LARGE INTESTINE

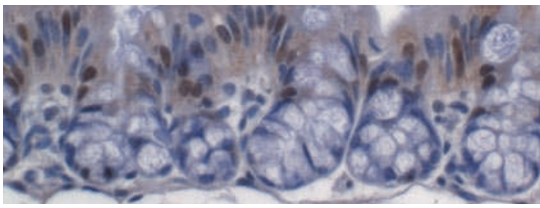
VDR signaling is altered by exposure to enteric bacteria

The vitamin D receptor (VDR) signaling pathway has important immunoregulatory and anti-inflammatory roles in gastrointestinal diseases, such as IBD and colorectal cancer. A mouse study published in the *American Journal of Pathology* now shows that VDR signaling protects against excessive immune responses to organisms in the intestinal lumen. "We found that VDR expression determines how intestinal epithelial cells respond to pathogenic bacterial triggers," explains Jun Sun, the study's corresponding author. Importantly, the effects of bacteria on VDR signaling seem to be independent of vitamin D_3, which is the VDR ligand.

Interestingly, VDR expression correlated with bacterial load, being highest in the proximal colon, where enteric bacteria grow strongly, and reduced in the distal colon, an area in which bacterial growth is limited. Furthermore, VDR-null mice exhibited a proinflammatory phenotype—indicated by increased activity of nuclear factor κB (NFκB) and high serum levels of interleukin 6—even in the absence of infection. VDR-null mice also showed a heightened response to infection with *Salmonella* compared with wild-type mice (mice lacking VDRs had greater cecal shortening, worse intestinal inflammation and increased mortality).

In wild-type mice, VDR is normally expressed by fully differentiated intestinal cells at the top of crypts. However, both VDR expression and transcriptional activity increased as a direct result of *Salmonella* infection, in conjunction with relocation of VDR expression to cells further down the crypts. "Intestinal VDR signaling responds to both commensal and pathogenic bacterial stimulation," says Sun.

The VDR forms a complex with NFκB subunit p65 in osteoblasts, and Sun and colleagues demonstrated that this interaction also occurs in the mouse intestine *in vivo*. NFκB is an essential regulator of the innate and adaptive immune responses, but the functional relevance of this interaction has yet to be elucidated. The researchers showed that deletion of VDR completely abolished the formation of the complex with NFκB and allowed nuclear translocation of the p65 subunit, which might account for the proinflammatory features of VDR-null mice.



Courtesy of J. Sun

"VDR is an important contributor to intestinal homeostasis and host protection from bacterial invasion and infection," conclude the researchers. "Future research could establish VDR signaling as a new target for treatment of infection and inflammatory bowel disease," suggests Sun.

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Original article Wu, S. *et al.* Vitamin D receptor negatively regulates bacterial-stimulated NF-κB activity in intestine. *Am. J. Pathol.* **177**, 686–697 (2010)