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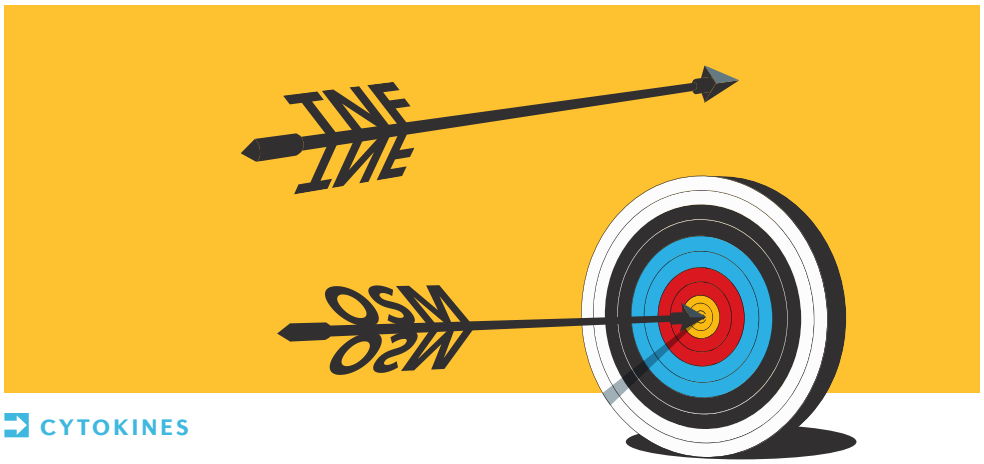

CYTOKINES

Oncostatin M – a new target in IBD?

The inflammatory bowel diseases (IBDs) are chronic conditions of the gastrointestinal tract that are characterized by dysregulated cytokine networks. Although drugs targeting tumour necrosis factor (TNF) are commonly used to treat IBDs, up to 40% of patients do not respond. Fiona Powrie and colleagues now report that the interleukin-6 (IL-6) family member oncostatin M (OSM) is upregulated in patients with IBDs, promotes intestinal inflammation and can predict whether a patient will respond to anti-TNF therapy.

Initially, the authors assessed cytokine mRNA expression in biopsies from patients with active Crohn's disease or ulcerative colitis. Out of 64 candidate cytokines, the expression of only 4 cytokine mRNAs — *IL6*, *IL1A*, *IL1B* and *OSM* — was significantly higher in biopsies from patients with IBD. The authors chose to focus on OSM, which is the least well-characterized of these cytokines, and through a series of analyses confirmed that OSM and its receptor (OSMR) are highly expressed in patients with active IBDs; moreover, their levels of expression were found to correlate with disease severity in patients. Hierarchical clustering analyses of gene expression in IBD cohorts showed that OSM is associated with a discrete module of inflammatory mediators. Notably, the presence of this OSM inflammatory module correlated with non-responsiveness to anti-TNF therapy in patients with IBDs.

Further analyses showed that IBD tissues with high levels of OSM and OSMR expression were enriched in genes associated with leukocyte chemotaxis, extracellular matrix organization and mesenchymal development, suggesting that OSM may act on stromal cells. In keeping with this, the authors found that OSMR was strongly expressed by most stromal cells in the human intestine but was not expressed by epithelial cells or haematopoietic cells. By contrast, OSM was expressed by haematopoietic cell populations, including $CD4^+$ T cells and antigen-presenting cells. Experiments using cells from a human colonic fibroblast cell line and primary colonic stromal cells showed that approximately half of the OSM inflammatory module genes were directly induced by OSM stimulation. Interestingly, stromal cells from patients with IBDs were more sensitive to OSM-mediated stimulation than stromal cells from non-IBD controls.

> “a potentially useful strategy for treating patients with IBDs who do not respond to anti-TNF therapy”

The authors used a mouse model of colitis induced by infection with *Helicobacter hepaticus* and IL-10 receptor blockade to more closely examine the functions of OSM *in vivo*. Of note, this IBD model is resistant to anti-TNF therapy. When the authors induced colitis in wild-type and OSM-deficient mice, they found that early inflammatory responses in the intestines were comparable; however, OSM-deficient mice showed markedly reduced leukocyte infiltration and disease pathology at later time-points, suggesting that OSMR signalling promotes chronic intestinal inflammation. Neutralization of OSM also reduced colitis severity in wild-type mice and this was associated with suppression of the OSM inflammatory module.

These findings indicate a previously unappreciated role for OSM in driving intestinal inflammation and suggest that targeting this cytokine could be a potentially useful strategy for treating patients with IBDs who do not respond to anti-TNF therapy. Furthermore, the OSM inflammatory module defined in this study could be used to identify patients that are likely to respond (or not) to anti-TNF therapy.

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ORIGINAL ARTICLE West, N. R. *et al.* Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. *Nat. Med.* http://dx.doi.org/10.1038/nm.4307 (2017)