Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

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Departments of [1]Medicine and [4]Pathology, The University of Chicago, Chicago, Illinois; [2]The Huck Institutes for Life Sciences, The Pennsylvania State University, University Park, Pennsylvania; and [3]Gastroenterology and Hepatology Division, Department of Medicine, University of Rochester Medical Center, Rochester, New York

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Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Li YC. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 294: G208–G216, 2008. First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.—Emerging evidence supports a pathological link between vitamin D deficiency and the risk of inflammatory bowel disease (IBD). To explore the mechanism we used the dextran sulfate sodium (DSS)-induced colitis model to investigate the role of the vitamin D receptor (VDR) in mucosal barrier homeostasis. While $VDR^{+/+}$ mice were mostly resistant to 2.5% DSS, $VDR^{-/-}$ mice developed severe diarrhea, rectal bleeding, and marked body weight loss, leading to death in 2 wk. Histological examination revealed extensive ulceration and impaired wound healing in the colonic epithelium of DSS-treated $VDR^{-/-}$ mice. Severe ulceration in $VDR^{-/-}$ mice was preceded by a greater loss of intestinal transepithelial electric resistance (TER) compared with $VDR^{+/+}$ mice. Confocal and electron microscopy (EM) revealed severe disruption in epithelial junctions in $VDR^{-/-}$ mice after 3-day DSS treatment. Therefore, $VDR^{-/-}$ mice were much more susceptible to DSS-induced mucosal injury than $VDR^{+/+}$ mice. In cell cultures, 1,25-dihydroxy-vitamin D_3 [$1,25(OH)_2D_3$] markedly enhanced tight junctions formed by Caco-2 monolayers by increasing junction protein expression and TER and preserved the structural integrity of tight junctions in the presence of DSS. VDR knockdown with small interfering (si)RNA reduced the junction proteins and TER in Caco-2 monolayers. $1,25(OH)_2D_3$ can also stimulate epithelial cell migration in vitro. These observations suggest that VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of junction complexes and the healing capacity of the colonic epithelium. Therefore, vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.