

Abstract

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Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn's disease.

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BACKGROUND: Vitamin D signaling through its nuclear vitamin D receptor has emerged as a key regulator of innate immunity in humans.

OBJECTIVE: Here we show that hormonal vitamin D, 1,25-dihydroxyvitamin D(3), robustly stimulates expression of pattern recognition receptor NOD2/CARD15/IBD1 gene and protein in primary human monocytic and epithelial cells.

METHODS: The vitamin D receptor signals through distal enhancers in the NOD2 gene, whose function was validated by chromatin immunoprecipitation and chromatin conformation capture assays.

RESULTS: A key downstream signaling consequence of NOD2 activation by agonist muramyl dipeptide is stimulation of NF-kappaB transcription factor function, which induces expression of the gene encoding antimicrobial peptide defensin beta2 (DEFB2/HBD2). Pretreatment with 1,25-dihydroxyvitamin D(3) synergistically induced NF-kappaB function and expression of genes encoding DEFB2/HBD2 and antimicrobial peptide cathelicidin in the presence of muramyl dipeptide. Importantly, this synergistic response was also seen in macrophages from a donor wild type for NOD2 but was absent in macrophages from patients with Crohn disease homozygous for non-functional NOD2 variants.

CONCLUSION: These studies provide strong molecular links between vitamin D deficiency and the genetics of Crohn disease, a chronic incurable inflammatory bowel condition, as Crohn's pathogenesis is associated with attenuated NOD2 or DEFB2/HBD2 function.

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