Is RXR α Crucially Involved in Intestinal Inflammation?

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Retinoid X receptors (RXRs) are nuclear receptors that control several physiological processes [1]. Three closely related RXR isotypes are encoded on chromosome 9: RXR α (activated by 9-*cis*-retinoic acid), RXR β , and RXR γ . RXRs form heterodimers, either spontaneously or in a ligand-dependent manner, with other nuclear receptors including retinoic acid receptors (RAR), peroxisome proliferator-activated receptors (PPAR), estrogen receptors (ER), vitamin D receptors (VDR), thyroid hormone receptors (TR), farnesoid X receptors (FXR), liver X receptors (LXR), constitutive androstane receptors (CAR), and pregnane X receptors (PXR) [2, 3]. Dimerization of RXR with other nuclear receptors transcriptionally controls a variety of cellular processes by binding to specific DNA response elements within regions of target gene promoters [4]. Nuclear receptor binding to RXR can be functionally divided into “permissive” and “non-permissive” groups. Heterodimers that form when binding to a “permissive” receptor, for example PPAR, can be activated by agonists to either heterodimeric partner. In contrast, “non-permissive” RXR nuclear receptor heterodimers, for example VDR and THR, can be activated only by agonists binding to the partner of RXR [5].

1,25(OH) $_2$ D $_3$ binds to its receptor, VDR, which requires RXR to bind to vitamin D response elements for transcriptional regulation. Several pieces of evidence are indicative of loss of vitamin D-VDR signals in the pathogenesis of inflammatory bowel disease. First, VDR polymorphisms are associated with IBD risk in some

populations [6]. In a murine model, VDR/IL-10 double knockout mice develop more severe colitis and mortality is higher [7]. In IL-10(–/–) mice, vitamin D deficiency exacerbates the symptoms of colitis, whereas vitamin D supplementation ameliorates symptoms and reduces inflammation [8]. Another mechanism whereby vitamin D protects against IBD development is by maintaining or restoring the integrity of the intestinal mucosal barrier by preventing intestinal epithelial apoptosis [9]. In this regard, 1,25(OH) $_2$ D $_3$ has several effects on the immune system, including suppression of T cell activation and modulation of antigen presentation [10]. Furthermore, VDR signaling is also involved in regulation of the innate immune response in macrophages [11].

In this issue of *Digestive Diseases and Sciences*, Knackstedt et al. report the potential involvement of RXR α in mucosal inflammation [12]. Although the study did not demonstrate differences in colitis between RXR α heterozygotes and wild-type mice in a murine model of early colitis, there were significant increases in Snail1 and Snail2 in the RXR+/- mice. Snail 1 and Snail 2 are transcription factors linked to the epithelial–mesenchymal transition that mediate cell migration during inflammation [13]. These transcription factors are up-regulated in ulcerative colitis and can silence VDR expression, which is often down-regulated in active mucosal inflammation and colon cancer [9, 14]. Through this mechanism, RXR α is likely to be important in modulating inflammation and carcinogenesis, because, for example, RXR and VDR polymorphisms alter the risk of sporadic colon cancer [15, 16]. It is difficult to understand, however, why mucosal inflammation was no different despite up-regulation of Snail 1 and Snail 2 in this study. Although the RXR α heterozygous model used in this work did not result in significant down-regulation of RXR α protein expression, a model with conditional RXR α homozygous deletion might

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reveal a greater effect on mucosal inflammation. Furthermore, extending the time of investigation from a model of early colitis to one of chronic colitis might reveal different effects of RXR α hemizygous deletion in colonic inflammation. Nevertheless, further mechanistic evaluation of the effect of RXR α in mucosal inflammation is needed, because it is unknown whether the RXR–VDR heterodimer, as suggested by the authors, or alternative nuclear receptors or other pathways regulate the inflammatory cascade or mediate carcinogenesis, as supported by the observation that RXR and PPAR γ agonists reduced inflammation in a TNBS-induced colitis murine model [17].

There is increasing evidence that low serum vitamin D concentrations are a risk factor for the development of inflammatory bowel disease [18]. Although evidence for humans is lacking, in murine models, treatment with vitamin D does improve symptoms of colitis [8]. Potentially, therapy targeting RXR α , in conjunction with vitamin D, could also be used to treat bowel inflammation. Because VDR forms a non-permissive heterodimer with RXR, RXR agonists are unlikely to be beneficial in regulating transcription at VDREs. Furthermore, because RXR α seems to be excess in most cells, therapeutic intervention to increase RXR expression is unlikely to enhance RXR–VDR signaling [19]. For this reason, the greatest potential for therapeutic intervention involving this pathway is likely to involve increasing the interaction of RXR with its heterodimeric partners.

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