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Review Article

Cytokines and irritable bowel syndrome: Where do we stand?

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ABSTRACT

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, which presents with one or more gastrointestinal symptoms without any structural or organic abnormality. The etiology and pathophysiological mechanisms of IBS remain uncertain. Residual or reactivated inflammation at the molecular level is considered the underlying mechanism of post-infectious IBS. On the other hand, genetic variations in the immunological components of the body, including cytokine gene polymorphisms, are proposed as a potential mechanism of IBS even in patients without previous gastrointestinal infection. Several studies have suggested imbalanced cytokine signaling as an etiology for IBS. In this review, recent findings on cytokine profiles and cytokine gene polymorphisms in patients with IBS are described and the role of cytokines in animal models of IBS is discussed.

1. Introduction

Functional gastrointestinal (GI) disorders may present with one or multiple gastrointestinal symptoms and are defined as having abdominal pain and/or altered bowel functions including diarrhea and constipation. Despite altered physiology and sensation, no structural or organic abnormality is detected with standard investigations [1,2]. Abnormal gut–brain interactions [3], changes in the normal microbiota of the GI tract [4], food allergies or poorly balanced diets [5,6], and dysfunction of the molecular regulation of mucosal inflammatory mediators [7,8] have all been proposed as etiologies in functional GI disorders.

Irritable bowel syndrome (IBS) is a highly prevalent functional GI disorder [9], which typically presents with abdominal pain and changes in GI motility, such as chronic diarrhea and/or constipation. Similar to other functional GI disorders, the mucosal histology of the GI tract is normal in IBS patients [10].

The pathophysiology of IBS is not well understood [8]. The theory of post-infectious IBS (PI-IBS) introduces a larger role for the primary and secondary immune system in the development of IBS symptoms. Post-inflammatory changes in the gut may produce chronic alteration of the immune system at the molecular level which may target the enteric nervous system and smooth muscle fibers, as well as the secretory function of the gut mucosa [11,12]. These chronic and histologically undetectable phenomena present as IBS following the infectious episode. Altered cytokine profiles in IBS patients have been shown in some studies [13,14]. Moreover, mutations in cytokine genes may make individuals more susceptible to infectious gastroenteritis, which could consequently cause PI-IBS, or lead to the development of primary IBS [15–17]. In spite of these findings, the complete mechanism of immunological changes observed in IBS is not yet known. Whether immunological alterations are restricted to acquired PI-IBS, or whether there are genetic susceptibilities for IBS development are the key questions to be answered.

This review explains: (a) the most recent findings on cytokine profiles, (b) cytokine gene polymorphisms in patients with IBS, and (c) current evidence regarding the role of cytokines in animal models of IBS/gut inflammation.

2. Classification of the cytokines

Cytokines are primarily synthesized by the immune cells. They regulate differentiation and activation of these cells, and are involved in their immunological functions [18].

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T-cells that produce cytokines are divided into T-helper (Th)-1, Th2, Th17, and T-regulatory (Treg) cells. Th1 cells produce interferon (IFN)-γ, interleukin (IL)-2, and IL-18, which act against intracellular microbes by promoting cellular defence and inflammatory responses. Th2 cells produce IL-4, IL-5, IL-6, and IL-13, which are involved in allergic disorders and protection against extracellular pathogens such as gastrointestinal nematodes by regulating the activation of B lymphocytes. Treg cells, which release IL-10 and TGF-β, are important in prevention of autoimmunity. On the other hand, Th17 cells, which produce IL-17, can induce autoimmunity. Moreover, many other cells including macrophages, dendritic cells, and likely epithelial cells produce cytokines [18].

Functionally, cytokines can be divided into pro-inflammatory (TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-8, IL-12, IL-17, and IL-18) and anti-inflammatory (IL-4, IL-10, TGF-β) cytokines. In inflammatory diseases such as Crohn's disease and rheumatoid arthritis, there is an imbalance between pro-inflammatory and anti-inflammatory cytokines [19,20]; however, there is no definitive evidence that the imbalance between pro- and anti-inflammatory cytokines can actually determine the severity and extent of even clear auto-immune diseases.

3. Cytokines in IBS: clinical data

3.1. Systemic cytokines in IBS

Systemic and mucosal cytokine profiles in human IBS were investigated in a number of studies (Table 1). Elsenbruch et al. [13], with the aim of investigating the neuroimmune axis in IBS, conducted a case-control study on 15 female IBS patients and 15 healthy women. In the fasting state and after ingestion of a standardized liquid meal, TNF-α and IL-6 concentrations from lipopolysaccharide (LPS)-stimulated whole blood cell culture were measured. According to this study, IBS patients had a lower baseline TNF-α level and a similar baseline IL-6 compared to the healthy controls. During postprandial evaluations, TNF-α was significantly decreased in the control group, but IL-6 was decreased in both groups. These results suggested that pro-inflammatory cytokine activity may be altered in IBS.

In a clinical trial by O'Mahony et al. [21], with the aim of assessing the effect of probiotics in IBS, a comparison for blood cytokine levels was performed between a group of around 70 IBS patients and 20 matched healthy controls. Regarding the predominant symptoms, 45%, 28%, and 26% were mixed (M-IBS), diarrhea predominant (D-IBS), and constipation predominant (C-IBS), respectively. According to this study, IL-10 secretion from peripheral blood mononuclear cells (PBMCs) of the patients with IBS was lower than the controls, whereas IL-12 level was higher in the patient group. The ratio of IL-10/IL-12 level was significantly lower in the IBS patients. These data indicated a pro-inflammatory Th-1 state in IBS. In this study, patients treated with *Bifidobacterium* had a greater reduction in symptom scores, abdominal pain/discomfort, and bloating/distension compared to the placebo group, and the treatment was accompanied by normalization of the IL-10/IL-12 ratio. Whether the observed differences are due to a dominant change in the cytokine parameters of an IBS-subgroup is not clear. This study suggested an obvious role for the cytokines in the pathophysiology and clinical presentations of IBS.

Dinan et al. [22] performed a case-control study on 76 patients with IBS (30 M-IBS, 36 D-IBS, and 10 C-IBS) and 75 healthy controls to investigate hypothalamic–pituitary–adrenal (HPA) axis and plasma cytokine profiles. Here it was shown that baseline IL-6, soluble interleukin-6 receptor (sIL-6R), and IL8, but not TNF-α, were higher in the IBS patients. Comparing IBS subgroups, IL-6 and sIL-6R levels were similar in M-IBS, D-IBS, and C-IBS. The IL-8 level was higher in C-IBS, compared to D-IBS and M-IBS. IL-10 level was normal in IBS patients. The plasma level of cortisol was higher in IBS patients, and following corticotropin-releasing hormone (CRH) infusion, an exaggerated release of both adrenocorticotropic hormone (ACTH) and cortisol was seen in IBS patients; however, dexamethasone suppression of cortisol was similar in patients and healthy controls. IL-6 level correlated with ACTH response and ACTH/cortisol response ratio. The higher cortisol level and exaggerated release of cortisol and ACTH could be considered as compensatory mechanisms for the control of pro-inflammatory conditions in IBS patients [23,24].

In a case-control study by Liebregts et al. [14], 55 patients with IBS (18 M-IBS, 20 D-IBS, and 17 C-IBS) and 36 healthy

Table 1
Cytokine levels in patients with irritable bowel syndrome.

References	Country	Number of patients/ controls	Sample	Cytokines in IBS vs. control	
				Pro-inflammatory cytokines	Anti-inflammatory cytokines
Elsenbruch [13]	Germany	15/15	Blood	TNF-α↓, IL-6→	N.A.
O'Mahony [21]	Ireland	~70/20	Blood	IL-12↑	IL-10↓
Dinan [22]	Ireland	76/75[a]	Blood	IL-6↑, IL-8↑, TNF-α→	IL-10→
Liebregts [14]	Australia	55/36	Blood	TNF-α↑, IL-1 β↑, IL-6↑	N.A.
Dinan [25]	Ireland	37/37	Blood	IL-6↑, IL-8↑	IL-10→
Kindt[b] [26]	Belgium	30/32	Blood	IFN-γ→, IL-5↑, IL-6→, IL-12↓, IL-13↑	IL-10[c]→↓
Öhman [27]	Sweden	74/30	Blood	IFN-γ→, IL-1β↑, IL-2→	IL-10→
Scully [28]	Ireland	121/54	Blood	IFN-γ→ , TNF-α[d]↑, IL-1β↑[d], IL-6↑, IL-8↑, IL-12→, IL-13→	IL-10→
Goral [29]	Turkey	72/50	Blood	TNF-α →, IL-1→, IL-6→, IL-8→, sIL-2R↑	N.A.
Hua [30]	Taiwan	35/25	Blood	TNF-α↑, IL-6↑	IL-10↓
McKernan [31]	Ireland	30/30	Blood	TNF-α→, IFN-γ→, IL-1b→, IL-2→, IL-4→, IL5→, IL-6↑, IL-8↑ , IL-12→, IL-13→	IL-10→
Del Valle-Pinero [32]	USA	12/12	Blood	TNF→ , IL-1α→, IL-1β→, IL-6→, IL-8 →, IL-9→, IL-18→, IL-22 →	IL-9→, IL-10→, IL-22 →
Gwee[e] [33]	Singapore	8/18	Rectal mucosa	IL-1β↑	N.A.
Macsharry [34]	Ireland	59/39	Rectosigmoid mucosa	TNF-α→, IL-1β↓, IL-6→, IL-8↓, IL-12→	TGF-β↓, IL-10↓

No difference, →; increased, ↑; decreased, ↓; N.A., not available.
[a] 49 patients and 48 controls had measured cytokine levels.
[b] In functional gastrointestinal disorders including irritable bowel syndrome.
[c] Basal vs. stimulated.
[d] Increased in patients with extra-intestinal co-morbidities.
[e] In post-infectious irritable bowel syndrome.