a new approach, Pharmacol. Rev. 55 (2003) 241–269.
[93] M.G. Thomas, K.P. Nugent, A. Forbes, R.C. Williamson, Calcipotriol inhibits rectal epithelial cell proliferation in ulcerative proctocolitis, Gut 35 (1994) 1718–1720.
[94] M. Stio, A.G. Bonanomi, G. d'Albasio, C. Treves, Suppressive effect of 1,25-dihydroxyvitamin D3 and its analogues EB 1089 and KH 1060 on T lymphocyte proliferation in active ulcerative colitis, Biochem. Pharmacol. 61 (2001) 365–371.
[95] M. Linker-Israeli, E. Elstner, J.R. Klinenberg, D.J. Wallace, H.P. Koeffler, Vitamin D(3) and its synthetic analogs inhibit the spontaneous in vitro immunoglobulin production by SLE-derived PBMC, Clin. Immunol. 99 (2001) 82–93.
[96] M.W. Vaisberg, R. Kaneno, M.F. Franco, N.F. Mendes, Influence of cholecalciferol (vitamin D3) on the course of experimental systemic lupus erythematosus in F1 (NZBxW) mice., J. Clin. Lab. Anal. 14 (2000) 91–96.
[97] M.T. Cantorna, J. Humpal-Winter, H.F. DeLuca, Dietary calcium is a major factor in 1,25-dihydroxycholecalciferol suppression of experimental autoimmune encephalomyelitis in mice, J. Nutr. 129 (1999) 1966–1971.
[98] K. Uyemura, M. Yamamura, D.F. Fivenson, R.L. Modlin, B.J. Nickoloff, The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response, J. Invest. Dermatol. 101 (1993) 701–705.
[99] D.M. Ashcroft, A.L. Po, H.C. Williams, C.E. Griffiths, Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis, BMJ 320 (2000) 963–967.
[100] M. Barna, J.D. Bos, M.L. Kapsenberg, F.G. Snijdewint, Effect of calcitriol on the production of T-cell-derived cytokines in psoriasis, Br. J. Dermatol. 136 (1997) 536–5341.
[101] S. Kang, S. Yi, C.E. Griffiths, L. Fancher, T.A. Hamilton, J.H. Choi, Calcipotriene-induced improvement in psoriasis is associated with reduced interleukin-8 and increased interleukin-10 levels within lesions, Br. J. Dermatol. 138 (1998) 77–83.
[102] M. Komine, Y. Watabe, S. Shimaoka, F. Sato, K. Kake, H. Nishina, M. Ohtsuki, H. Nakagawa, K. Tamaki, The action of a novel vitamin D3 analogue, OCT, on immunomodulatory function of keratinocytes and lymphocytes, Arch. Dermatol. Res. 291 (1999) 500–506.
[103] T.N. Dam, S. Kang, B.J. Nickoloff, J.J. Voorhees, 1alpha,25-Dihydroxycholecalciferol and cyclosporine suppress induction and promote resolution of psoriasis in human skin grafts transplanted on to SCID mice, J. Invest. Dermatol. 113 (1999) 1082–1089.
[104] Y. Fukuya, M. Higaki, Y. Higaki, M. Kawashima, Effect of vitamin D3 on the increased expression of Bcl-xL in psoriasis, Arch. Dermatol. Res. 293 (2002) 620–625.
[105] T.P. Staeva-Vieira, L.P. Freedman, 1,25-Dihydroxyvitamin D3 inhibits IFN-gamma and IL-4 levels during in vitro polarization of primary murine CD4+ T cells, J. Immunol. 168 (2002) 1181–1189.
[106] L. Overbergh, B. Decallonne, M. Waer, O. Rutgeerts, D. Valckx, K.M. Casteels, J. Laureys, R. Bouillon, C. Mathieu, 1alpha,25-Dihydroxyvitamin D3 induces an autoantigen-specific T-helper 1/T-helper 2 immune shift in NOD mice immunized with GAD65 (p524–543), Diabetes 49 (2000) 1301–1307.
[107] F.E. Nashold, K.A. Hoag, J. Goverman, C.E. Hayes, Rag-1-dependent cells are necessary for 1,25-dihydroxyvitamin D3 prevention of experimental autoimmune encephalomyelitis, J. Neuroimmunol. 119 (2001) 16–29.
[108] M. Cippitelli, C. Fionda, D. Di Bona, F. Di Rosa, A. Lupo, M. Piccoli, L. Frati, A. Santoni, Negative regulation of CD95 ligand gene expression by vitamin D3 in T lymphocytes, J. Immunol. 168 (2002) 1154–1166.
[109] M. Vulcano, S. Struyf, P. Scapini, M. Cassatella, S. Bernasconi, R. Bonecchi, A. Calleri, G. Penna, L. Adorini, W. Luini, A. Mantovani, J. Van Damme, S. Sozzani, Unique regulation of CCL18 production by maturing dendritic cells, J. Immunol. 170 (2003) 3843–3849.
[110] M. Inaba, Y. Nishizawa, K. Song, H. Tanishita, S. Okuno, T. Miki, H. Morii, Partial protection of 1 alpha-hydroxyvitamin D3 against the development of diabetes induced by multiple low-dose streptozotocin injection in CD-1 mice, Metabolism 41 (1992) 631–635.