
The Role of Cytokines in Irritable Bowel Syndrome: Review Article

Ahmed Hussein Zwamel¹, Mohammed Abdulrazzaq Assi², Shahlaa Kh. Chabuk³, Irfan Abdulzahra Al-Khazaali⁴, Maha Chasib Munshid⁵, Ali A. Al-fahham^{6*}

¹ Department Medical laboratory Technology, College of Medical Technology, The Islamic University, Najaf, Iraq.

² Department of Anesthesia Techniques, College of Health and Medical Techniques/ Baghdad, Middle Technical University, Iraq.

³ Physiology department, Hammurabi medical college, Babylon university, Iraq.

⁴ Department of adult nursing, college of nursing, University of Al-Qadisiyah,

⁵ College of Nursing, National University for Science and Technology, Thi-Qar, Iraq.

^{6*} Faculty of nursing, University of Kufa, Iraq.

ABSTRACT: (IBS) or Irritable bowel syndrome is a complicated health condition with different causative factors, including inflammation and infection, that have recently acquired as significant triggers of IBS. Inflammatory response might serve as a critical pathway in the progression of IBS, beside inequality in cytokines within the plasma and/or intestinal mucosal lining. Many biomarkers have been associated to possible mechanisms underlying IBS and are used to make differentiation between IBS and non-IBS subjects. Incorporation of these biomarkers into routine clinical work is important for fast and accurate diagnosis and effective treatment. Because IBS patients often experience ambiguous and overlapping symptoms, the creation of precise biomarkers for IBS could significantly enhance both diagnosis and patient care. This review examines the cytokines used in the diagnosis and treatment of IBS, Classifying these cytokines as either pro-inflammatory or anti-inflammatory and understanding their involvement in the development of irritable bowel syndrome.

INTRODUCTION

Signs of the physiological gastrointestinal (GI) illness known as irritable bowel syndrome (IBS) include abdominal pain or distress, anorexia, constipation, and diarrhoea. Irritable bowel syndrome (IBS) is observed to occur at a higher frequency among women, accounting for approximately 11% of worldwide cases (Kumar et al., 2022). Irritable bowel syndrome can result from both hereditary and acquired causes, particularly psychological distress, to a considerable extent, contributes to the onset of IBS. The changes in cytokines within the body's systems, both systemic and within the mucosa, along with variations in cytokine genes, appear to be critical in the progression of irritable bowel syndrome. The disorder's pathophysiology is thought to involve various factors including gut inflammation, changes in visceral sensitivity, food sensitivities, genetic predisposition, disturbances in the communication between the brain and the stomach, and changes to the microbiota of the gut. This review focuses on treatment strategies for IBS centered around anti-inflammatory cytokines. (Surdea_ Blaga et al., 2012). Examining the function of cytokines in the development and management of irritable bowel syndrome is the objective of this article review.

PATHOGENESIS

According to research, irritable bowel syndrome (IBS) is a frequent disorder that serves a variety of functions; it is distinguished by painful or spastic stomach cramps and/or irregular stool movements. Basically, IBS has been diagnosed as a condition that involves altered GI movement., internal hypersensitivity, disorder of nerve axis from brain to gut resulting in changed bowel motility, imbalances of neurotransmitters and psychosocial distress are among the most critical pathophysiological factors (Mitselou et al., 2020). Inflammation is highly probable to play a significant influence in the onset and advancement of irritable bowel syndrome (IBS). Inflammation of the gut mucosa leads to an increase in the number of immunocompetent cells, such as T-cell lymphocytes, mast cells, and neutrophilic cells. This provides more evidence that immunological factors contribute to the pathophysiology of the intestinal mucosa. The most common symptom of irritable bowel syndrome (IBS) is an increase in mast cells in the gastrointestinal tracts, although earlier research has revealed that people with IBS are more likely to have a higher prevalence of several common inflammation indicators' (Piche et al., 2009).

Mast cells have various functions in the body, including promoting wound healing, defending against infections, and triggering hypersensitive reactions in the gastrointestinal mucosa. When activated, they release inflammatory and immune substances, drawing

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more inflammatory cells to the gastrointestinal lining. Numerous studies have associated elevated mast cell levels in IBS patients with particular symptoms like bloating and abdominal discomfort (Cremon et al., 2009). Activated T lymphocytes in mucosal biopsy samples from individuals with irritable bowel syndrome (IBS) have the function of eliminating infected host cells, as well as stimulating the activation of T lymphocytes and macrophages. Individuals who are afflicted with irritable bowel syndrome (IBS) and have peripheral blood mononuclear cells and a heightened concentration of pro-inflammatory cytokines may also have an increased propensity for an overactive immune system. Evidence for inflammatory and proinflammatory cytokine involvement in irritable bowel syndrome (IBS) is discussed in the following sections (Martínez et al., 2012).

CYTOKINES

Cytokines can be categorised into two groups according to their function in the inflammatory response: pro-inflammatory cytokines (e.g., IL-6 and IFN- γ) and anti-inflammatory cytokines (e.g., IL-10). Pro-inflammatory cytokines trigger the activation of helper T-cell cells and their subsequent differentiation into various subtypes. Th2 or Th1 cells are generated (Bashier Eltayeb et al., 2020). Secreted by immune cells, cytokines play a crucial role in the immune system's signalling pathways. They establish a connection between cytotoxic T lymphocytes (Tc cells) and T helper cells (TH1 & TH2). They also serve as significant regulators of intestinal inflammation. Certain cytokines, like anti-inflammatory IL-10, reduce the risk of IBS, while others, such as pro-inflammatory cytokines like IL-1, IL-6, IL-8, IL-12, IL-18, and TNF- α , are associated with IBS development as they consistently promote inflammatory responses (Lazaridis et al., 2018).

When considering inflammatory bowel syndrome, the significance of cytokines cannot be overlooked. Scientific evidence has definitively shown that an inequilibrium between pro-inflammatory and anti-inflammatory cytokines is a pivotal factor in the formation of irritable bowel syndrome (IBS). This phenomenon has been extensively described in several articles worldwide (Kumar et al., 2017). A number of cytokines, including those that promote inflammation and those that inhibit it, have important roles in controlling immune responses and may contribute to inflammation in the intestines. Genetic factors govern cytokine production, and an imbalance in their secretion levels can lead to susceptibility to disease and associated clinical symptoms. The complicated interactions among these drugs and the delicate balance between pro- and anti-inflammatory responses have been the subject of several studies. Multiple studies provide evidence indicating persistent inflammation in individuals with irritable bowel syndrome (IBS). Studies have indicated that individuals with inflammatory bowel syndrome (IBS) commonly exhibit either heightened levels of pro-inflammatory cytokines or reduced levels of anti-inflammatory cytokines. This observation implies that individuals with irritable bowel syndrome (IBS) have an anti-inflammatory cytokine abundance that is disproportionately low (Lazaridis et al., 2018).

The intricate interplay among the systems responsible for maintaining homeostasis involves the interconnectedness of the nervous, immune, and endocrine systems, with the brain serving as a central regulator orchestrating both humoral and neurological processes within a complex network of multidirectional communication pathways. The immune response in the gastrointestinal tract is tightly regulated, and the balance between pro-inflammatory and anti-inflammatory cytokines or mediators is a crucial determinant of the gut's immunological state (Bashashati et al., 2017).

PRO-INFLAMMATORY CYTOKINES ASSOCIATED WITH IBS

Interleukin-producing interleukins (IL-6), TNF-, and IL-8 are the principal pro-inflammatory cytokines that may impede IBS. Elevated levels of IL-6, IL-8, and IL-12 have been documented in certain studies (Lazaridis et al., 2018).

A diverse range of immune cells produce IL-6, which makes it a versatile cytokine. These cells include endothelial cells, macrophages, adipocytes, and fibroblasts. It may play an important part in the host's defence systems by regulating immunological responses, hematopoiesis, and acute-phase reactions. In contrast, monocytes contribute to the production of TNF- α , a multifunctional pro-inflammatory cytokine, but macrophages are the main source. Because of its effects on neutrophil activation and vascular endothelial cell characteristics, it plays a major role in chronic inflammation. The reason TNF- α is commonly called the "Master-regulator" cytokine is because of its regulatory role on other cytokines. The chemical IL-8, often referred to as "Chemokines CXCL8," is secreted by a diverse range of cells, including the smooth muscle cells that make up the epithelium and endothelium of the airways. In patients with irritable bowel syndrome (IBS), increased levels of IL-8 trigger and intensify both acute-phase and chronic-phase inflammatory responses. Therefore, increased IL-8 levels could potentially serve as a marker of inflammation in IBS (Patel et al., 2017).

Among individuals suffering from active inflammatory bowel disease (IBD), both serum and tissue exhibit notably elevated levels of IL-6 expression, which has been linked to disease severity and serves as a predictor of disease activity. T-cells accumulate due to their resistance to apoptosis, leading to persistent inflammation. Using antibodies that target the IL-6 receptor can slow down this process. Disruption of both the innate and adaptive immune responses may contribute to the advancement of chronic diseases, according to multiple studies that highlight the importance of IL-6 in both processes (Mitselou et al., 2020).

The inflammatory effects of TNF- α in IBS have been extensively studied. According to previous studies, individuals with irritable bowel syndrome (IBS) had greater serum levels of TNF- α and IL-6 than healthy controls, which may indicate that they continue to experience low-grade inflammation. Further evidence of immunological dysregulation was provided by higher levels of

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IL-6, IL-8, and TNF- α in a subgroup of female patients with irritable bowel syndrome (IBS) who also had extraintestinal comorbidities. In keeping with this research, another found that irritable bowel syndrome individuals had elevated cytokine levels, which may indicate immunological dysfunction. The pro-inflammatory cytokines TNF- α and IL-6 can both control the release of corticotrophin-releasing hormone. There is no text provided. This hormone plays a crucial role as a peptide in regulating the hypothalamic-pituitary-adrenal (HPA) axis. Consequently, the elevated levels of these cytokines observed in individuals with irritable bowel syndrome (IBS) may lead to an excessively active hypothalamic-pituitary-adrenal (HPA) system. This may be due to the association between inflammatory bowel syndrome and an elevated production of pro-inflammatory cytokines and an intensified cellular immunological reaction (Vara et al., 2018).

Current study indicates that persons with irritable bowel syndrome (IBS) have lower levels of the anti-inflammatory cytokine IL-10 and greater levels of the pro-inflammatory cytokines IL-6 and IL-8. This being said, it is beyond dispute that IL-6 levels are not significantly different between those with and without IBS, which goes against the results of a plethora of previous research (Mitselou et al., 2020).

It is postulated that the proinflammatory cytokine IL-1 significantly influences the pathogenesis of inflammatory bowel disease (IBD) through its ability to stimulate immune responses and induce inflammation. Interleukin-1 (IL-1) is mostly produced by monocytes and macrophages and stimulates cellular responses in the intestines. These cells include fibroblasts, smooth muscle cells, neutrophils, and macrophages. The cells in question secrete prostaglandins, proteases, chemotactic cytokines, and additional inflammatory mediators in response to this stimulation (Galani et al., 2017). IL-1 β , in particular, was selected due to its pivotal role in inflammatory conditions like IBD. It's well-established that glucocorticoids released during stress effectively dampen IL-1 β activity. But how IL-1 β plays a role in irritable bowel syndrome is still up for debate, therefore more study is needed to determine its biomarker potential and relevance (Nakov et al., 2022).

ANTI-INFLAMMATORY CYTOKINES

In the gut, there is a delicate equilibrium between cytokines that promote inflammation and those that inhibit it. Nevertheless, disturbances such as changes in the typical bacteria in the gut, sudden infections in the gastrointestinal tract. The intestinal lining cells may have increased permeability, which could allow cytokines and chemokines to enter the body through sore spots. Proinflammatory cytokines, including TNF- α , interferon- γ , and IL-12, together with anti-inflammatory cytokines such as IL-10 and transforming growth factor- β , have a vital function in causing inflammation in the intestines. Therefore, a possible therapy strategy for controlling mild inflammation in individuals with irritable bowel syndrome (IBS) may consist of delivering anti-inflammatory cytokines such as IL-10 directly to the affected area (Kumar et al., 2017).

IL-10 is released by dendritic cells, various cancer cells, immunological cells such as T and B cells, monocytes, macrophages, and mast cells, as well as different types of tumour cells. Macrophages are acknowledged as substantial *in vivo* producers of IL-10. IL-10 engages in interactions with IL-10 receptor (IL-10R), a protein that is linked to the cell membrane and can be found on many different types of cells, including immune cells. When IL-10 is present in the body, it stops the production of cytokines that cause inflammation. The mentioned substances are interferon- γ , IL-2, IL-3, and TNF- α . Macrophages, natural killer cells, Th1 cells, and B cells are responsible for producing the majority of these cytokines. It is important to note that a prior investigation found that persons diagnosed with both irritable bowel syndrome (IBS) and anxiety-depression had higher levels of IL-1 β and lower levels of IL-10 compared to the control group (Amani et al., 2018).

Kindt and colleagues found that elevated blood IL-10 levels were significantly associated with major depressive disorder, although they found no such association with anxiety. So, symptoms of Irritable Bowel Syndrome (IBS) may occur as a result of a relationship between mental health concerns such as depression and anxiety and an imbalance of pro- and anti-inflammatory cytokines (Kindt et al., 2009). A recent study discovered that individuals diagnosed with irritable bowel syndrome (IBS) experience heightened permeability in their intestines when peripheral blood mononuclear cells are activated by IL-10. This finding may indicate an altered immune response. The study discovered that patients diagnosed with IBS who had the most severe overall IBS symptom scores showed increased permeability in their gastrointestinal tract. In contrast, those with lower symptom scores showed normal intestinal permeability and lower levels of IL-10. Moreover, there was a direct association observed between IL-10 levels and the extent to which daily activities, work productivity, composite symptom scores, and stomach pain or discomfort were present. The absence of healthy controls was a significant limitation in this investigation. However, it was noted that there was no correlation between IL-10 levels and the intensity or frequency of discomfort in people with IBS-D. In addition, the study found that blood IL-10 levels were similar among patients with IBS. However, lower serum IL-10 levels were linked to more severe symptoms in these patients (Dothel et al., 2023).

Some studies have found a link between IL-17 and irritable bowel syndrome, and reported that providing patients with vitamin D can reduce the level of IL-17 (Amani et al., 2018). Another study found that IL-35 and IL-17 may play a major role as anti-inflammatory cytokines in bowel inflammatory diseases (Hadi et al., 2022).

CONCLUSIONS

Research on the cause and development of irritable bowel syndrome has shown that pro-inflammatory cytokines play a significant role. Cytokine homeostasis impairment may be a contributing factor in the onset of irritable bowel syndrome. Furthermore, anti-inflammatory cytokines are believed to be most beneficial for IBS patients with low-grade inflammation.

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