Vitamin D receptor polymorphisms in primary biliary cirrhosis: A functional connection?

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See Article, pages 1202–1209

The bioactive form of vitamin D3, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], is a secosteroid hormone with a central function in calcium and bone metabolism, able to regulate cell proliferation and differentiation, and endowed with exquisite immunoregulatory properties [1]. Vitamin D3 can be obtained through the diet, but it is mainly biosynthesized from 7-dehydrocholesterol in skin exposed to ultraviolet light. Vitamin D3 is then transported to the liver where it is hydroxylated to produce 25(OH)D3, a reliable indicator of vitamin D status, and is further hydroxylated in the kidney to form the active hormone, 1,25(OH)2D3 [2]. The biological effects of 1,25(OH)2D3 are mediated by the vitamin D receptor (VDR), a nuclear hormone receptor expressed in most cell types, functioning as a ligand-activated transcription factor that binds to vitamin D-responsive elements in the promoter region of target genes, and ultimately influences their rate of RNA polymerase II-mediated transcription [3].

The vitamin D endocrine system is involved in a variety of biological processes that modulate immune responses [4], and has an important role in the control of autoimmune diseases [1]. Vitamin D status is a crucial environmental factor that affects the prevalence of autoimmune diseases, as shown by the higher incidence of several autoimmune diseases in northern latitudes where lower amounts of vitamin D3 are synthesized from sunlight exposure [2,5]. Epidemiological analysis reveals strong ecological and case-control evidence that the vitamin D system reduces the risk of several autoimmune diseases, including multiple sclerosis, type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, and systemic lupus eritematosus [2,6]. 1,25(OH)2D3 is produced by macrophages, dendritic cells (DCs), T and B cells, and contributes physiologically, via the VDR expressed in these cell types, to the autocrine and paracrine regulation of both innate and adaptive immune responses [4]. In addition to exerting direct modulatory effects on T and B cell function, VDR agonists influence the phenotype and function of DCs, promoting tolerogenic properties that favor the induction of regulatory, rather than effector, T cells [7]. These intriguing actions of VDR agonists have been demonstrated in several experimental models of autoimmune diseases and appear to represent important components of immune system homeostasis. In addition to psoriasis, a Th1 and Th17 cell-mediated autoimmune disease of the skin, VDR agonists could be exploited to treat a variety of autoimmune diseases and other immune-mediated pathologies that are characterized by chronic inflammatory responses [1].

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by a progressive portal lymphocytic inflammatory response with destruction of intrahepatic bile duct epithelial cells leading to cholestasis, liver fibrosis and eventually cirrhosis [8]. The serological hallmark of the disease is the presence of circulating anti-mitochondrial antibodies, reflecting the induction of autoreactive T and B cells to the inciting antigens, mainly E2 subunits of mitochondrial pyruvate dehydrogenase [9]. Although the etiology of PBC is still unclear, both genetic and environmental components
are known to contribute to susceptibility and progression of the disease [10]. Familiarity among PBC patients is frequently observed, and the prevalence of PBC clustering in a representative family with affected patients is much higher than in the general population [11]. In addition, the concordance rate for PBC is remarkably higher in monozygotic compared to dizygotic twins, scoring as the highest among autoimmune diseases [12]. MHC class II polymorphisms were found to be associated with both increased risk and protection from PBC in recent large-size studies [13,14]. Conversely, analysis of non-MHC gene polymorphisms has provided inconsistent results, possibly due to small sample size and ethnic differences in the frequency of minor alleles. As a notable exception, analysis of VDR polymorphisms has consistently demonstrated an association with susceptibility to PBC in different populations [15–18].

DNA sequence variations occurring frequently in the population are defined as “polymorphisms” and can have subtle but real biological effects. Several polymorphisms have been identified in the VDR gene, but their influence on VDR protein function and signalling is largely unknown. The genomic organization of the human VDR locus at chromosome 12q13.1 shows that the VDR gene itself is quite large (over 100 kb) with 11 exons, and has an extensive promoter region capable of generating multiple tissue-specific transcripts [19]. VDR polymorphisms have been analyzed so far mostly in Caucasians, usually by studying three adjacent restriction fragment length polymorphisms (RFLP) for BsmI, ApaI, and TaqI, respectively, at the 3’ end of the VDR gene [19]. Because these polymorphisms are probably non-functional, linkage disequilibrium with one or more truly functional polymorphisms elsewhere in the VDR gene, or in nearby gene/s, is assumed to explain the associations observed [20].

VDR gene polymorphisms have been found to be associated with osteoporosis, a common complication observed in about 25% of PBC patients although not specific to the disease [21], in which VDR genotypes have been reported to predict lower bone mineral density [22]. However, VDR genotypes may play only a minor role in the development of osteoporosis in PBC, where duration and severity of cholestasis are associated with degree of bone loss and may exceed the potential effect of gene polymorphisms [23]. Conflicting results have also been reported for the association of VDR gene polymorphisms with PBC. Studies performed in the Hungarian population have supported a positive association between susceptibility to PBC and BsmI polymorphism at the VDR locus [15,17]. Conversely, the German [16] and Chinese [18] studies have revealed a protective association of BsmI VDR polymorphism with PBC. These discrepant results could be due to different causes, including ethnic diversity, relatively small sample size, linkage disequilibrium, population stratification and environmental confounding factors.

In this issue, Tanaka et al. [24] report the genetic association of BsmI, ApaI, and TaqI VDR gene polymorphisms with PBC in large and well characterized patient series from Japan and Italy. Results in this paper indicate that RFLPs for BsmI and ApaI are significantly associated with the susceptibility of PBC, and that the ‘B’ allele is more frequently distributed in PBC patients [24]. In contrast to previous studies, Tanaka et al. have analyzed a large number of PBC cases and controls, 334 and 335, respectively, performing three statistical tests for each genotype. Importantly, this study has investigated VDR allele frequencies in Japanese and Italian subjects, completely diverse populations but both ethnically homogeneous, thereby preventing population stratification. The significant association of BsmI polymorphism in both Japanese and Italian populations indeed suggests a general contribution of VDR gene polymorphism to PBC susceptibility [24].

The interpretation of polymorphic variations in the VDR gene is blurred by the fact that until now only a few polymorphisms in this large gene have been studied and most are anonymous RFLPs, with an unknown functional effect. Nevertheless, results from the current study demonstrate the possibility that VDR polymorphism represents a genetic marker for the risk of PBC. In particular, the odds ratio (OR) of genotype ‘BB’ at the BsmI polymorphism in Japanese subjects was 13.7, supporting the rationale that genotype ‘BB’ might be used as a diagnostic tool and/or a predictive marker for PBC [24].

In the absence of a clear link between VDR polymorphisms and function of the vitamin D endocrine system, it is possible only to speculate about the underlying mechanisms. Vitamin D deficiency does not appear to be widespread among PBC patients [25], who experience a lower frequency of 25(OH)D deficiency compared to other autoimmune diseases [2]. 25-hydroxylation of vitamin D3, which takes place in the liver, is normal in PBC patients [26]. Cholestatic liver injury is counteracted by a variety of adaptive hepatoprotective mechanisms, including modulation of bile acid transport, synthesis and detoxification, which are mediated by a complex network of nuclear receptors involving the farnesoid X receptor, pregnane X receptor, constitutive androstane receptor, and VDR [27]. VDR also functions as a receptor for the secondary bile acid lithocholic acid [28], which is hepatotoxic, providing a possible association between PBC and VDR polymorphisms. Mice treated with 1,25(OH)2D3 after bile duct ligation (BDL) did not show decreased bile acid levels in plasma and liver, but the treatment suppressed mRNA expression of pro-inflammatory cytokines in the liver and strongly decreased plasma levels of proinflammatory cytokines...
[29], suggesting that 1,25(OH)2D3 targets the inflammatory rather than the cholestatic aspect of the disease. If the VDR polymorphisms described by Tanaka et al. reflect a deranged capacity of the vitamin D system to promote tolerogenic DCs, enhance regulatory T cells and/or inhibit pathogenic Th1 and Th17 cells in PBC patients, these would represent plausible explanations for the association of the observed VDR polymorphisms with PBC.

Future research should document additional polymorphisms across the VDR gene to verify these hypotheses, trying to understand the functional consequences of the receptor variations. Until then, the role of VDR polymorphisms in PBC, as in any other autoimmune disease, will remain a topic for debate. Unfortunately, the complex organization of the VDR gene will make the identification of these functional polymorphisms a somewhat daunting task.

References


