Case Study

Identifying specific cytokines that may play a role in understanding inflammatory bowel disease

Problem: Despite exhibiting inflammation and IL-6 signatures, many inflammatory bowel disease patients do not respond to IL-6 inhibitors or tumor necrosis factor inhibitor therapy

Inflammatory bowel disease (IBD) is an umbrella term used to describe two conditions, ulcerative colitis and Crohn's disease, which are characterized by compromised functioning of the gastrointestinal (GI) tract due to chronic inflammation[1]. While the exact triggers for the inappropriate immune response that leads to inflammation are not completely understood, recent studies have identified genetic factors that increase the likelihood of developing IBD[2].

Genes that are involved in the production of cytokines—particularly IL-6—have been reported to be excessively active in IBD patients[3]. Yet treatment of IBD with classic anti-inflammatory drugs or IL-6 inhibitors either shows no response or can lead to severe complications such as intestinal perforations and abscesses[4,5].

Like IL-6, tumor necrosis factor (TNF) is a major mediator of intestinal inflammation. While anti-TNF therapy has been shown to be more effective than targeting IL-6, 40% of patients still do not respond to anti-TNF therapy, and many of those who do respond will eventually lose their response[4-7].

Solution: Oncostatin M is a promising biomarker for predicting therapy response

A recent meta-analysis conducted at the University of Oxford highlighted five candidate biomarkers for predicting response to TNF inhibitor therapies. The analysis compared available high-throughput RNA gene expression datasets from clinical trials conducted for IBD treatment[8]. West *et al.* identified the IL-6 family cytokine Oncostatin M (OSM) and its receptor (OSMR) as two of the most enriched genes in IBD patient mucosa.

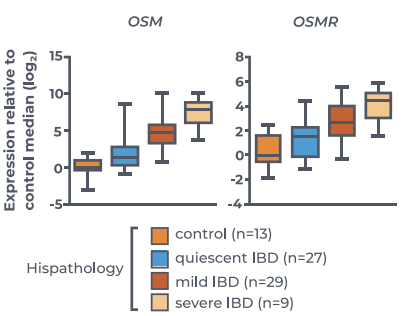

***Figure 1**. Relationship between OSM/OSMR expression and disease presence/severity as determined in a one-way ANOVA with Tukey's multiple comparison tests by West* et al*[8].*

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Analysis of a different clinical trial dataset revealed that patients with elevated OSM-OSMR expression subsequently had decreased responsiveness to TNF inhibitor therapy[8]. A more recent study also demonstrated that pediatric patients that had elevated levels of OSM and OSMR in their plasma responded poorly to infliximab treatment compared to patients that had low levels of OSM-OSMR[9]. There is currently interest in researching OSM as both a prognostic and therapeutic target for IBD[10].

Context: Probing the OSMR mechanism of action in biopsies and mouse models

Based on what they found in their meta-analysis, West *et al.* went on to probe the cause of OSMR overexpression in IBD[8]. Analysis of biopsy specimens showed that OSMR was selectively enriched only in intestinal stromal cells in both IBD patients and healthy donors, suggesting that elevated OSMR from IBD patients is a result of a greater number of OSMR-positive stromal cell population within intestinal tissue rather than increased OSMR expression per cell. This was confirmed in a mouse model of TNF inhibitor therapy-resistant IBD, which displayed increased numbers of OSMR-positive stromal cells in intestinal tissue when compared to healthy mice.

Genetic deletion of OSM or OSM blockade by neutralizing antibodies against OSM significantly suppressed colitis in anti-TNF-resistant mice. OSMR overexpression was strongly correlated with the upregulation of inflammatory cytokines IL-1b and IL-6 and intestinal stromal cell genes such as ICAM1.

Opportunities for applying the HTG EdgeSeq Immune Response Panel

Research into IBD needs to consider the gene expression of cytokine biomarkers like OSMR that could play a role in promoting IBD pathogenesis before deciding on anti-TNF regimens. Given the intricate and varied cytokine networks that operate in autoimmune patients, profiling the expression of autoimmune-related genes can also decipher the mechanism of action regarding why patients failed to respond to therapies. For example, an imbalance in the expression of biomarkers like OSM can have downstream consequences on the expression of other cytokines that are regulated by OSM, which can have potentially adverse clinical consequences.

The HTG EdgeSeq Immune Response Panel includes OSM, OSRM, IL-6, and TNF and can be used to evaluate the signatures of many different autoimmune-implicated genes to potentially unravel the therapeutic mechanism of action by elucidating a drug's effects on multiple autoimmune pathways.

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Rev 2: 21-OCT-2020