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EDITORIAL

Osteopontin Biomarker in Inflammatory Bowel Disease, Animal Models and Target for Drug Discovery

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Inflammatory bowel disease (IBD) is an immune-mediated disease caused by abnormal mucosal T-cell response to bacteria in the intestinal lumen. In Crohn's disease (CD), mucosal T cells exhibit the TH1 phenotype, whereas ulcerative colitis (UC) is believed to have a TH2 phenotype [1].

In the absence of a single test, calculating disease activity in IBD remains a complicated task. An accurate and reliable marker for measuring CD or UC activity for routine clinical practice and in clinical trials has to be based on clinical judgment of histologic and endoscopic imaging. Therefore, validated accurate and objective measures of inflammatory activity in IBD using a reliable, non-invasive biomarker is needed [2]. Proteonome biomarkers are used in the diagnostics of IBD, but they are expensive and not all of them are validated [3].

Several recent reports have suggested an important role for osteopontin (OPN) in the pathogenesis of IBD as well as its possible use as a biomarker [4–10]. Masuda et al. demonstrated that expression of OPN is significantly elevated in the mucosa of patients with UC [6]. Elevated OPN expression in UC was demonstrated using immunohistochemistry and ultrastructure analysis [7, 8]. In CD, Gassler et al. reported an elevated OPN expression in plasma cells, but not in epithelial cells [9]. Moreover, Sato et al. observed an elevated plasma OPN and significant correlation with disease activity in CD, but not in UC [10].

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Osteopontin, a Th1 cytokine, is up-regulated in relation to the severity of the disease [11]. Moreover, since it is an adhesive glycoprotein containing the peptide sequence glycine ± arginine ± aspartate ± serine it promotes cell attachment [12]. Osteopontin and tumor necrosis factor receptor signaling (TNFRS) F14 are genes associated with fibrosis/cell adhesion molecules [1, 13]. Blockade of these cell adhesion molecule interactions prevents the trafficking of leukocytes across the vascular endothelium and, subsequently, into the parenchymal tissue [14–16]. Alpha-4 integrins bind additional ligands in tissues, including OPN and epitopes of fibronectin. This is the rationale for using the mechanism of monoclonal antibodies in clinical practice. The scope may be to suppress ongoing inflammatory reactions in diseased tissues by inhibition of α4-positive leukocytes with ligands. Inhibiting the existing inflammatory activity at the disease site, along with inhibition of further recruitment of immune cells into inflamed tissue, via interaction with adhesion molecules such as the vascular adhesion molecule will reduce the inflammation and intestinal fibrosis [17–19].

On the basis of these findings, several researchers described animal models that can mimic the OPN-induced colitis in vivo as well as block OPN-induced inflammation [20–23].

In this issue is the article "Osteopontin ablation attenuates progression of TNBS-induced colitis model." In this study, Oz et al. elegantly demonstrate that by ablating the OPN activity the colitis is suppressed [24]. The developmental stages of colonic inflammation in a modified trinitrobenzene sulfonic acid (TNBS) model that mimics Crohn's disease have been defined as acute, subacute, and chronic. The researchers used OPN deficient mice, with a targeted disruption of the *opn* gene in a C57BL/6. TNBS-treated wildtype mice developed severe colitis but OPN-deficient mice were significantly protected.

Animal models using OPN-deficient mice have the ability to conclude that OPN plays a role in acute and chronic intestinal inflammation. This will prove to be a fertile area for future research in drug discovery. Animal models mimicking OPN-induced colitis and responses to drugs can also be an attempt to match individual therapies to individual patients. In addition, OPN shows promise as a useful clinical marker of disease activity in IBD and may have a role in the day-to-day management of patients.

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