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A role for oncostatin M in inflammatory bowel disease

Walter M Kim,

Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Arthur Kaser, and

Division of Gastroenterology and Hepatology, Department of Medicine, University of Cambridge, Cambridge, UK

Richard S Blumberg

Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

A new study identifies oncostatin M (OSM) as a potential biomarker and therapeutic target for anti-tumor necrosis factor (TNF)-refractory inflammatory bowel disease (IBD), and pinpoints mucosal stromal cells as key players in OSM-mediated inflammation.

Crohn's disease (CD) and ulcerative colitis (UC), the two main forms of IBD, are chronic debilitating inflammatory disorders of the gastrointestinal tract. Initially recognized as conditions that afflict populations primarily in Europe and North America, their prevalence and incidence have been increasing at alarming rates around the world¹. Current therapies for IBD are aimed at ameliorating mucosal inflammation. Among these, neutralizing antibodies directed against the proinflammatory cytokine TNF represent the standard of care for moderate to severe disease, but are ineffective for 40% of treated patients². Treatments directed at alternative targets, such as $\alpha_4\beta_7$ integrin to block immune cell trafficking into intestinal tissues³ or interleukin (IL)-12 and IL-23 (ref. 4) to target cytokines upstream of TNF, are also used in IBD and exhibit good efficacy in patients who are naive to anti-TNF antibodies. Interestingly, therapeutic responses to anti- $\alpha_4\beta_7$ integrin are markedly lower in patients who have previously failed anti-TNF treatment⁵, which implies the presence of a distinct disease biology in the anti-TNF-resistant population. More broadly, no biomarkers have been identified in IBD that predict response or failure to anti-TNF therapy. In this issue of *Nature Medicine*, West *et al.*⁶ identify OSM as a strong predictor of anti-TNF treatment failure in IBD, and implicate it as a potential therapeutic-drug target.

OSM is a member of the IL-6 cytokine family and has a role in hematopoiesis, bone remodeling and liver regeneration, as well as multiple chronic inflammatory conditions, including rheumatoid arthritis⁷. Owing to its reported proinflammatory and anti-inflammatory effects, the function of OSM has been enigmatic, with an ill-defined role in

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IBD. A previous study⁸ demonstrated that adenoviral-vector transfer of OSM in mice had opposite effects in two different types of chemically induced models of colitis. A more recent study⁹ demonstrated that OSM was overexpressed in the colonic lesions of patients with active CD, but attributed its function to the promotion of epithelial repair as a counter-regulatory mechanism against inflammation.

In this issue, West *et al.*⁶ first identified *OSM* as the most transcriptionally upregulated cytokine in inflamed intestinal mucosa from patients with CD and as among the most upregulated in patients with UC, when compared to mucosa from healthy individuals. The authors also demonstrate that *OSM* upregulation in the intestinal mucosa is mirrored by overexpression of its unique receptor, *OSMR*, suggesting a specific role of OSM–OSMR interactions in IBD pathogenesis. *OSM* and *OSMR* expression positively correlated with the severity of mucosal inflammation, and strikingly, were abundantly observed pretreatment in patients with IBD who subsequently failed anti-TNF therapy (Fig. 1). This indicated that *OSM* and *OSMR* expression might be predictive of primary treatment failures, which the authors supported by analysing an independent data set derived from a previously published¹⁰ clinical trial of golimumab, an anti-TNF agent, in UC. The authors also found that *OSM* and *OSMR* are associated with upregulation of various clusters of genes involved in nonhematopoietic stromal cell function, such as intercellular adhesion molecule-1 (*ICAM1*) and podoplanin (*PDPN*, also known as gp38). They further observed that OSMR surface expression is largely restricted to the CD45⁺EpCAM⁺CD31⁺ stromal cell population and exists at similar surface-expression levels in both patients with IBD and healthy controls. Taken together with the transcriptional changes, the augmentation of *OSMR* expression in diseased intestinal tissue, the authors concluded, was a consequence of an increase in absolute numbers of OSMR-expressing stromal cells.

In light of these results, the authors sought to understand the functional role of the OSM–OSMR interactions in the development of IBD. They used a previously described mouse model of IBD¹¹ in which mice are infected with *Helicobacter hepaticus* and treated with an anti-IL-10 receptor (R) monoclonal antibody to block the signaling associated with this important anti-inflammatory cytokine, thereby inducing colitis. This model of intestinal inflammation is known to be markedly resistant to anti-TNF-antibody treatment¹². They show in this model that *Osm* expression and numbers of OSMR-positive stromal cells expressing proinflammatory cytokines such as *Il1b* and *Il6* were increased in *H. hepaticus* and anti-IL-10-R-antibody-treated mice, as compared to those in healthy mouse controls, consistent with their observations in human tissues. In addition, intestinal stromal cells from humans with IBD or experimentally treated mice responded more vigorously than their respective healthy controls to OSM stimulation, and with a similar pattern of cytokines and chemokines. Furthermore, the expression of proinflammatory chemokines, such as CXCL9 and CCL2, by the human stromal cells in response to OSM was further increased by the addition of TNF, which suggests that the binding of OSM to the intestinal stromal cells triggers proinflammatory synergism with other signals. Importantly, OSM-deficient mice exhibited significantly less intestinal pathology in response to *H. hepaticus*-induced colitis than seen in OSM-sufficient mice. The authors also observed that the greatest effects of OSM deficiency on intestinal pathology occurred during the later phases of the inflammatory response, which suggests that OSM–OSMR signaling in stromal cells was

important for propagating the inflammation and development of chronic disease. The authors concluded their study with an important therapeutic insight, by demonstrating that the *H. hepaticus* model of intestinal inflammation could be effectively treated after the initiation of inflammation by using a heterodimeric OSMR–gp130-Fc fusion decoy receptor, which functions to sequester OSM. Thus *OSM* and *OSMR* might be not only elegant biomarkers for anti-TNF failure in IBD, but highly promising therapeutic targets.

These studies are an elegant blueprint for how a careful analysis of transcriptional-expression studies from diseased human tissues can foster the identification of biomarkers with potential therapeutic importance. Here the authors revealed an intriguing and unexpected role of stromal cell expression of OSMR as part of a unique pathway that contributes to the chronicity of intestinal inflammation, and reveal that OSM/OSMR may be a potential therapeutic target in humans with IBD. In addition, they show that OSM/OSMR is a highly attractive biomarker for determining candidacy for anti-TNF therapy, which deserves testing in future clinical studies. It will be interesting to explore whether its applicability extends beyond predicting nonresponse to not only anti-TNF therapy but also other approved treatments, such as anti-IL-12/23 and anti-integrin therapies, as well as how OSM/OSMR expression renders tissues resistant to anti-TNF treatment. The application of OSM and OSMR expression testing as a diagnostic tool for early stratification of patients with IBD undoubtedly offers the potential for important progress toward the development of personalized medicine and improved patient outcomes.

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Figure 1.

OSM and OSMR are upregulated in severe anti-TNF-therapy-refractory IBD. West *et al.*⁶ demonstrate that OSM expression increases with disease severity. OSM binds to OSMR–gp130 expressed primarily on intestinal stromal cells, and increased stromal cell occupation of the lamina propria accounts for the augmented levels of OSMR present in the subset of IBD patients refractory to anti-TNF. Markedly increased levels of OSM and OSMR expression in severely inflamed colonic lesions are highly associated with anti-TNF-refractory disease.