A single-nucleotide polymorphism in the vitamin D receptor gene is associated with a B3-penetrating phenotype in Crohn's disease

Gisbert-Ferrándiz L [1], Hinojosa J [2], Barrachina MD [1], Hernández C [3]

[1] Departamento de Farmacología and CIBERehd, Facultad de Medicina, Universidad de Valencia, Valencia
[2] Servicio de Gastroenterología, Hospital de Manises, Valencia
[3] FISABIO, Hospital Dr. Peset, Unidad Mixta en Biomedicina y Farmacología FISABIO-UVEG, Valencia
chernans77@gmail.com

Background and Aims: Vitamin D signaling modulates inflammation through the vitamin D receptor (VDR) which is a member of the nuclear receptor family of transcription factors. The presence of C instead of T in the single-nucleotide polymorphism (SNP) rs731236 in the VDR gene has been associated with a higher risk for Crohn's disease (CD). We analyzed the differences in VDR expression levels between CD patients homozygous for allelic variants in this SNP and the relevance for disease course.

Methods: DNA was extracted from blood samples of CD patients and SNP genotyping was performed by PCR-RFLP. Fresh blood from patients was used to isolate peripheral blood mononuclear cells (PBMCs) or to determine the expression of adhesion molecules by flow cytometry. In PBMCs we quantified the gene expression of VDR and several cytokines by RT-PCR and the protein levels of VDR by Western blot. In addition, we collected complete clinical data for a group of 103 patients in order to compare patient characteristics between genotypes.

Results: We found that CD patients homozygous for the risk allele presented a lower level of VDR protein in PBMCs, with no differences in the mRNA expression. This is associated with a significant upregulation of IL1β mRNA in PBMCs, which also showed a non-significantly higher expression of IL8, IL18, IFNγ and TNFα mRNAs. These patients also had an increased expression of CD11a, CD11c and CD49D integrins in lymphocytes, as well as a reduced CD62L level, indicating inflammatory activation. In addition, they exhibited a significant higher risk to develop a B3-penetrating phenotype and to undergo surgery.

Conclusion: Our study indicates that CD patients homozygous for the allele C in the SNP rs731236 have a lower level of VDR protein and highlights the relevance of the vitamin D/VDR signaling in modulating subjacent inflammation leading to CD-related complications.