The vitamin D receptor and T cell function

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INTRODUCTION

The purpose of the immune system is to recognize and clear pathogens from the body. However, occasionally unwanted immune reactions against self-tissue that lead to autoimmune diseases occur. The frequency of autoimmune diseases such as type 1 diabetes mellitus (Staples et al., 2003; Sloka et al., 2010), rheumatoid arthritis (Vieira et al., 2010), multiple sclerosis (MS) (Hogancamp et al., 1997), and inflammatory bowel disease (Khalili et al., 2012) has been linked to geographic location. One explanation of this geographical distribution is a higher exposure to sunlight and hence lower levels of vitamin D (25(OH)D3) at higher degrees of latitude. Another possible explanation of these diseases at higher degrees of latitude is a higher incidence of these diseases at higher latitudes. One explanation of this geographical distribution is a higher exposure to sunlight and hence lower levels of vitamin D (25(OH)D3) at higher degrees of latitude, as confirmed by studies showing an association between low serum levels of 25(OH)D3 and development of autoimmune diseases (Pierrot-Deseilligny and Souberbielle, 2010; Rossini et al., 2010; Greer et al., 2012). Low serum levels of 25(OH)D3 have also been linked to higher susceptibility to infections such as tuberculosis (Nnoaham and Clarke, 2008), influenza (Cannell et al., 2006; Grant, 2008), HIV (Rodriguez et al., 2009), respiratory syncytial virus (Grant, 2008), and viral infections of the upper respiratory tract (Ginde et al., 2009). It is therefore apparent that vitamin D plays a role in immune modulation. A recent acknowledgment that the majority of immune cells expresses the vitamin D receptor (VDR) (Kreutz et al., 1993; Hewison et al., 2003; Baek et al., 2010; von Essen et al., 2010; Goldmeyer-Hilt et al., 2011; Joseph et al., 2012) and also the enzyme CYP27B1 used for internal conversion of circulating 25(OH)D3 to the VDR-ligand 1,25(OH)2D3 (Hewison et al., 2003; Baek et al., 2010) has further strengthened this perception.

VITAMIN D, VDR, AND T CELL FUNCTION

MECHANISM OF 1,25(OH)2D3 ACTION

The cellular actions of 1,25(OH)2D3 are mediated by the VDR, a ligand-dependent transcription regulator molecule belonging to the superfamily of nuclear receptors. In the absence of 1,25(OH)2D3, VDR is mainly distributed to the cytoplasm (Nagpal et al., 2005). Interaction of VDR with its ligand 1,25(OH)2D3 induces formation of two independent protein interaction surfaces on the VDR, one that facilitates association with the retinoid X receptor (RXR) necessary for DNA binding, and one that is required for recruitment of co-regulators necessary for gene modulation (Pike et al., 2012). Following interaction with 1,25(OH)2D3-VDR dimerizes with RXR and translocates to the nucleus where it binds to vitamin D response elements (VDRE) in vitamin D responsive genes. Depending on the target gene either co-activators or co-repressors are attracted to the VDR/RXR complexes to induce or repress gene transcription (Nagpal et al., 2005; Pike et al., 2012; Haussler et al., 2013). Even though details of how these co-regulatory complexes work are only slowly beginning to emerge, it is now evident that they include ATPase-containing nucleosomial remodeling capabilities, enzymes with chromatin histone modifying abilities (e.g., acetyl- or methyl-transferases) and proteins involved in recruitment of RNA polymerase II (Pike et al., 2012; Haussler et al., 2013). Besides regulation through VDRE, VDR can inhibit genes by antagonizing certain transcription factors (Alroy et al., 1995; Takeuchi et al., 1998; Towers and Freedman, 1998). One such example is VDR-dependent inhibition of the T cell cytokine IL-2. Here, VDR first competes with the transcription factor NFAT1 for binding to the enhancer motif of AP1 and subsequently VDR binds to c-Jun. This co-occupancy of
VDR-c-Jun to AP1 leads to inhibition of IL-2 expression. The VDR inhibition of the IL-2 gene requires that VDR dimerizes with RXR, illustrating a need for 1,25(OH)2D3 (Alroy et al., 1995; Takeuchi et al., 1998; Towers and Freedman, 1998). Overall, the cellular action of vitamin D therefore depends on sufficient production and delivery of 1,25(OH)2D3 and adequate expression of VDR and its associated proteins. Since the VDR in 1983 was reported to be expressed in immune cells (Bhalla et al., 1983; Provvedini et al., 1983) an increasing effort to elucidate the importance of vitamin D on immune function has been undertaken. It has become increasingly clear that a major mechanism to control the immune regulatory effect of vitamin D is adjustment of the expression level and activity of the VDR.

**VDR EXPRESSION AND DEVELOPMENT OF T CELLS**

Due to the importance of T cells in protective immunity and in development of inflammatory and autoimmune disorders, several studies have examined the impact of VDR expression on T cell development, differentiation, and function. One approach to determine the role of VDR expression in development of T cells has been to study mice lacking the VDR (VDR-KO). These mice show normal numbers of CD4+ T cells and display normal frequencies of CD8+ T cells, but do not allow for the development of complete CD8α+FoxP3+ nTreg cells (Yu et al., 2008). VDR expression therefore contributes to priming and proliferation of naïve T cells to proliferate they need the cytokine IL-2. IL-2 is produced and secreted by T cells in response to antigen-induced T cell stimulation. In an autocrine and paracrine fashion IL-2 binds to high affinity IL-2 receptors on the same or adjacent T cells, inducing cell proliferation and hence a clonally expanded population of antigen-specific effector T cells (Cantrell and Smith, 1984; Smith, 1988). As VDR expression has been shown to inhibit transcription of the IL-2 gene (Alroy et al., 1995; Takeuchi et al., 1998), it is likely that upregulation of VDR serves as a negative feedback mechanism to control potential overreactions of the immune system. Besides inducing the early priming phase of naïve human T cells and possibly ensuring immune integrity, Mathieu and coworkers showed that a 1,25(OH)2D3 agonist drastically changed the surface expression of homing receptors on both CD4 and CD8 T cells, resulting in a phenotype corresponding to an increased migration ability to sites of infection (Baeke et al., 2011); and hence implying a role for VDR in all phases of T cell differentiation.

In agreement with a suggested role of VDR in preventing immune overreaction, a changed distribution of naïve and antigen-experienced T cells was observed in a VDR-KO study performed by Bruce et al. (2011). The CD4+ T cells had a more activated phenotype and readily developed into the proinflammatory Th17 effector cells that produced twice as much IL-17 as their WT counterparts in vitro (Bruce et al., 2011). Furthermore, vitamin D has been shown to modify the phenotype of antigen presenting dendritic cells (DC) to a more tolerogenic phenotype that favors differentiation of inducible Treg (iTreg) cells instead of the inflammatory Th1 and Th17 cells (Griffin et al., 2001; Adorini et al., 2003; Adorini and Penna, 2009). In VDR-KO mice, the frequency of total DC populations were not affected, but a significant reduction in tolerogenic DCs was observed (Bruce et al., 2011). In accordance with the reduced population of tolerogenic DCs and increased population of activated inflammatory T cells, a decrease in the population of iTregs that differentiated from naïve T cells.

**VDR EXPRESSION AND DIFFERENTIATION OF T CELLS**

Adaptive immune responses require priming and proliferation of naïve T cells followed by migration of the resulting effector T cells to the site of infection. Antigen-specific triggering of TCRs expressed on the surface of antigen-naïve T cells together with co-stimulation induces intracellular signaling events that promote upregulation of the VDR (Provvedini et al., 1983; von Essen et al., 2010). This activation-induced upregulation of VDR in naïve human T cells encourages 1,25(OH)2D3-VDR signaling. 1,25(OH)2D3-VDR signaling induces upregulation of the VDRE containing enzyme PLC-γ1, which is a central molecule in the classical TCR signaling pathway. Following VDR-induced PLC-γ1 upregulation classical TCR signaling is established and full T cell activation accomplished (von Essen et al., 2010). VDR expression therefore contributes to priming of naïve human T cells. Interestingly, this VDR-induced PLC-γ1 upregulation is not a mechanism involved in T cell priming of mouse T cells, as naïve mouse T cells already expresses substantial amounts of PLC-γ1 (Ericsson et al., 1996). In order for T cells to proliferate they need the cytokine IL-2. IL-2 is produced and secreted by T cells in response to antigen-induced T cell stimulation. In an autocrine and paracrine fashion IL-2 binds to high affinity IL-2 receptors on the same or adjacent T cells, inducing cell proliferation and hence clonally expanded population of antigen-specific effector T cells (Cantrell and Smith, 1984; Smith, 1988). As VDR expression has been shown to inhibit transcription of the IL-2 gene (Alroy et al., 1995; Takeuchi et al., 1998), it is likely that upregulation of VDR serves as a negative feedback mechanism to control potential overreactions of the immune system. Besides inducing the early priming phase of naïve human T cells and possibly ensuring immune integrity, Mathieu and coworkers showed that a 1,25(OH)2D3 agonist drastically changed the surface expression of homing receptors on both CD4 and CD8 T cells, resulting in a profile corresponding to an increased migration ability to sites of infection (Baeke et al., 2011); and hence implying a role for VDR in all phases of T cell differentiation.
VDR EXPRESSION AND FUNCTION OF T CELLS

REGULATION OF VDR EXPRESSION AND ACTIVITY

Ligand availability

The role of the VDR ligand 1,25(OH)_2D_3 is to convert VDR into a functional active protein that can bind to co-activator and co-repressor molecules necessary for modulation of gene expression (Pike et al., 2011; Pike et al., 2012). Since VDR is a member of the nuclear receptor superfamily, activation of this receptor requires binding to DNA sequences, and co-activators and co-repressors to aid in transcriptional activation or suppression, respectively. The binding of 1,25(OH)_2D_3 to VDR triggers conformational changes in the receptor that enhance its DNA-binding affinity and transcriptional activity.

VDR activity

The VDR is a ligand-dependent transcription factor that regulates the expression of a variety of genes involved in immune cell function, including those encoding cytokines, chemokines, and adhesion molecules. In the presence of 1,25(OH)_2D_3, VDR binds to specific DNA sequences in the promoter regions of target genes and activates transcription by recruiting co-activators and modulating the activity of other transcription factors. The ability of VDR to modulate gene expression is influenced by various factors, including the presence of VDR polymorphisms, the availability of 1,25(OH)_2D_3, and the interaction with other transcription factors and regulatory proteins.

VDR expression and function

The expression and function of VDR in immune cells are influenced by a variety of factors, including genetic polymorphisms, environmental factors, and immune status. The VDR gene is polymorphic, and the most common polymorphism is the FokI polymorphism, which results in an allelic variation in the 228-bp DNA-binding domain of the VDR gene. This polymorphism has been associated with altered VDR function, and it has been implicated in the susceptibility to autoimmune diseases and cancer. Additionally, the availability of 1,25(OH)_2D_3 and other factors that influence VDR expression and function are critical in determining the immune response.

In conclusion, the expression and function of VDR in immune cells play a crucial role in regulating immune responses, and understanding the regulation of VDR expression and function is essential for the development of new therapeutic strategies for autoimmune diseases and cancer.
FIGURE 1 | Proposed model for VDR signaling in T cells. Various extracellular signals including infection, inflammation, steroid and peptide hormones, and diet are involved in regulation of the intracellular VDR level. During an immune response the TCR is triggered by specific antigens, inducing a cascade of intracellular signaling events. Among these, Ick and ZAP-70 are activated leading to activation of the p38 kinase which in naïve human T cells induce expression of VDR. TCR triggering also promotes expression of the 1,25(OH)2D3 synthesis enzyme CYP27B1. Through intrinsic synthesis of 1,25(OH)2D3 and uptake of 1,25(OH)2D3 from the extracellular environment, VDR is activated and translocated into the nucleus where it either induce or suppress transcription of a variety of genes. As an example, VDR induce upregulation of PLC-γ1 in naïve human T cells. Once PLC-γ1 is expressed, TCR induced activation of PLC-γ1 leads to activation of PKA and PKC and an increase in the intracellular calcium level. In other cell types PKA and PKC has been shown to modulate expression of VDR, depending on the particular cell type and cellular differentiation state investigated. An increase in intracellular calcium concentration activates NFAT1 a necessary transcription factor for expression of IL-2 and other cytokines. IL-2 is a cytokine required for proliferation of T cells and one mechanism by which VDR adjust T cell activity is to outcompete NFAT1’s binding to the IL-2 promoter and furthermore to down-regulate the actual expression of NFAT1. To control VDR activity a series of negative feedback loops exists; activated VDR both induce expression of the 1,25(OH)2D3 degrading enzyme CYP24A1 and down-regulates expression of the 1,25(OH)2D3 synthesizing enzyme CYP27B1.

subsequently converted into 1,25(OH)2D3 through the action of the enzyme CYP27B1 (Figure 1) (Jeffery et al., 2012). CYP27B1 has been identified in most cells of the immune system (Fritsche et al., 2003; Liu et al., 2006; Sigmundsdottir et al., 2007; Krutzik et al., 2008; Corrèale et al., 2009; Backe et al., 2010), however, it is not clear whether all cells can take up the precursor 25(OH)D3 and convert it. When 1,25(OH)2D3 is synthesized a great part is secreted to adjacent cells, minimizing the need for endogenous
production in all immune cells (Jeffery et al., 2012). In addition, 1,25(OH)\(_2\)D\(_3\) holds the capacity to restrict its own synthesis by exerting a negative feedback on the vitamin D signaling system. 1,25(OH)\(_2\)D\(_3\) induces displacement of a key transcriptional factor responsible for CYP27B1 expression leading to a decrease in CYP27B1 (Murayama et al., 1999) and also induces a rapid binding of VDR-RXR to the promoter sequence of the 1,25(OH)\(_2\)D\(_3\) degrading enzyme CYP24A1 leading to an increase in CYP24A1 (Figure 1) (Obyama et al., 1996; Kim et al., 2005). The net result is a reduction in endogenous 1,25(OH)\(_2\)D\(_3\). As illustrated by Vidal et al. this negative feedback mechanism can be partly prevented by inflammatory-induced proteins. In this study, they showed that IFN-γ induced activation of STAT1 promoted binding of STAT1 to the DNA-binding domain of VDR, preventing VDR from inducing expression of CYP24A1 (Vidal et al., 2002).

A major determinant of 25(OH)D availability is the carrier protein DBP that binds most circulating vitamin D in the serum. In immune reactions DBP restricts the availability of 25(OH)D\(_3\) to the immune cells (Chun et al., 2010; Jeffery et al., 2012). More than 100 genotypes of DBP have been documented but most people express the three most common variants GC1S, GC1F, and GC2 (Arnaud and Constans, 1993). These DBP variants have different properties including a difference in their affinity for 25(OH)D\(_3\) (Arnaud and Constans, 1993; Wood et al., 2011). In vitro studies performed with immune cells using different DBP genotypes in addition to 25(OH)D\(_3\) have shown that the particular genotype used influences the magnitude of the immune response (Chun et al., 2010; Jeffery et al., 2012). Along this line, an association between DBP genotype and development of inflammatory diseases has been described (Papiha and Pal, 1985; Speckaert et al., 2006; Martineau et al., 2010). 1,25(OH)\(_2\)D\(_3\) availability therefore is the sum of the circulating 25(OH)D\(_3\) level, DBP genotype, CYP27B1 function, near proximity to other cells that produces and secretes 1,25(OH)\(_2\)D\(_3\) and 1,25(OH)\(_2\)D\(_3\) self-restriction.

**EXTRACELLULAR SIGNALS THAT MODULATE VDR EXPRESSION**

Vitamin D receptor expression can be modulated by numerous physical stimuli such as dietary composition (e.g., calcium and phosphorus), steroid hormones, growth factors, peptide hormones (Feldman et al., 2011), and inflammatory agents (Provedini et al., 1983; Liu et al., 2006, 2009; von Essen et al., 2010; Joseph et al., 2012). For example, VDR expression is significantly regulated by the steroid hormones estrogen, glucocorticoid, and retinoids which appears to be rather cell specific (Feldman et al., 2011). The effect of glucocorticoid on VDR expression in the immune system has not been evaluated, but glucocorticoids are known to have a profound anti-inflammatory and immune suppressive effect (Miller and Ranatunga, 2012). Glucocorticoid therapy is used to suppress inflammation implicated in the pathogenesis of various inflammatory diseases (Hanaoka et al., 2012; Miller and Ranatunga, 2012), and it could be speculated that one mechanism used by glucocorticoids to suppress immune responses is by increasing the expression levels of VDR. Estrogen (Chighizola and Meroni, 2012) and retinoids (Cassani et al., 2012) also appear to have strong immunomodulatory effects, but like glucocorticoid the implication of VDR regulation as a possible mechanism to modulate immune function has not been investigated. Receptors for the peptide hormone parathyroid hormone (PTH) was recently identified on T cells (Geara et al., 2010). This renders PTH-induced modulation of VDR expression in T cells a possibility as observed for other cell types (Feldman et al., 2011). Again, this is an unexplored territory even though PTH possesses an immune regulatory ability (Geara et al., 2010). The most well described hormonal effect on VDR activity and expression is that of 1,25(OH)\(_2\)D\(_3\) itself, as 1,25(OH)\(_2\)D\(_3\) directly influences the expression levels of VDR by homologous regulation. Although varying between different cell types, 1,25(OH)\(_2\)D\(_3\) in general increases VDR-mRNA production (McDonnell et al., 1987), stabilizes VDR-mRNA, and protects the VDR against degradation (Feldman et al., 2005), altogether increasing the total amount of the VDR.

Various inflammatory signals have also been shown to induce upregulation of VDR in immune cells. During an innate immune response, pathogen-induce activation of toll-like-receptors on human monocytes and macrophages results in upregulation of the VDR (Liu et al., 2006). Likewise, antigen-induced activation of TCR on human naïve T cells induce upregulation of the VDR (Provedini et al., 1983; von Essen et al., 2010; Joseph et al., 2012). Furthermore, T cell cytokines induced during inflammation can modulate VDR expression (Edfeldt et al., 2010; Spanier et al., 2012), illustrating that regulation of the VDR level is a common mechanism used in the defense against pathogens.

**INTRACELLULAR SIGNALING PATHWAYS THAT MODULATE VDR_EXPRESSION**

Modulation of VDR expression as a result of physical stimuli is mediated by various intracellular signaling pathways. Although only a sparse numbers of publications concern this issue, a few studies agree that activation of the cAMP-dependent protein kinase A (PKA) pathway leads to an increase in VDR abundance (Pols et al., 1988; Krishnan and Feldman, 1992; Song, 1996). Both cellular responses to PTH (Pols et al., 1988) and to prostaglandin (Smith et al., 1999) activate PKA causing an increase in the VDR level. In contrast, Feldman and coworkers showed that stimuli that induce protein kinase C (PKC) activity down-regulate both VDR-mRNA and VDR protein levels in fibroblastic cells (Krishnan and Feldman, 1991). Moreover, Reinhardt and Horst (1994) has shown that the impact of PKC activation on the VDR-mRNA level highly depends on the particular cellular differentiation state investigated. This suggests that other signaling pathways may cooperate to determine the final effect on VDR expression. In support of this idea, a study by Krishnan and Feldman (1992) indicated a mutual antagonism between the PKA and PKC pathways in regulation of the VDR level, an observation confirmed by others (van Leeuwen et al., 1992). Furthermore, it has been suggested that the intracellular calcium level that is known to influence and be influenced by PKC activity is implicated in PKA induced VDR upregulation (Figure 1) (van Leeuwen et al., 1990). A new signaling pathway which leads to VDR expression has recently been described in human naïve T cells. Here, TCR stimulation induces VDR expression through activation of the p38 mitogen activated protein kinase by ZAP-70 (Figure 1) (von Essen et al., 2010). In contrast, Gocek et al. (2007) showed that VDR expression was controlled by Erk and PI3K signaling in a myeloid leukemia cell
line where p38 activity appeared irrelevant. This implies that not only might different intracellular signaling pathways cooperate to regulate the expression of VDR, but also that the implicated signaling events differs between different cell types and different differentiation states of the cells.

TRANSCRIPTIONAL REGULATION OF VDR

Until recently the regulatory responses to hormones at the VDR-gene promoter were unknown. To clarify this, Zella et al. (2010) used ChIP–chip analysis to investigate the VDR gene transcription. These investigations revealed the presence of several enhancers, including the transcription factor C/EBPβ involved in basal expression of VDR as well as the transcription factor glucocorticoid receptor (GR) which mediates the action of glucocorticoids, the transcription factor retinoid acid receptor (RAR) mediating the action of retinoic acid, and the transcription factor CREB mediating the action of PTH (Zella et al., 2010). In case of VDR enhancement by 1,25(OH)2D3, Zella et al. (2006, 2010) found accumulation of VDR-RXR and RNA pol II at the VDR gene together with an increase in C/EBPβ binding. They also detected a substantial increase in histone H4 acetylation associated with enhancer regions across the VDR locus (Zella et al., 2010). An induction of transcription from promoters is often associated with an increase in H4 acetylation, and the observations therefore indicated the existence of multiple enhancers in the VDR-gene locus that may contribute to 1,25(OH)2D3-induced VDR expression. Transcriptional regulation of the VDR gene therefore includes the presence and activity of a wide range of enhancers induced by extracellular signals as well as induction of various epigenetic changes. In case of inflammatory-induced VDR upregulation, the regulatory responses at transcriptional level have not been investigated. As new techniques such as ChIP–chip and ChIP–seq have emerged, this topic will likely be explored in nearby future.

POSTTRANSLATIONAL MODIFICATIONS OF VDR

In addition to transcriptional regulation of VDR, several in vitro studies have suggested that VDR can be post-translationally modified. Studies by Haussler and coworkers revealed that 1,25(OH)2D3 binding to VDR led to serine phosphorylation at multiple sites of the receptor. PKC was implicated in phosphorylation at serine 51, an event that partly inhibited VDR transcriptional activity (Hsieh et al., 1991). Although not required for VDR transcriptional activity, casein kinase II (CK II)-induced phosphorylation at serine 208 led to an enhancement of VDR transcriptional activity (Jurutka et al., 1996). As both PKC and CKII activity is induced in cells in response to various stimuli, it can be proposed that these posttranslational modifications although probably not obligatory for VDR function represents a mode to adjust the activity of VDR according to the specific signals received by the cell. Disease-induced posttranslational modifications leading to a dysfunctional VDR has also been documented. In a study by Patel et al. (1995) plasma toxins from uremic patients was shown to bind to the patients VDR, thereby disrupting binding of VDR-RXR to DNA resulting in a diminished VDR response. It so appears that posttranslational modifications of VDR adjust VDR activity in both health and disease.

RXR AND OTHER CO-REGULATORS OF VDR

The genomic actions of 1,25(OH)2D3 also highly depends on the abundance and activity of proteins that interact with VDR. Binding of VDR to its ligand 1,25(OH)2D3 facilitates association with RXR and in the absence of RXR, VDR is unable to bind to most VDRE in vitamin D target genes (Kliwer et al., 1992; Forman et al., 1995; Chambon, 1996). In addition to RXR binding, VDR interacts with various co-activators or co-repressors once bound to the DNA (Nagpal et al., 2005; Pike et al., 2012; Haussler et al., 2013). These co-regulatory complexes are necessary for the VDR-RXR heterodimer to either induce or suppress gene transcription and include ATPase-containing nucleosomal remodeling capabilities, enzymes with chromatin histone modifying abilities (e.g., acetyl- or methyl-transferases), and proteins involved in recruitment of RNA polymerase II (Pike et al., 2012). GRIP1 (Issa et al., 2001), RAC3 (Issa et al., 2001), SRC-1 (Masuyama et al., 1997a), TIF-1 (vom et al., 1996), ACTR (Chen et al., 1997), pCIP (Torchia et al., 1997), and Mediator (Oda et al., 2010) are some of the described co-activator proteins and co-activator complexes to date. These co-activators all regulate VDR function through co-assembling with VDR but they modulate VDR activity via distinct mechanisms. GRIP1 and RAC3 for example regulate VDR activity by modulating crosstalk between VDR and RXR (Issa et al., 2001), ACTR encompass histone acetyltransferase capacity and can recruit other nuclear factors (Chen et al., 1997), and Mediator which is a large complex composed of several MED-proteins activates transcription by direct recruitment of the RNA polymerase II transcriptional machinery (Oda et al., 2010). Although most co-activators facilitate VDR-induced transcriptional activation by binding to VDR, others are shown to be released from VDR to enable transcription, e.g., TFIIB (Masuyama et al., 1997b); illustrating the functional complexity of these co-activator complexes. Only a few co-repressor proteins involved in VDR silencing of genes have been described. As an example NcoR-1, NcoR-2, and Hairless can recruit histone deacetylase activity to VDR-target genes, leading to chromatin compaction and hence gene silencing (Nagpal et al., 2005). A recent study by Singh et al. (2012) furthermore showed that recruitment of co-repressors inappropriately can change during disease, causing a deregulation of VDR-target genes. In addition to transcriptional control of VDR, co-repressor proteins can modulate VDR abundance by enhancing degradation of VDR. Certain cellular signaling events have been shown to motivate the physical interaction of VDR-1,25(OH)2D3 with SUG1 of the proteasome complex, targeting VDR for ubiquitination and subsequent proteolysis (Masuyama and MacDonald, 1998). Therefore, it is evident that regulation of the expression level of RXR and other co-regulators is important to modulate the activity of VDR, and it could be speculated that expression of particular co-regulators are dictated by the inflammatory environment.

T CELLS MODULATE VDR EXPRESSION IN OTHER IMMUNE CELLS

A recent study by Edfeldt et al. revealed that VDR expression is not only modulated on a single cell level. Their study showed that VDR expression of innate immune cells could be regulated by nearby T cells (Edfeldt et al., 2010). In innate immunity, pathogen-induced signaling through Toll-like-receptors on human monocytes and macrophages up-regulate the expression of VDR. This in turn,
leads to VDR-induced expression of the antimicrobial peptide cathelicidin resulting in killing of microbes (Liu et al., 2006). VDR-induced cathelicidin expression by human monocytes was shown to be adjusted by cytokines produced by T cells. By modulating the level of VDR and the amount of VDR-ligand available by adjusting the CYP27B1 level, the T cell cytokine IFN-γ increases cathelicidin expression and IL-4 attenuates cathelicidin expression (Edfeldt et al., 2010). This example illustrates how interplay between innate and adaptive immunity cooperates to mount an appropriate response to infection through regulation of the VDR-system.

**CONCLUDING REMARKS**

This review indicates that VDR expression and activity are important for all stages of a T cells life, ranging from development to differentiation and elicitation of effector functions. In concordance, VDR expression and activity are associated with immunity against certain infections and with the prevalence of some autoimmune diseases. In animal models 1,25(OH)₂D₃ has been shown to prevent development of autoimmune diseases. This includes experimental autoimmune encephalomyelitis (EAE), the animal model for MS (Mayne et al., 2011). EAE studies performed in VDR-KO animals (Bouillon et al., 2008) or in animals with a dysfunctional VDR (Mayne et al., 2011) illustrates the requirement of a functional VDR in 1,25(OH)₂D₃ mediated EAE-inhibition. Furthermore, a study by Hayes and coworkers showed that VDR-gene inactivation selectively in the T cells completely eradicated the ability of 1,25(OH)₂D₃ to inhibit EAE (Mayne et al., 2011). The biological relevance of low levels of VDR in development of MS was confirmed in a microarray analysis performed by Achiron et al. Here they compared blood mononuclear cells from healthy subjects that later developed MS with healthy subjects that remained MS-free. One of the early disease markers identified turned out to be suppressed VDR expression (Achiron et al., 2010). These observations may not only reflect a change in conventional T cells (e.g., development of more memory T cells that are predisposed to develop into Th1 and Th17 cells as observed in VDR-KO mice (Bruce et al., 2011) but also a reduced development of iNKT cells (as observed in VDR-KO mice, Yu and Cantorna, 2008; Ooi et al., 2012). iNKT cells are negative regulators of EAE (Matsuda et al., 2008) and furthermore, fewer iNKT cells can be found in the blood of MS patients (Araki et al., 2003). Along this line Araki et al. (2003) showed that an increase in iNKT cell number is associated with remission from symptoms in MS patients. Altogether, these observations emphasize a role for VDR expression in development and progression of autoimmunity.

Most experiments investigating susceptibility to a given autoimmune disease is, however, based on animal models. The question therefore remains whether these animal models which are executed in a pathogen free environment reflect the real life situation where humans continuously are bombarded with a variety of pathogens. It is slowly becoming apparent that the microbial environment has a greater influence on development of autoimmune diseases than previously anticipated. For example, certain microbes have been shown to slow innate immune defenses by dysregulating the VDR. One mechanism used by the innate immune system to clear a pathogen is VDR-induced production of the antimicrobial peptide cathelicidin which possesses antiviral, antibacterial, and antifungal activity. Therefore, any microbe capable of dysregulating expression of the VDR would enhance its chance for survival (Waterhouse et al., 2009; Proal et al., 2013). Klein and coworkers illustrated in *vitro* that Epstein-Barr virus (EBV) were able to effectively down-regulate expression of VDR in B cells (Yenamandra et al., 2009), Modlin and coworkers that *Mycobacterium leprae* inhibits VDR activity through down-regulation of CYP27B1 in monocytes (Liu et al., 2012), Wang and coworkers that *Mycobacterium tuberculosis* down-regulate expression of VDR in macrophages (Xu et al., 2003), and McElvaney and coworkers that the fungus *Aspergillus fumigatus* secretes a toxin capable of down-regulating VDR in macrophages (Coughlan et al., 2012). This allows pathogens to accumulate in tissue and blood and the weakened innate defense further causes susceptibility to additional infections. As more pathogens are incorporated into this microbiome, people start to show symptoms characteristic of inflammatory and autoimmune diseases. Accumulating evidence now supports the observation that a number of autoimmune diseases can be reversed by restoring VDR function (using the VDR agonist olmesartan) along with antibiotics. This includes rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, scleroderma, psoriasis, Sjögren’s syndrome, autoimmune thyroid disease, and type I and II diabetes mellitus (Waterhouse et al., 2009; Proal et al., 2013). Knowledge of the regulation of VDR abundance and activity in immune cells potentially is of great therapeutic importance, and therapeutic enhancement of VDR should therefore be considered in the clinic today.

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