Pathology Elsewhere

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Peroxisome proliferator-activated receptors: potential new therapeutic targets for idiopathic inflammatory bowel disease

Inflammatory bowel disease (IBD) is a growing concern in Western countries because of its rising incidence and its lack of satisfying long-term medical treatment without significant side effects. Studies have been conducted in animal models in an attempt to elucidate the pathogenesis and to find more effective medical therapy. Recently, the use of selective peroxisome proliferator-activated receptor (PPAR)- γ agonists in the treatment of IBD has received attention. PPAR are members of nuclear hormone receptor superfamily of small, lipophilic ligand-dependent transcription factors. There are three PPAR subtypes, namely PPAR- α , PPAR- β/δ , and PPAR- γ that are selectively expressed in different tissues or cells including the human colon. Their selective distribution pattern and significant anti-inflammatory properties make PPAR and their agonists promising therapeutic candidate agents for IBD. Among the three subtypes, PPAR- γ has been best characterized. PPAR- γ is expressed in high levels in adipose tissue and the colonic epithelium, and in lower levels in other tissue or cells including lymphocytes, hepatocytes, skeletal muscle, breast, prostate, and monocytes/macrophages. During chronic inflammation, lower expression of PPAR- γ is observed. Normal levels, however, can be restored or enhanced by delivery of PPAR- γ agonists. The implications of the interaction between PPAR- γ and their agonists (ligands) are unclear, but are believed to involve modulation of inflammatory responses. Naturally occurring PPAR- γ ligands are weak activators of PPAR- γ , for example, polyunsaturated fatty acids, oxidized LDL, some eicosanoids and others. Interestingly, some synthetic agonists or drugs currently used for other purposes, such as thiazolidinediones (TZD) for type II diabetes mellitus, have a high affinity towards PPAR- γ and have important antineoplastic and anti-inflammatory properties.

In a recent article by **Bassaganya-Riera *et al.***¹ diet supplemented with conjugated linoleic acid (CLA) ameliorated colitis in dextran sodium sulfate (DSS)- and CD4⁺-induced IBD mouse models, especially early in the life of these animals. CLA significantly induced expression of PPAR- γ , δ ; and transcriptionally modulated their target genes, which were involved in lipid metabolism and epithelial maturation. In addition, CLA repressed tumor necrosis factor α (TNF- α) expression and NF- κ B activation, and induced the immunoregulatory cytokine trans-

forming growth factor β 1 (TGF- β 1). This study suggests that CLA protects DSS and CD4⁺-transfer induced inflammatory bowel disease in mice through a PPAR- γ -dependent mechanism.

In this issue of *Laboratory Investigation*, **Cuzzocrea *et al.***² examined the inhibitory effects of PPAR- α ligands on the development of dinitrobenzene sulfonic acid (DNBS)-induced colitis in mice. Although the anti-inflammatory activity of PPAR- α was less characterized than that of PPAR- γ , PPAR- α knockout mice suffered inflammatory activity and clinical symptoms, more so than the wild-type mice. Furthermore, they found that the exogenous PPAR- α agonist, WY 14643, could significantly protect the colon from inflammatory injury in the wild-type mice, but not in the PPAR- α knocked out mice. Many PPAR- α ligands, for example, the fibrate ligands, are currently used to treat hyperlipidemia. Like TZD, these drugs may have new therapeutic values in IBD. Both studies have provided a new strategy to design and develop synthetic ligands or drugs with higher selectivity toward their respective PPAR subtypes for the treatment of IBD.

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Is 'normal' mucosa in colon cancer actually abnormal?

Colorectal cancer is one of the most extensively studied tumors at the molecular level. The known genetic alterations from adenoma to frank colon carcinoma have served as a paradigm for tumor progression. Most studies have assumed that morphologically normal colon mucosa is metabolically normal and have used such tissue as a baseline for comparison.

In a recent analysis, **Chen *et al.***¹ attempted to validate this general assumption by comparing gene expression profiles of the so-called normal colon mucosa from patients with colon carcinoma with those from patients without cancer. A total of 15

genes that were altered in the late stages of human colon cancers were analyzed. At least six of them were significantly upregulated in the morphologically normal mucosa from cancer patients, that is, MCSF-1, OPN, IL-8, COX-2, CXCR2 and CD44; whereas at least two genes, PPAR δ and γ , were significantly down regulated. Similar findings were observed in mice carrying a mutation in the *adenomatous polyposis coli* (APC) gene, the APC^{min} mice. Several genes in the APC^{min} mice were upregulated dramatically, at levels 80–400 times greater than in wild-type controls. They also found that there was considerable variability in the expression level from one area to another, and that the differences did not correlate with its distance from the tumor, suggesting that the changes did not appear to result from a field effect.

The researchers speculated that these metabolic alterations might be an early event in carcinogenesis and that the morphologically normal mucosa might be abnormally sensitive to events that did not affect metabolically normal mucosa, hence predisposed colon mucosa to the development of cancer. Furthermore, identifying these altered genes in normal-appearing colon mucosa might be useful

targets for cancer prevention as well as early markers for cancer screening and diagnosis.

In this issue, Colnot *et al*² emphasized the importance of genetic and particularly environmental modifiers in the pathogenesis of colon cancer. Different housing conditions produced variations in the distribution and extent of colorectal polyposis in a mouse model with APC mutations. Both studies suggest that secondary microenvironmental insults might be an important factor for the development of polyps.

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