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Conformational Changes of Vitamin D Receptor as a Potential Cause of Multiple Sclerosis

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Abbreviations: MS: Multiple Sclerosis; CNS: Nervous System; IL2RA: Interleukin-2Receptor Alpha Gene; IL7RA: Interleukin-7 Receptor Alpha Gene; EBV : Epstein-Barr Virus ; UTR: Untranslated Region; VDREs : Vitamin D Responsive Elements; VDR: vitamin D Receptor; miRNAs: MicroRNAs; SLE: Systemic lupus Erythematosus; RXR: Retinoid X Receptor; mRNAs: Messenger RNAs; EBV: Epstein-Barr virus

Mini Review

Multiple sclerosis (MS) is an autoimmune inflammatory disorder of unknown etiology affecting central nervous system (CNS)characterized by demyelination and variable degrees of axonal loss [1]. The etiology of MS is still unknown; however, it is believed to be caused by combination of immune dysregulation, genetic and environmental factors [2]. Recent studies have revealed severeal genes as risk factors including MHC HLA DR15/DQ6 allele being the strongest one, alleles of interleukin-2 receptor alpha gene (IL2RA) and interleukin-7 receptor alpha gene (IL7RA) have also been identified [3]. The pathogenesis of MS includes immune attack against CNS antigens through activation of CD4+ myelin-reactive T cells and a possible contribution by B cells [4]. Furthermore, there are some environmental factors related to increased risk of developing MS like Epstein-Barr virus (EBV) infection and vitamin D deficiency [5,6,7]. Prevalence of MS is increased in geographic areas further away from the equator [8]. This could be related to reduced sun exposure leading to vitamin D deficiency as a possible contributing factor [6,7].

Also, studies have shown that higher levels of vitamin D could be protective in certain patient populations [9,10]. Recently, there is a growing number of studies showing how vitmin D deficiency is related to MS development. Approximately one billion people worldwide have vitamin D deficiency or insufficiency [11]. Vitamin D is a fat-soluble vitamin existing in two forms – ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) which is more bioactive than vitamin D2. It can be consumed in food or synthesised in skin by sun exposure [12]. The vitamin D binding protein transports vitamin D3 to the liver where it is hydroxylated, this process results in the formation of 25-hydroxyvitamin D3 (25(OH)D3), the 25(OH)D3 metabolite is also hydroxylated by renal CYP27B1 to 1,25-dihydroxyvitamin D [1,25(OH)2D; calcitriol], the most bioactive vitamin D metabolite [13-15]. When calcitriol binds to the vitamin D receptor (VDR),it forms a nuclear heterodimer with the retinoid X receptor so this complex binds to genomic vitamin D response elements and downregulates expression of a variety of genes [16].

There are many binding patterns throughout heterodimerisation or overlaps of vitamin D responsive elements (VDREs) in the DNA [17]. Furthermore, it is considered that conformational changes between retinoid X receptor (RXR) and vitamin D receptor (VDR) through their heterodimerisation can activate different signaling pathways resulting in production of a large number of proteins involved in cell function [18]. It is known that MS is more prevalent in higher latitudes, where sunlight is of lower intensity and several studies found that increased body exposure to sunlight is also associated with a decreased risk of MS, especially if the sun exposure occurred during childhood and adolescence [19-21]. Recently, it is found that the birth month is correlated with MS risk; individuals born in the fall (whose mothers were exposed to summer sunlight) have a low MS risk, whereas individuals born in the spring have a higher risk of MS [22]. This could be a possible association between sunlight exposure during pregnancy, vitamin D status and the risk of MS, but it is still unknown if provocative factor for MS is vitamin D deficiency or reduced sunlight exposure by itself.

Also, there is a growing number of studies investigating intracellular pathways including vitamin D and VDR. As mentioned previously, these pathways are dependent on conformational changes between VDR and retinoid X receptor and they result in different signaling pathways activation and production of a large number of proteins involved in cell function, moreover VDR can autoregulate its own acitivity depending on vitamin D serum levels [23]. New studies are showing potential role of microRNA in VDR regulating pathways. MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate the expression of multiple target genes by targeting the 3'-untranslated region (UTR) of messenger RNAs (mRNAs), resulting in degradation or translational repression of mRNA. In the immune system, miRNA modulate both innate and adaptive immune responses [24]. Altered miRNA expression has been reported in the pathology of autoimmune diseases, cancer and coronary artery disease and also it could be related to vitamin D deficiency [25-27].

There is a study of Chen et al. Showing how vitamin D deficiency reduced expression of miRNA in systemic lupus erythematosus (SLE), furthermore vitamin D supplement alter those miRNAs expression in isolated T cells from patients with SLE (25). This could be a potential cuase for other autoimmune diseases development, but for MS also. It is still unknown what are the "cut-off" levles of vitamin D for unfavorable immunological response so this should be investigated further. Considering this, it is known how serum levels of vitamin D are important for VDR pathways activation, but intracellular levels of vitamin D could also be essential. We think it is important to measure serum vitamin D levels, but also intracellular levels of vitamin D because it can give us more information about vitamin D concentration needed for normal cell function, it can help us detect vitamin D deficiency even though when its serum levels are normal. Future studies are needed to assess vitamin D deficiency mechanisms on intracellular levels and their influence on risk of developing MS.

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