

THE PROSPECTIVE USE OF CYTOKINE MARKERS FOR THE EVALUATION OF INFLAMMATORY BOWEL DISEASE SEVERITY



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ABSTRACT

Inflammatory Bowel Disease (IBD) is a group of chronic inflammatory diseases separated into two major subtypes: ulcerative colitis (UC), characterized by continuous inflammation of the colon and rectum, and Crohn's disease (CD), characterized by patchy inflammation of the small intestine and colon. Currently, there are no proposed blood biomarkers for the diagnosis of IBD. Endoscopy remains the gold standard for IBD diagnosis, but it is a resource-intensive and invasive procedure. Fecal calprotectin is a widely used biomarker that assesses IBD disease severity, but the marker has its own limitations because of its high same-day variability. Moreover, fecal lactoferrin, fecal microbiota, antineutrophilic cytoplasmic antibody, and anti-*Saccharomyces cerevisiae* antibody are proposed novel biomarkers, but they are underdeveloped and lack absolute specificity and sensitivity. IBD is marked by a state of enteric dysbiosis and elevated intestinal mucosa permeability. When exposed to the gut immune system, commensal bacteria induce the release of pro-inflammatory cytokines. UC and CD are predominantly characterized as having T-helper 2 and T-helper 1/T-helper 17 related cytokines, respectively. Dysregulated cytokine networks can disrupt immune tolerance and drive pro-inflammatory effector T-cell generation. The purpose of this study was to determine the use of cytokines markers in IBD diagnosis and disease severity. Relevant studies were compiled for analysis using online databases such as PubMed, and other available resources including discussions with the faculty whose expertise is in IBD diagnosis and management. The outcomes of this study show that cytokine markers can be used as indices for enteric perturbation or disease progression. In addition, cytokine markers may be useful in the future as an adjunct diagnostic tool for the differentiation of IBD subtypes. Interleukin-17 and interleukin-23, for example, are prospective cytokine serum biomarkers that have the potential to be used in the evaluation of IBD severity.

INTRODUCTION

- Inflammatory Bowel Disease (IBD) is a group of autoimmune, chronic inflammatory diseases of the gastrointestinal tract separated into two major subtypes based on the type and location of inflammation: ulcerative colitis (UC) and Crohn's disease (CD).
- Currently, the pathogenesis of IBD is unknown, but almost all cases of IBD are marked by increased permeability of the gut epithelial barrier, microbial dysbiosis, and hyper belligerent T-cell response.
- Interleukin-17 and Interleukin-23 (IL-17 and IL-23) are blood cytokine markers that are upregulated in both CD and UC.
- The purpose of this study was to identify the unique cytokine signatures of each IBD subtype and assess the effectiveness of various blood cytokine markers in IBD severity grading.

RESULTS

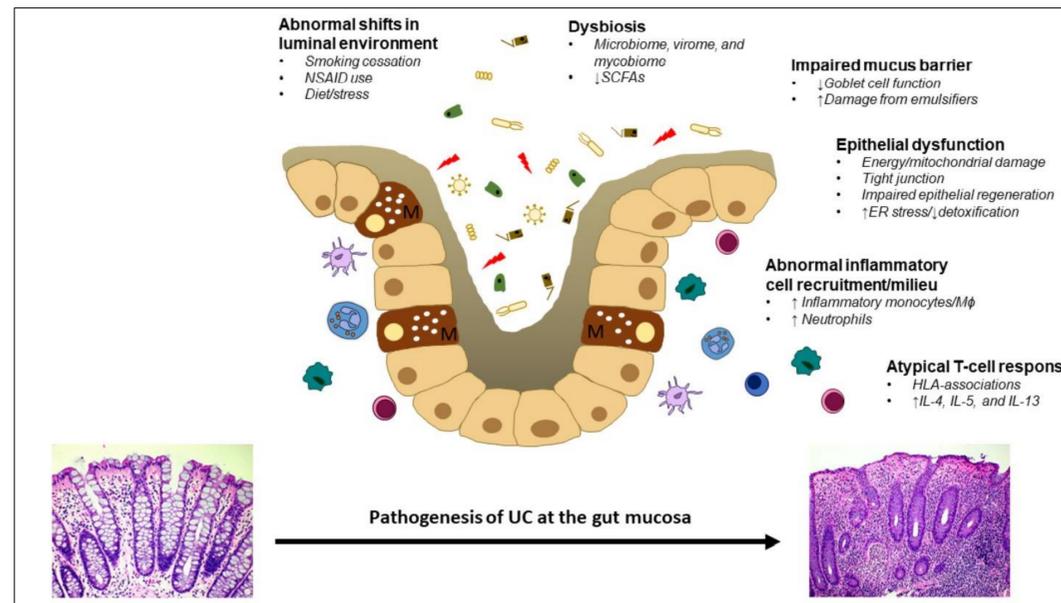


Figure 1: Schematic of the factors responsible for the manifestation of UC which includes epithelial dysfunction, microbial dysbiosis, and an atypical T-cell response. (Porter et al., 2020).

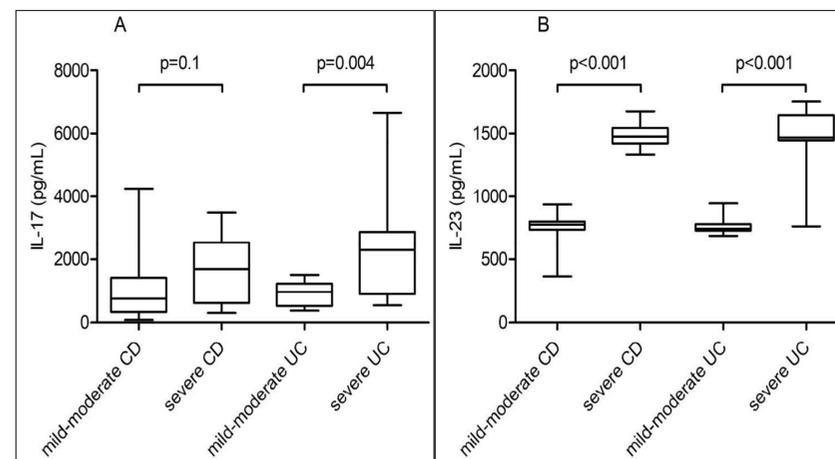


Figure 2: Box and whisker plot that represents the concentrations of IL-17 and IL-23 in varying severities of UC and CD. (Lucaci et al., 2021)

- IL-23 differentiates CD4+ naive T-cells and maintains T-helper 17 cell activity. IL-17 producing cells are gathered in the submucosa and muscularis propria of CD patients. (Figure 3)
- Depleted *Clostridium spp.* and *Bacteroides spp.* inhibit antigenic signals that trigger T-regulatory cell expansion, a subset of T-cells that have anti-inflammatory activity. Furthermore, segmented filamentous bacteria that are abundant in dysbiosis patients, induce pro-inflammatory T-helper 17 cell activity.

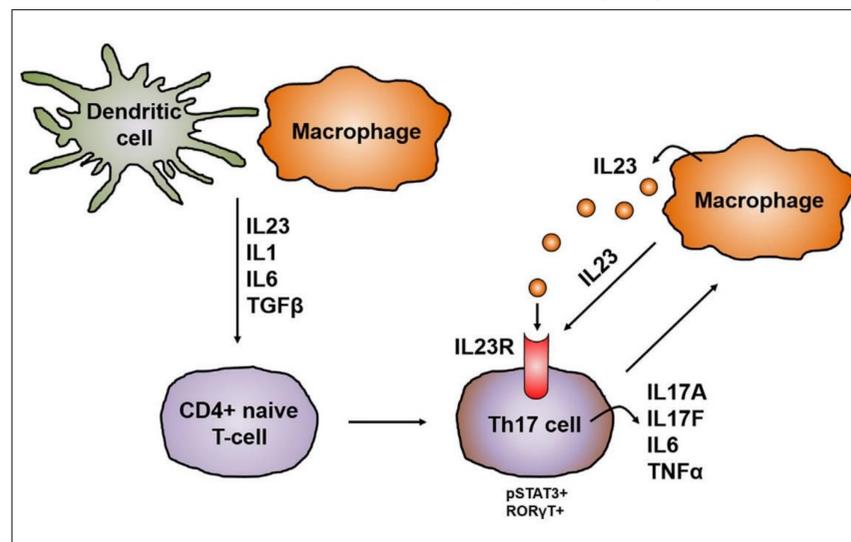


Figure 3: Macrophages and dendritic cells promoting the differentiation of Th17 through IL-23, IL-1, and TGF-β and maintenance of Th17 through IL-23 (Schmitt, et al., 2021)

- Reduction of energy-providing short chain fatty acid producers, depleted goblet cell function, and dysfunctional tight junctions act to increase commensal bacterial antigens to interact with gut immune system. (Figure 1)

- IL-17 and IL-23 serum concentrations can potentially grade disease severity of IBD subtypes. IL-23 is significantly elevated in severe CD and UC while IL-17 is only significantly elevated in severe UC.
- In severe CD, IL-23 had a 100% sensitivity and 100% specificity, respectively, and IL-17 had a 53.33% sensitivity and 87.50% specificity, respectively. In the severe UC cohort, IL-23 had a 94.12% sensitivity and 100% specificity, respectively. IL-17 had 94.17% sensitivity and 100% specificity, respectively. (Figure 2)

METHODS

- This project reviewed and compiled recent findings on hypotheses on the pathogenesis of IBD, IBD subtype-specific cytokine signatures and T-cell ratios. Research and literature were found through online databases such as Google Scholar and PubMed and discussion with the faculty advisor.

DISCUSSION

- The definitive factors associated with the development of IBD remains unclear, but identifying these factors may contribute to new avenues of treatment or preventative measures.
- Further exploration on the influence of specific cytokine markers in each IBD subtype is warranted. Moreover, the dynamic progression and balance of cytokine and chemokine levels throughout the IBD course need further investigation.
- Further investigation is warranted because data remains scarce on the unique blood cytokine signatures of CD, UC, and other minor IBD subtypes.

CONCLUSION

- IBD pathogenesis is triggered by the damage of the intestinal epithelial barrier and subsequent exposure of commensal bacteria antigens which trigger an overreactive inflammatory immune response.
- IL-17 and IL-23 are examples of potent blood cytokine biomarkers in identifying the severity of UC and CD. IL-23, for example, is superior in discriminating CD severity in comparison to the currently used fecal calprotectin marker.
- IL-23 plays a proliferative role in the pathogenesis of CD by inducing the proliferation of T-helper 17 cells and secretion of the pro-inflammatory IL-17 family.

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