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LIGAND-ASSOCIATED ACTIVATION OF VITAMIN D RECEPTORS AND POTENTIAL POINTS OF APPLICATION OF ITS EFFECTS IN THE MORPHOGENESIS OF IMMUNE INFLAMMATION: LITERATURE REVIEW

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ABSTRACT

According to recent data, vitamin D is classified as a substance with hormonal activity, which, in addition to classical, has "non-classical" effects caused by the complex relationship between vitamin D and effector cells of the immune system. This relationship is based on the expression of the vitamin D receptor (VDR) on immune cells, which is encoded by the corresponding VDR gene. Vitamin D receptor specifically binds the active form of vitamin D (1,25(OH)$_2$D$_3$). As a result, a D$_3$-VDR complex is formed, which mediates the effects of vitamin D through the formation of intracellular signaling pathways that transform the activity of certain target genes. However, it is not entirely clear how vitamin D realizes its effects at the cellular and receptor levels. According to the literature, studies of recent decades have revealed a significant role of vitamin D and immune checkpoint receptors (PD-1 (programmed cell death), PD-L (PD ligand), CTLA (cytotoxic T-lymphocyte associated protein)) in autoimmune diseases. This review outlines possible mechanisms for the interconnection of these pathways. A deeper understanding of the intercellular interactions mediated by ligand-associated activation of vitamin D receptors, D$_3$-VDR complex and immune checkpoint receptors (PD-1, PD-L, CTLA) in inflammation may become the basis for the development of new strategies for the diagnosis, prognosis and treatment of various diseases.

Key words: *vitamin D, VDR, immune granuloma, immune checkpoint proteins PD-1, PD-L, CTLA*

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ЛИГАНД-АССОЦИИРОВАННАЯ АКТИВАЦИЯ РЕЦЕПТОРОВ ВИТАМИНА D И ПОТЕНЦИАЛЬНЫЕ ТОЧКИ ПРИЛОЖЕНИЯ ЕЁ ЭФФЕКТОВ В МОРФОГЕНЕЗЕ ИММУННОГО ВОСПАЛЕНИЯ: ОБЗОР ЛИТЕРАТУРЫ

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РЕЗЮМЕ

Согласно последним данным, витамин D относят к веществам с гормональной активностью, который, помимо классических, имеет «неклассические» эффекты, обусловленные наличием сложной взаимосвязи между витамином D и эффекторными клетками иммунной системы. Данная взаимосвязь обусловлена экспрессией рецептора витамина D (VDR, vitamin D receptor) на иммунных клетках, который кодируется соответствующим геном VDR. Рецептор витамина D специфически связывает активную форму витамина D ($1,25(OH)_2D_3$). В результате образуется сложный комплекс D_3-VDR, который опосредует эффекты витамина D путём образования внутриклеточных сигнальных путей, трансформирующих активность определённых таргетных генов. При этом до конца не ясно, каким образом витамин D реализует свои эффекты на клеточном и рецепторном уровнях. По данным литературы, исследования последних десятилетий выявили значимую роль витамина D и рецепторов иммунных контрольных точек (PD-1 (programmed cell death), PD-L (PD ligand), CTLA (cytotoxic T lymphocyte associated protein)) в аутоиммунных заболеваниях. В этом обзоре излагаются возможные механизмы взаимосвязи данных путей. Более глубокое понимание межклеточных взаимосвязей опосредованных лиганд-ассоциированной активацией рецепторов витамина D, комплекса D_3-VDR и рецепторов иммунных контрольных точек (PD-1, PD-L, CTLA) в воспалении может стать основой для разработки новых стратегий диагностики, прогноза и лечения различных заболеваний.

Ключевые слова: *витамин D, VDR, иммунная гранулема, белки иммунных контрольных точек PD-1, PD-L, CTLA*

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INTRODUCTION

Until recently, the role of vitamin D was considered only from the standpoint of its effect on calcium and phosphorus metabolism in the body. However, over the past 15 years, new effects of vitamin D, such as neuroregenerative, neurosteroid and immunomodulatory effects have been identified [1]. Nevertheless, the role of vitamin D (VD), one of the most important vitamins in the body, remains insufficiently studied due to the pleiotropic nature of its effects. Modern data indicate a close relationship between vitamin D_3 (calcitriol) and immune cells [2], as well as autoimmune diseases [3, 4], which allows us to consider it as an important regulatory link in a complex system of intercellular interactions. On the other hand, studies in recent decades have also revealed a significant relationship between immune checkpoint proteins (ICPs) and immune cells [5, 6], which is manifested in fine regulation of the balance between tolerance and immunopathology. It is possible that these links in immune regulation are interconnected. However, due to limited information, which confirms the relevance of this problem, this literature review presents key information concerning modern concepts of the structural and functional organization of the VD gene and receptor (VDR, vitamin D receptor), «non-classical» effects of VD in the morphogenesis of immune inflammation, potential relationships between the D_3-VDR complex and immune checkpoint receptors and possible points of application of this relationship within the framework of granulomatous inflammation.

1. Modern concepts of the structural and functional organization of the gene and receptor of vitamin D

The literature contains a fairly broad range of data on the role of VD, the *VDR* gene, and the VDR receptor in the development of various pathological processes and diseases. To some extent, this is due to the fact that, according to modern scientific knowledge, VD has endocrine functional activity, similar to a hormone [7], which attaches to and interacts with its specific receptors (VDR) on various cells, thus exerting numerous effects on various body systems.

The *VDR* or *NR1I1* gene (nuclear receptor subfamily 1 group I member 1) is encoded by a relatively large gene (> 100 kb) and is localized on the submetacentric 12^{th} chromosome, its long arm (12q12-q14). The *NR1I1* gene has about 60 thousand nucleotide pairs and consists of 14 exons and intermediate introns. The *VDR* gene can be divided into two regions: coding and noncoding. The noncoding region of the *VDR* gene includes 6 of the 14 exons: 1A, 1B, 1C, 1D, 1E and 1F. The remaining 8 exons are part of the coding region of the *VDR* gene, which encodes information about the primary structure of the VDR gene protein, consisting of 4 functional domains [8].

The *NR1I1* gene exerts its effects through genomic (nuclear) and extragenomic mechanisms.

The genomic pathway leading to changes in gene transcription takes from several hours to several days [9]. The *VDR* gene encodes the nuclear VDR, which, together with the retinoic acid receptor (RAR), retinoid X receptor (RXR), and peroxisome proliferator-activated receptor (PPAR), is part of the second group of the nuclear receptor (NR) family [10]. The first group includes estrogen, androgen, progesterone, and mineralocorticoid receptors [11]. The second group of receptors can form heterodimers with each other (e.g., VDR-RXR), and also function and exert effects through interaction with certain ligands [10, 11].

In addition to the classical target cells (enterocytes, parathyroid cells, and nephrocytes), which are directly involved in maintaining calcium homeostasis, the *VDR* gene is also expressed in immune system cells (monocytes, macrophages, dendritic cells, lymphocytes) [12]. In addition, *VDR* gene expression was detected in brain neurons, cardiomyocytes, smooth muscle cells, vascular endothelium, breast cells, prostate cells, skin, and other organs [13].

The extragenomic pathway and its effects, according to the latest updated data, are mediated by the synthesis of secondary messengers (cyclic adenosine monophosphate, inositol triphosphate, etc.), which are associated with the steroid receptor MARRS (membraneassociated rapid response steroid), which contributes to a faster response – from several seconds to several minutes [14], – in contrast to the genomic pathway. Thus, the extragenomic effects of VD are realized much faster than the genomic ones.

Upon entering the cell, VD3 binds to VDR. VDR consists of 427 amino acids and has 4 main functional domains:

1. the highly variable N-terminal A/B domain is responsible for the transactivated functions of VDR induced by ligands, but its structural elements are poorly defined;
2. the DNA-binding domain (DBD) is the central DNA-binding domain;
3. the ligand-binding domain (LBD) is the ligand-binding domain at the C-terminus;
4. the flexible region connecting the DBD and LBD is called the hinge domain.

After binding to VD3, VDR forms an active D_3-VDR complex, which is transported across the nuclear membrane directly into the cell nucleus [15].

An even more complicated complex is then formed by binding of the D3-VDR complex to one of the three retinoid X receptors (RXRα, RXRβ, RXRγ). Subsequently, this D_3-VDR-RXR complex binds to VDREs (vitamin D response elements) on the surface of the DNA of target genes. VDREs are multiple regions of the genome whose activity is under the control of D_3. After binding of D_3-VDR-RXR to VDREs, activation or, conversely, suppression of the corresponding target genes occurs [16]. Thus, an important conclusion can be made that calcitriol mediates its effects through ligand-associated activation of vitamin D_3 receptors (D_3-VDR complex).

VDR is mainly concentrated in the nucleus, cytosol, and cytoplasmic membrane. VDR specifically binds the active form of VD ($1,25(OH)_2D_3$) and mediates its actions. Thus, the effects of VD are directly due to a complex interaction with its receptor VDR. This D_3-VDR complex cannot be considered separately, since it functions as a single mechanism. The absence, deficiency, or structural defect of any of the components of the complex (D_3 or VDR) disrupts the functioning of its components and the implementation of its effects – both genomic and extragenomic. A striking example of disruption of the D_3-VDR complex is VD deficiency in adults, usually associated with the development of osteoporosis and osteomalacia, as well as hereditary mutations of the VDR gene, which lead to the development of vitamin D-resistant rickets in children, characterized by muscle weakness, growth retardation, bone deformities, and secondary hyperparathyroidism.

It is currently known that ligand-associated activation of VD receptors has multiple effects, since VDR receptors are expressed in many tissues of the body [17]. The ubiquitous distribution of VDR reflects its pleiotropic biological activity [18]. In the nuclei of target cells, an active nuclear D_3-VDR complex functions, which controls the transcription of about 3% of the entire human genome. In addition, in the cytoplasmic membranes of cells, the D_3-VDR complex functions as a modulator of gene expression and a coordinator of a number of important biochemical processes [19].

Many genes with the expression regulated by ligand-associated activation of VDR have been described: for example, activation of the *DEFB4A* and *CAM*P genes encoding cathelicidin and defensin-β2 [20], as well as suppression of the IL-2 gene activity in activated T lymphocytes [21]. The listed genes are located "far" from chromosome 12 encoding VDR, but, nevertheless, are under the control of vitamin D. It is possible that the genes encoding ICT proteins are also under the influence of vitamin D. In addition, the D_3-VDR-RXR complex suppresses gene expression and synthesis of interferon γ (IFN-γ), which is a key cytokine of Th1 lymphocytes in humans, by competitively inhibiting the NF-kB factor (nuclear factor kappa-light-chain-enhancer of activated B cells) [22]. Thus, by increasing or decreasing the expression level of various genes, the D_3-VDR-RXR complex implements the "classical" and "non-classical" effects of VD.

At present, the biological effects of VD can be divided into "classical" (calcitropic, regulating phosphorus-calcium metabolism) and "non-classical" (regulation of metabolism and cell cycle, anti-inflammatory, antibacterial, antitumor, antihypertensive effects). Moreover, VD is directly involved in the regulation of the functioning of immune system elements.

2. "Non-classical" effects of vitamin D in the morphogenesis of immune inflammation

Morphogenesis of immune inflammation implies strengthening or weakening of the immune response during inflammation (including granulomatous inflammation) as a result of changes in the receptor and cytokine profile, cellular subpopulations, including under conditions of ligand-associated activation of vitamin D receptors.

Vitamin D deficiency, according to the latest data from world literature, has become a new pandemic of the 21st century, which is especially pronounced in northern latitudes, due to a deficiency of ultraviolet (UV) radiation in residents of megacities. In addition, vitamin D is pathogenetically associated with a progressive increase in the prevalence of various diseases, including autoimmune diseases such as type 1 diabetes mellitus, bronchial asthma, atopic dermatitis, alopecia areata, systemic lupus erythematosus (SLE), psoriasis, etc. [23]. This is far from a complete list of all diseases that are associated with VD deficiency. In particular, in northern latitudes, the prevalence of multiple sclerosis and rheumatoid arthritis is inversely proportional to the level of UV radiation, which may indirectly indicate the participation of VD in the manifestation and pathogenesis of these diseases [24]. Moreover, according to B. Terrier et al., vitamin D supplements statistically significantly increased the number of Treg lymphocytes and decreased the number of Th1 and Th17 cells [25]. However, the mechanism of the relationship between VD deficiency and autoimmune processes underlying the above-mentioned diseases is not fully understood.

Current data indicate that VD suppresses acquired immunity but stimulates innate immunity. The first evidence that VD is a significant stimulator of innate immunity may be data on the treatment of tuberculosis with fish oil [26], as well as the synthesis of antimicrobial peptides such as defensin-β2 and cathelicidin [27]. In addition, defensin-β2 transcription is directly activated by the D_3-VDR-RXR genomic complex [27, 28]. For example, cathelicidin gene expression is enhanced after pathogen recognition by TLRs (toll-like receptors) as a result of the interaction of mature monocytes with *Mycobacterium tuberculosis*, thus promoting increased synthesis and secretion of 1α-hydroxylase and VDR [29]. These studies provide more detailed explanations of the mechanisms which help VD potentiate the antimicrobial action of monocytes and macrophages, which are key effector cells in the fight against pathogens such as *Mycobacterium tuberculosis*.

The level of VDR expression changes dynamically during the formation and maturation of various effector cells of the immune system. On the one hand, naive T lymphocytes are characterized by a relatively low level of VDR expression, while mature forms of T lymphocytes are distinguished by a high level of VDR expression [30]. On the other hand, monocytes in the process of differentiation into macrophages and dendritic cells (DCs) show, on the contrary, a decrease in the level of VDR expression [31]. Thus, the level of VDR expression, and accordingly, the susceptibility of effector cells of the immune system to VD are manifested differently depending on the degree of cell maturity, which may play a key role in the complex system of regulation

of the immune response, as well as its specificity, reactivity and plasticity.

Peculiarities of the influence of the D_3-VDR complex on innate immune cells: macrophages and dendritic cells

Blood monocytes undergo differentiation into macrophages, which are the main cells of the human immune system, through which interaction and coordination of innate and acquired immunity occurs. Mature macrophages are capable of activating the immune response by chemotaxis, phagocytosis, and presentation of antigen to T-helpers (Th). In particular, macrophages, unlike monocytes, can undergo so-called polarization, i.e. differentiate into two phenotypes (M1 or M2) depending on inducing factors and cytokines. For example, macrophages with the M1 phenotype destroy bacteria, viruses and tumor cells, are formed under the direct influence of lipopolysaccharides, tumor necrosis factor α (TNF-α), IFN-γ, while macrophages with the M2 phenotype destroy extracellular pathogens and are formed upon stimulation of interleukin (IL) 4 and IL-13. Immunogenic macrophages with the M1 phenotype activate the Th1 immune response as a result of the synthesis of a certain spectrum of cytokines, while the tolerogenic phenotype of M2 macrophages shifts the balance of Th cells towards Th2 [32]. In addition, macrophages express VDR, which makes them susceptible to VD [33].

The D_3-VDR complex exerts mainly suppressive effects on monocytes by decreasing the expression of MHC II (major histocompatibility complex), TLR2 and TLR4 molecules, which leads to anergy of further responses. Moreover, ligand-associated activation of VDR reduces the expression level of CD40, CD80, CD86, which promote co-activation and stimulation of the immune response, and also suppresses the synthesis of IL-1α, IL-1β, IL-2, IL-6, IL-12, TNF-α and IFN-γ. Among the activating effects of the D_3-VDR complex, there is an increase in the synthesis of anti-inflammatory cytokines: IL-10, IL-4 and IL-5 [34].

Based on the foregoing, it follows that the D_3-VDR complex inhibits the immunogenic, proinflammatory responses of macrophages with the M1 phenotype, contributing to a decrease in their activity. On the other hand, the D_3-VDR complex polarizes macrophages towards the tolerogenic M2 phenotype.

However, other studies refute the theory that the D_3-VDR complex suppresses macrophages with the M1 phenotype. For example, according to data from N. Wafa et al., exposure to the D_3-VDR complex in the presence of *Pseudomonas aeruginosa* stimulated the synthesis of IL-1β, which increased the M1/M2 ratio [35].

Red bone marrow progenitor cells initially differentiate into immature DCs, which are transformed into mature DCs through migration and phagocytosis of various pathogens. During phagocytosis, antigenic determinants (epitopes) are formed from various microorganisms, which bind to MHC class II in the Bjorkman cleft and are expressed on the cell surface. At the same time, DCs express CD40, CD80, and CD86 (costimulatory proteins) and acquire the ability to migrate to regional lymph nodes, where they present a ready-made MHC-II complex bound to the epitope to Th0 cells [36]. When the D_3-VDR complex acts on immature DCs, effects similar to those of macrophages develop. On the one hand, the level of expression of costimulatory proteins and MHC class II is suppressed, which contributes to a decrease in the synthesis and secretion of IL-12, suppression of antigen presentation on the surface of DCs, and on the other hand, the synthesis of IL-10 is enhanced [37].

The activity of Th1 and Th17 lymphocytes, which play a key role in the pathogenesis of autoimmune diseases, sharply decreased as a result of a decrease in the synthesis of IL-12 and IL-23 by dendritic cells after ligand-associated activation of VDR [38]. Moreover, the D_3-VDR complex inhibits the differentiation of monocytes into DCs and their subsequent maturation [34]. This pattern may explain the reason for the increase in the number of tolerogenic DCs, since they consist to some extent of immature cells [39].

Features of the influence of the D_3-VDR complex on the components of acquired (adaptive) immunity (T- and B-lymphocytes)

The precursor of T lymphocytes, like all formed elements of the blood, is a pluripotent hematopoietic stem cell, and its marker is CD34. From the red bone marrow, early pre-T lymphocytes migrate to the thymus gland, where antigen-independent differentiation of T lymphocytes and the process of so-called "positive" and "negative" selection occur [40].

After selection and exit from the thymus, T lymphocytes, like macrophages, undergo polarization. According to the literature, Th0 lymphocytes can differentiate in one of four directions:

1. Th1 lymphocytes, which are capable of destroying foreign pathogens, virus-infected and oncotransformed cells, and can also cause autoimmune diseases and delayed type IV hypersensitivity reactions, synthesize IL-2, IL-12, IL-15, IFN-γ and TNF-α and thus activate cellular immunity;
2. Th2 lymphocytes, which synthesize anti-inflammatory cytokines such as IL-4, IL-5, IL-6, IL-10, IL-13, and participate in humoral immunity;
3. Th17 lymphocytes, which synthesize mainly IL-17. These cells protect against pathogens by synthesizing IL-8 and thus mobilizing neutrophils to the site of inflammation. In addition, Th17 lymphocytes damage their own cells and tissues in various autoimmune diseases [41]. On the one hand, as shown above, VDR-mediated activation inhibits Th17 lymphocytes and, accordingly, tissue damage in immune inflammation, which complicates treatment with immune checkpoint inhibitors; on the other hand, VD enhances PD-L1 expression on both epithelial and immune cells, which is reflected in their synergistic effect;
4. in Treg lymphocytes (T-suppressors), which have a specific $CD4^+CD25^+FOXP3^+$ phenotype. Treg cells synthesize IL-10, TGF-β and are functional antagonists

of Th1, Th2 and Th17 lymphocytes [42]. The main function of Treg cells is to prevent autoimmune reactions [43]. Moreover, Treg lymphocytes express CTLA-4 [44] and PD-1 [45].

In addition, another type of T-helper subpopulation is distinguished – the so-called Th3 lymphocytes with immunoregulatory and immunosuppressive functions, which are induced by the introduction of a foreign oral antigen. TGF-β is the main anti-inflammatory cytokine of these cells. Th3 cells have been described as $CD4^{+-}$ $FOXP3^{-}$-regulatory T cells, i.e., unlike the well-characterized Treg cells, Th3 lymphocytes do not express the FOXP3 transcription factor [46]. It is still unclear how the D_3-VDR complex acts on Th3 lymphocytes.

As mentioned above, the D_3-VDR complex inhibits IL-12 synthesis by macrophages and DCs. As a result, Th0 lymphocytes differentiate not into Th1 but into Th2 lymphocytes [47]. Treatment of T lymphocytes with VD promotes suppression of the synthesis and secretion of proinflammatory cytokines by Th1 lymphocytes (IL-2, IFN-γ, TNF-α) [48], and also initiates the secretion of anti-inflammatory cytokines by Th2 lymphocytes (IL-3, IL-4, IL-5, IL-10) [47]. Moreover, proliferation and homing of $CD4^{+}$ T cells to lymph nodes is significantly reduced as a result of suppression of E-selectin ligand synthesis in endothelial cells after ligand-associated activation of VDR [49].

It has been shown that higher levels of VD can induce a variety of anti-inflammatory functions, including an increase in Treg cell numbers. In addition, experimental studies have shown that other small molecules, including retinol, niacin, and short-chain fatty acids, can potentiate Treg cell functions. However, the relationship between VD therapy and changes in Treg cell numbers or function in patients or healthy volunteers has not been clearly defined [50].

B-lymphocytes are similar to T lymphocytes and are susceptible to the action of VD. On the one hand, VD directly inhibited the differentiation and proliferation of B lymphocytes in patients with SLE [51]. However, on the other hand, ligand-associated activation of VDR did not have a direct effect on B lymphocytes, suppressing their proliferation and differentiation, but only an indirect effect, by inhibiting active T lymphocytes. As a result, either the functional activity of B lymphocytes decreased, which was manifested by a decrease in the synthesis of IgM and IgE, or B cells died completely as a result of apoptosis [52].

In summary, it can be concluded that key cells of the immune system, such as monocytes, macrophages, dendritic cells, T- and B-lymphocytes, are susceptible to ligand-associated activation of VDR, which is reflected in the dynamics of cytokine synthesis and modification of their receptors as a result of the interaction of the D_3-VDR complex with the corresponding target genes. In addition, the active D_3-VDR complex helps to reduce the concentration of proinflammatory cytokines (IL-1, IL-6, IL-12, IL-17, etc.) as a result of inhibition of their biosynthesis and, conversely, to increase the concentration of anti-inflammatory cytokines (IL-3, IL-4, IL-5, IL-10 and IL-13). This cytokine rearrangement is a mirror image of the effect of the active D_3-VDR genomic complex on the polarization of naive Th0 lymphocytes into Th1 and Th17 cells and naive Th0 lymphocytes into Th2 and Treg lymphocytes. The above-mentioned effects of ligand-associated VDR activation may contribute to a decrease in the incidence of various immune and autoimmune reactions, primarily Th1-dependent, and may also contribute to the alleviation of the patient's clinical symptoms. In reality, the immune complex effect of ligand-associated VDR activation on the immune system is undoubtedly deeper and more multifaceted, and it remains to be studied.

3. Potential relationship of the D_3-VDR complex with immune checkpoint receptors

The immune checkpoint family is one of the key elements of the regulatory link of the immune response. According to the literature, the ICP family consists of several main proteins. First of all, these are the programmed cell death receptor PD-1 and the programmed cell death ligand PD-L, as well as the cytotoxic protein CTLA4. On the one hand, these ICP receptors are susceptible to the effects of various viruses, as well as neoplastic cells, which ultimately leads to the suppression of antiviral and antitumor immunity, respectively [53]. On the other hand, ICP inhibitors in the form of various drugs open up new prospects not only in the immunotherapy of tumor processes, transplant immunity, allergies, but also in the control of autoimmune processes.

T-lymphocyte is activated as a result of the simultaneous action of two key signals. First of all, this is the binding and interaction of proteins expressed on the surface of effector cells, namely the T cell receptor (TCR) of the lymphocyte with MCH antigen-presenting cells (APC), respectively, which is necessary for the specificity of the immune response. At the same time, the interaction of the CD28 protein expressed on the surface of the T-lymphocyte occurs in a similar way with CD80 (B7-1) or CD86 (B7-2) on the surface of APC, resulting in the formation of a secondary costimulatory signal that ensures the maintenance of the primary signal. However, the absence of the secondary signal contributes to the development of anergy or apoptosis of the T lymphocyte [54].

ICT proteins, along with other receptors and cytokines, provide a fine mechanism for regulating cytotoxic lymphocytes during their activation upon interaction of TCR with the peptide associated with MHC class I. At the same time, as a result of the interaction of PD-L on the surface of the target cell with PD-1 on the surface of T cells, two important events occur. First, the "switching off" or even death of the T-lymphocyte, and second, the survival and preservation of the target cell. This "rescue" mechanism also has two opposite outcomes. First of all, a positive outcome is associated with the suppression of the development of autoimmune aggression, while a negative outcome is used by tumor cells

to protect themselves from antitumor immune surveillance [55].

The PD-1 protein (CD279) is one of the best known ICT proteins, which is expressed on immunocompetent cells such as monocytes, macrophages, DCs, natural killers, T and B lymphocytes. The PD-1 protein, together with the complementary ligands PD-L1 (CD274 or B7-H1) and/or PD-L2 (CD273 or B7-DC), forms the B7:CD28 receptor family, which contains inhibitory tyrosine-containing amino acid sequences (ITIM, immunoreceptor tyrosine-based inhibition motif) in the intracellular domain [56]. In addition, activated TCR on the T-lymphocyte surface potentiates PD-1 expression, while induction by type I and II IFN molecules together with JAK2-associated proteins increases PD-L1 expression [57]. Thus, PD-1 protein and VDR are expressed on the same cells, which indirectly confirms their relationship.

As a result of binding and interaction of the PD-1 receptor with its ligand PD-L1 and/or PD-L2, an intracellular signal is generated that stimulates phosphorylation of two sequences – ITIM and ITSM (immune receptor tyrosine-based switch motif) – with subsequent activation of two phosphatases: SHP-1 and SHP-2 (Src homology region 2 domain-containing phosphatase) [58]. In turn, SHP-1 and SHP-2 suppress phosphorylation of the PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) signaling pathway, association of ZAP-70 (Zeta-chain-associated protein kinase 70) and the CD3ζ complex, which leads to «switching off» of TCR on the surface of the T lymphocyte. On the one hand, T-cell inactivation is manifested by a decrease in their proliferation and functional activity, which is manifested in the form of a decrease in the synthesis of key cytokines, such as IL-2 and IFN-γ, on the other hand, their death occurs through apoptosis, which is a consequence of the inhibition of transcription factors NF-κB and AP-1 (activator protein 1). Similar effects in T-cells are caused by the D_3-VDR-RXR complex. Thus, it is possible that the potential relationship between vitamin D and ICT lies in the activation of the listed intracellular signaling pathways.

At the same time, cytotoxic T-lymphocyte-associated protein 4, also known as CTLA4 (CD152), is also expressed on the T-lymphocyte surface. CTLA-4 competes with the CD28 receptor for the B7 family ligand: B7-1 (CD80) and B7-2 (CD86). Upon binding to the B7 ligand, the activated CTLA-4 complex inhibits T-lymphocyte activation [59]. In addition, CTLA4 leads to the suppression of the downstream PI3K/Akt, cyclin D_3, CDK4/CDK6, and NF-kB pathways, thereby altering T-lymphocyte differentiation [60]. Ligand-associated activation of VDR has a similar inhibitory effect on NF-kB. At the same time, VD stimulates the PI3K/Akt pathway [61], unlike CTLA-4.

Based on modern scientific data, in addition to T lymphocytes, PD-1, PD-L1/2 and CTLA-4 are also expressed by tumor cells, thus suppressing neoplastic immune surveillance [62]. As an "antidote", corresponding monoclonal antibodies to ICT proteins were created, which neutralized the negative impact of malignant cells on the functions of T lymphocytes as a result of their "reanimation". These monoclonal antibodies are widely used in practical medicine.

Macrophages also express ICT proteins, namely PD-1. According to recent studies, PD-1 expression is more specific for the anti-inflammatory M2 phenotype of macrophages. Moreover, anti-PD-1 therapy can redirect macrophages from the M2 phenotype to the M1 phenotype [63]. Therefore, immune blockade of PD-1 will provoke an increase in phagocytosis activity and a decrease in tumor volume. At the same time, the active D_3-VDR complex transforms macrophages towards the tolerogenic M2 phenotype, which suggests a synergistic effect of VD with the PD-1 molecule.

In particular, the anti-inflammatory cytokines IL-10 and IL-4 stimulate PD-L1 expression on monocytes and PD-L2 expression on DCs [64]. Since the D_3-VDR complex increases the synthesis of IL-10 and IL-4, it is likely that it will also increase the expression of PD-L1 and PD-L2, respectively, but most likely indirectly (through intracellular signaling pathways) rather than directly. On the other hand, in severe COVID-19, vitamin D administration, on the contrary, inhibited PD-L1 expression [65]. Finally, it is not entirely clear how the D_3-VDR-PD-L1 axis and the D_3-VDR-PD-L2 axis, as well as the D_3-VDRCTLA-4 axis, play a gatekeeper role in the immunoregulation of cancer, autoimmune and allergic processes, which requires further research in this area.

4. Modern concepts of productive granulomatous inflammation and potential points of application of the D_3-VDR complex in its implementation

Immune granuloma (the most common type of granuloma) is a HRT IV involving T-helpers ($CD4^+$) and macrophage cells. First, monocytes differentiate into mature macrophages and DCs. Then, APCs (macrophages, DCs) phagocytose the pathogen, cleave it into epitopes, then bind them to MHC class II in the Bjorkman cleft and present them on their surface to naive $CD4^+$ lymphocytes. After contact with the epitope, Th0 lymphocytes differentiate into Th1 lymphocytes under the influence of macrophages synthesizing IL-12. Activated Th1 lymphocytes synthesize IFN-γ, the main cytokine of granulomatous inflammation [66].

At the cellular level, the key to the pathogenesis of granuloma is the differentiation of monocytes into mature macrophages [67]. This process can be determined histologically (a threefold increase in the size of the cell and its organelles, a corrugated cytoplasmic membrane) and microscopically (the appearance of vesicles and granules in the cytoplasm) [68], as well as immunohistochemically, since monocytes express mainly CD14 and CD16 on their cell surface, while macrophages express CD14, Cd11b, CD68, MAC-1 and MAC-3, EMR1 and Lysozyme M [69]. In addition, the D_3-VDR complex influences the differentiation of monocytes, promoting their differentiation into M2-phenotype macrophages, which express PD-L1 [70]. On the other hand, ligand-associated activation of VDR suppresses M1-phenotype macrophages, although these data are contradictory.

Theodor Langhans first described multinucleated giant cells (MGCs) in his studies of tuberculosis over 150 years ago, and these cells were posthumously named Langhans giant cells in his honor. Like epithelioid cells, MGCs can be identified histologically by their characteristic morphology: three or more nuclei of the same shape within a cell. Macrophages isolated from various tissues can differentiate into MGCs *in vitro* [71], as well as in the presence of IL-4 or IL-13, GM-CSF (granulocyte-macrophage colony stimulating factor) + IL-4, IFN-γ + IL-3, or mycobacterial glycolipids [72]. Thus, MGC formation is specific only to macrophages. On the other hand, it is completely unclear how the D_3-VDR complex promotes MGC formation in immune granuloma.

Several subpopulations of T lymphocytes can be found in immune granulomas: $CD4^+$ effector T cells, $CD4^+$ regulatory T cells, and $CD8^+$ cytotoxic T-cells. Depending on the etiology of the granuloma, different types of polarized effector $CD4^+$ cells can be identified, such as Th1, Th2, Th3, or Th17 lymphocytes (e.g., Th1 and Th2 cells are detected in tuberculosis and schistosome granulomas, respectively) [73]. In addition, T lymphocytes, along with monocytes, express VDR [74] and PD-L1 [62].

Among all cytokines, IFN-γ and TNF-α are most closely associated with granuloma formation. Both IFN-γ and TNF-α play a critical role in granuloma formation. The main function of these cytokines in tuberculous granuloma is to increase the bactericidal capacity and survival of macrophages and, thereby, to maintain the cellular integrity of the granuloma [75]. In addition, binding of PD-1 to its ligand PD-L1 and/or PD-L2 contributes to a decrease in IFN-γ production by T lymphocytes, similar to the effect of the D_3-VDR complex. At the same time, the mechanism of the relationship between ligand-associated activation of VDR and these signaling pathways is not entirely clear.

Ligand-associated activation of VDR inhibits the production of IFN-γ, lymphotoxin, IL-2 and proliferation of certain T-lymphocyte subsets [76]. *In vitro* studies have shown that 1,25(OH)2 D_3 stimulates proliferation, differentiation and transformation of monocytes into epithelioid cells [77]. On the other hand, VD inhibits the differentiation of macrophages into DCs and the maturation of the latter, while stimulating their apoptosis [78]. Thus, the effects of ligand-associated activation of VDR on granuloma development are ambiguous. In addition, to date, there are no data on the relationship between the D_3-VDR complex and immune checkpoint proteins (PD-1, PD-L, CTLA), which requires further research in this area.

CONCLUSION

Thus, according to the literature, ligand-associated activation of VDR initiates both genomic and extragenomic effects. These effects are mediated by the D_3-VDR complex. The absence, deficiency or structural defect of any of the components of the complex (D_3 or VDR) disrupts the functioning of its components and the implementation of "classical" and "non-classical" effects. Among the "non-classical" effects, special attention is paid to the action of VD on the immune system, which is manifested in general by an anti-inflammatory vector with the implementation of effects on antigen-presenting cells and lymphoid cells, including indirectly through the signaling pathways of immune checkpoints. The immunocorrective effects of calcitriol have opened up new possibilities for the therapeutic use of VD and its analogues (e.g., paricalcitol) to control autoimmune diseases associated with excessive synthesis of cytokines and the formation of autoreactive immune cells. In addition, the D_3-VDR complex stimulates cell differentiation and has antiproliferative activity, which may play a key role in inhibiting tumor processes. This is probably the result of the relationship between ligand-associated activation of VDR and immune checkpoint proteins (PD-1, PD-L, CTLA), which remains unexplored and seems to be a promising direction for further research.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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