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ИММУНОПАТОГЕНЕЗ И СЕРОЛОГИЧЕСКИЕ МАРКЕРЫ ПРИ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЯХ КИШЕЧНИКА

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Воспалительные заболевания кишечника (ВЗК), к которым относятся болезнь Крона (БК) и язвенный колит (ЯК), представляют значительные диагностические и терапевтические сложности. Патогенез ВЗК включает в себя наличие таких патогенных факторов, как аномальная микрофлора кишечника, нарушение регуляции иммунного ответа, изменения окружающей среды и вариабельность определенных генов. Несмотря на усилия исследователей в выявлении новых этиологических факторов, которые связаны с факторами окружающей среды, генетическими, микробиологическими и иммунными реакциями, полное понимание патогенеза ВЗК остается неясным. Цитокины играют решающую роль в патогенезе ВЗК, поскольку они контролируют множество аспектов воспалительной реакции. Роль цитокинов, вырабатываемых клетками врожденного и адаптивного иммунитета, а также их значение для будущей терапии ВЗК очень важны. Благодаря всестороннему анализу литературы подчеркиваются важность антител против Saccharomyces cerevisiae (ASCA) и перинуклеарные антинейтрофильные цитоплазматические антитела (pANCA) для различения БК и ЯК, прогнозирования течения заболевания и принятия решений о лечении. Несмотря на достигнутый прогресс, потребность в маркерах с повышенной специфичностью и чувствительностью очевидна. В статье рассматривается иммунопатогенез и роль серологических маркеров в лечении ВЗК, обсуждаются текущие проблемы

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и намечаются направления будущих исследований. Обзор завершается акцентом на роли микробиоты и цитокинов в патогенезе ВЗК, потенциале новых биомаркеров, персонализированной медицине и интеграции передовых технологий для усовершенствования методов лечения ВЗК.

***Ключевые слова*:** воспалительные заболевания кишечника (ВЗК), болезнь Крона (БК); язвенный колит (ЯК); иммунопатогенез; микробиота; цитокины; антитела против *Saccharomyces cerevisiae*; перинуклеарные антинейтрофильные цитоплазматические антитела; биомаркеры.

IMMUNOPATHOGENESIS AND SEROLOGICAL MARKERS ININFLAMMATORY BOWEL DISEASES

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Inflammatory Bowel Diseases (IBDs), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), presents significant diagnostic and therapeutic challenges. The pathogenesis of IBDs, including CD and UC, involves the presence of pathogenic factors such as abnormal gut microbiota, immune response dysregulation, environmental changes, and gene variants. Although many investigations have tried to identify novel pathogenic factors associated with IBDs that are related to environmental, genetic, microbial, and immune response factors, a full understanding of IBDs pathogenesis is unclear. Cytokines have a crucial role in the pathogenesis of IBDs, where they control multiple aspects of the inflammatory response. The role of cytokines produced by innate and adaptive immune cells, as well as their relevance to the future therapy of IBDs are very important. Through a comprehensive analysis of the literature, we highlight the importance of antibodies such as Anti-Saccharomyces cerevisiae Antibodies (ASCA) and Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (pANCA) in distinguishing between CD and UC, predicting disease behavior, and guiding treatment decisions. Despite the progress, the need for markers with improved specificity and sensitivity is evident. This review explores immunopathogenesis and the role of serological markers in IBDs management, discusses current challenges, and anticipates future research directions. The review concludes with an optimistic outlook on the role of microbiota and cytokine in pathogenesis of IBDs, potential of novel biomarkers, personalized medicine, and the integration of advanced technologies to transform IBDs management.

Keywords: Inflammatory Bowel Diseases (IBDs); Crohn's Disease (CD); Ulcerative Colitis (UC); Immunopathogenesis; Microbiota; Cytokines; Anti-Saccharomyces cerevisiae Antibodies; Perinuclear Anti-Neutrophil Cytoplasmic Antibodies; Biomarkers.

Introduction

The inflammatory bowel diseases (IBDs), represented mainly by ulcerative colitis (UC) and Crohn's disease (CD) but also including noninfectious inflammations of the bowel. IBD is thought to be the result of a disorder in the immune system of genetically susceptible individuals. IBD has become a global disease, with the highest prevalence in Westernized countries and the fastest growing incidence in newly industrialized countries [1].

In recent years, the focus of IBDs research has shifted towards. An ideal biomarker should be non-invasive, sensitive, disease specific, easy to perform, and cost-effective [2]. To date, there is no ideal biomarker that possesses all of the above qualities to accurately diagnose IBDs, differentiate between IBDs subtypes, or monitor disease activity. IBDs biomarkers have been found in colon tissue, blood, stool, urine and breath. Blood-based biomarkers are non-invasive, can be easily obtained, are not susceptible to contamination, and are the most widely used. Serological markers are mainly related to antimicrobial antibodies, antinuclear antibodies, and anticarbohydrate antibodies [3; 4].

Despite the increasing number of treatment options for IBDs in recent years, the quality of life of patients declines due to nonresponse to or loss of response to existing therapies. Thus, the understanding of the disease etiology and the exploration of its pathogenesis can provide new insights into the treatment strategies for IBDs. A large amount of evidence shows that IBDs are the result of the interaction of genetic/epigenetic, environmental, immune and microbial aspects (Fig. 1). Large-scale genetic study provides important insights into the pathogenesis of IBDs and highlights shared and unique genetic risk factors for CD and UC [5]. The common phenotypes of UC and CD include chronic inflammation and immunoinflammatory dysregulation. Therefore, most of the current studies on the pathogenesis of IBDs focus on the immune system, which may involve genetic factors, changes in the gut microbiome, and immune response cells, including cytokines and immune cells.

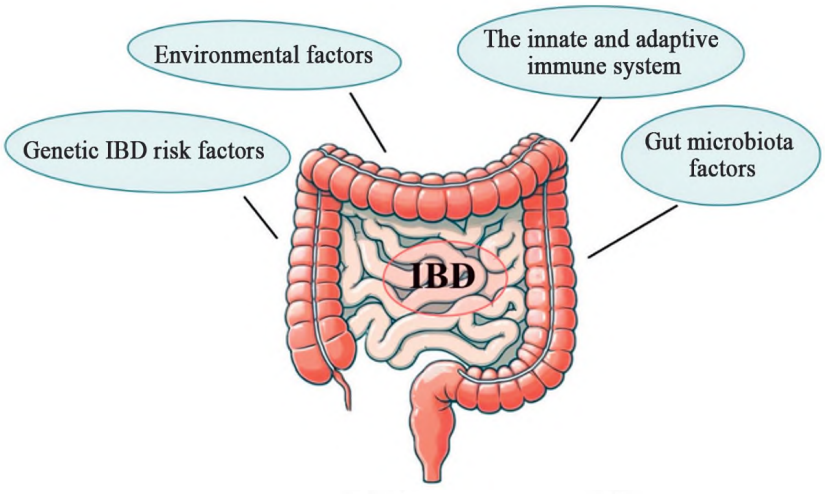

Fig. 1. Pathogenesis of inflammatory bowel disease

Here, we aim to review the immunological pathogenesis, diagnostic and serological markers of IBDs, with a view to providing new ideas for the diagnosis and treatment of IBDs.

Background of Inflammatory Bowel Disease. IBDs is a group of intestinal disorders of unknown etiology characterized by inflammation and caused by complex interactions between genetics, environmental factors, and immune responses. Current paradigms for classifying patients with Crohn's disease and ulcerative colitis classify them as having mild, moderate, or severe active disease [6]. These classifications are most typically based on a moment in time, with attributes describing recent disease symptoms and objective findings. This is very helpful for tracking a patient's disease course and clinical trials. However, it does not tell us about the severity of the disease or the patient's prognosis. Current assessments of disease activity would be more instructive if past disease complications and surgeries were included, as they are undoubtedly powerful reflections of disease burden and may influence future outcomes. A scoring system has been developed to assess the overall severity of disease [7].

Since 2011, the concept of precision medicine has become increasingly popular and attracted much attention. Xin-Yu Liu discusses strategies for classifying IBDs patients and biomarkers for identifying these subgroups at World J Gastroenterol 2023 January. Suggested application of multi-omics and artificial intelligence approaches can facilitate precise management of IBDs patients [8]. In the study of Xin-Yu Liu, it was shown that ASCA biomarkers and pANCA biomarkers in serum samples may be specific for the diagnosis of CD and UC (Table 1).

Table 1

Biomarkers of inflammatory bowel diseases

Sample	Biomarker	Outcome	Characteristic
Serum	ASCA	More aggressive fibro stenosing and internal penetrating disease behaviors	CD specificity
	pANCA	UC disease activity	UC specificity
	G-CSF, IL-1Ra	Endoscopically active disease	–
	Vitamin D	Vitamin	–
Feces	FC	Monitor disease activity and mucosal healing; early prediction of relapse risk	Higher sensitivity than CRP; confounding of non-IBD gut inflammation

Note. ASCA: Anti-Saccharomyces cerevisiae antibody; CD: Crohn's disease; CRP: C-reactive protein; FC: Fecal calprotectin; G-CSF: Granulocyte colony-stimulating factor; IL-1Ra: Interleukin 1 receptor antagonist; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

Pathogenesis of IBDs. IBDs is the result of a complex series of interactions between susceptibility genes, the environment, and the immune system. Multiple components of the mucosal immune system are involved in the pathogenesis of IBDs, including intestinal epithelial cells, innate lymphoid cells, cells of the innate immune system (macrophages/monocytes, neutrophils, and dendritic cells), and the acquired immune system (T cells and B cells), as well as their secretory mediators (cytokines and chemokines).

Genetic IBDs risk factors. Over the past few years, genome-wide searches for IBDs susceptibility loci have been very successful in identifying genes that contribute to disease susceptibility. In an initial screening effort, two groups used positional cloning and candidate gene approaches to identify NOD2 (also designated CARD15 and IBD1) as a CD susceptibility gene. Since then, several more susceptibility genes have been linked to inflammatory bowel disease and confirmed by replication: IBD5, IL23R, and ATG16L1. The identified genetic variants associated with CD risk demonstrate the importance of innate immunity, autophagy, and phagocytosis in the pathogenesis of CD. In particular, some genes associated with CD (IL23R, PTPN2) are also associated with other autoimmune diseases, suggesting that a subset of CD patients share common triggers with these diseases. Additionally, multiple disease-associated intergenic segments have been identified and replicated in genome-wide association studies [9]. These intergenic regions hint at novel genes and pathways - possibly including genes expressed within these regions and others that are remotely regulated to alter disease phenotypes. Further understanding of regulatory elements and gene-gene interactions within non-coding genomic regions will lead to a better understanding of the underlying mechanisms leading to disease. Genome-wide association studies (GWASs) have identified approximately 240 genetic loci associated with IBDs susceptibility [10]. Some studies use genetic profiling of blood samples to identify gene panels that may help differentiate IBDs from healthy controls [11], active from inactive CD [12], and CD from UC [13]. A different gene panel was also found in peripheral blood samples from pediatric IBDs patients in clinical remission compared with healthy controls. Other studies performed gene expression analysis on mucosal biopsies from IBDs patients, and identified distinct gene panels for IBDs versus healthy controls [14] and UC versus healthy controls. The use of genetics to identify loci associated with IBDs can potentially define causal disease mechanisms, which could, in turn, advance the biomarker discovery process.

Gut microbiota and IBDs. Bacteria associated with IBDs include *Escherichia coli*, bacillus fragile, ruminococcus, prevotella and rosetta. *E. coli* is a Gram-negative facultative anaerobic bacterium that is a normal inhabitant of the human gut. The bacteria found to be associated with IBDs include *Escherichia coli, Bacteroides fragilis, Ruminococcus gnavus, Faecalibacterium prausnitzii*, and *Roseburia* (Fig. 2). The gut microbiota of patients with IBDs showed an increased number of adhesive invasive *Escherichia coli* (AIEC) [15]. It can adhere to and pass through the intestinal mucosa of patients with IBDs, induce inflammation, and increase the permeability of the intestinal epithelium. After AIEC is engulfed by macrophages, it can survive and replicate, leading to the secretion of tumor necrosis factor (TNF), which leads to inflammation [16]. *Bacteroides fragilis* is an opportunistic pathogen with proinflammatory properties and is closely related to the development of IBDs. It can express zinc-dependent metalloproteinase called *Bacillus fragilis* toxin (BFT) [17].

BFT can affect WNT, NF-κB, STAT3 and MAPK signaling pathways, leading to the production of pro-inflammatory mediators. And it can activate STAT3 transcription factor, increasing Th17 and T regulatory cells (Treg), promoting the increase of mucosal permeability [19]. BFT can also induce the production of reactive oxygen species (ROS) and DNA damage by inducing the expression of spermine oxidase in colon cells. *Ruminococcus gnavus* is also associated with IBD. A. B. Hall, et al. found that in patients with severe CD, the content of *R. navus* is very high. *R. navus* can produce glucorhamnanol, and then induce dendritic cells (DC) to secrete inflammatory cytokines, such as TNF-α [20; 21]. *Faecalibacterium prausnitzii* is one of the most important butyric acid-producing bacteria found in the gastrointestinal tract and has played an important role in the prognosis of IBDs patients [22]. *F. prausnitzii* mediates anti-inflammatory effects by inhibiting the NF-κB pathway in intestinal epithelial cells and producing butyrate, which maintains Th17/Treg cell balanceIn addition, *F. prausnitzii* also stimulates the production of anti-inflammatory cytokines (such as IL-10) and inhibits the production of inflammatory cytokines (such as IL-12 and interferon-γ), to affecting the balance of inflammatory response and immunosuppression [23]. *Candida albicans* is a disease-causing fungus, and studies have reported increased numbers of Candida in IBDs patients, with the same results in animal models. There is growing evidence that *Candida albicans* can enhance inflammation by increasing the production of IL-17 and IL-23, leading to an increase in IBDs [24; 25].

IBDs-related immune cell and cytokines/chemokines. Immune cells secrete products that are actively involved in the initiation and preservation of inflammation, leading to gut tissue damage. In IBDs patients, colonic lesions show excessive immune cell infiltration and tissue devastation. Many cytokines and chemokines are associated with IBDs development [26].

In experimental colitis and IBDs, IL-6 production by lamina propria macrophages and $CD4^+$T cells is increased. In particular, $CD14^+CD33^+CD68^+CD163^{lo}$ myeloid cells that express some macrophage-associated and DC-associated markers were found to produce high amounts of IL-6 and IL-23. IL-6 binds to soluble IL-6R (sIL-6R), and the complex activates intestinal target cells by binding to gp 130 surface molecules. Therefore, IL-6 can exert its pro-inflammatory function by activating multiple target cells, including APC and T cells. In addition, IL-6 may also play a role in homeostasis by stimulating the proliferation and expansion of intestinal epithelial cells (IEC).

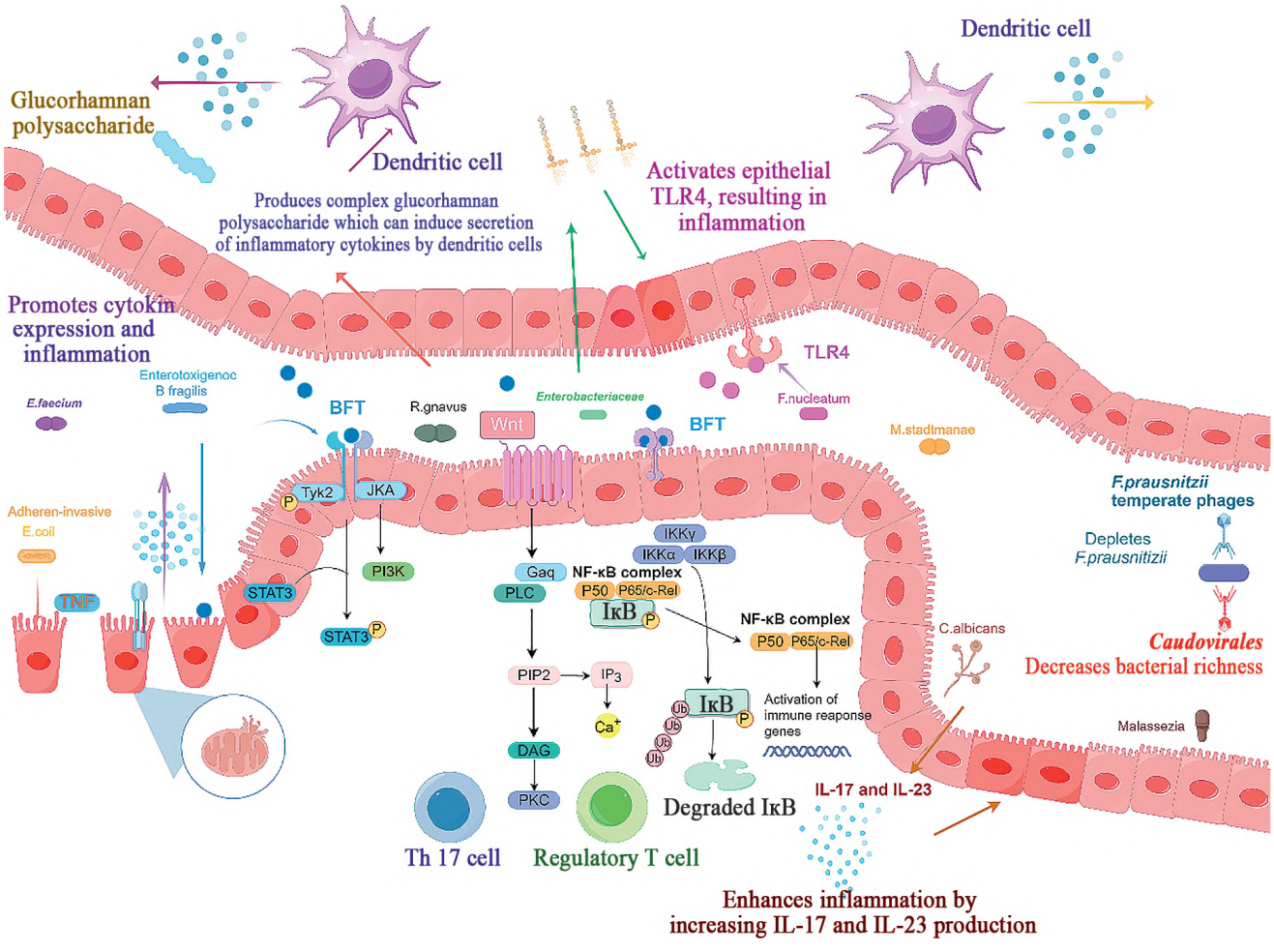

Fig. 2. Microbes involved in inflammatory bowel disease and their molecular mechanisms

Note. Figure created with BioRender: *B. fragilis*, *Bacteroides fragilis*; *E. faecium*, *Enterococcus faecium*; *E. coli*, *Escherichia coli*; *F. nucleatum*, *Fusobacterium nucleatum*; *F. prausnitzii*, *Faecalibacterium prausnitzii*; *M. stadtmanae*, *Methanosphaera stadtmanae*; *R. gnavus*, *Ruminococcus gnavus*; TLR4, Toll-like receptor 4; BFT, *B. fragilis* toxin; TNF, tumor necrosis factor; ETBF, enterotoxigenic *B. fragilis*; AhR, aryl hydrocarbon receptor; IL, interleukin; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C [18]

ILCs (intraepithelial lymphoid cells) are a recently discovered group of cells that control innate immunity at mucosal surfaces. These cells are now recognized as an important source of IFNγ and of IL-23-inducible pro-inflammatory cytokines, such as IL-17A and IL-17F, which mediate experimental innate immune-mediated colitis. In addition to IFNγ and IL-17, IL-22 is produced by mucosal ILCs via signaling events that involve the tyrosine-protein kinase LYN [27]. Moreover, IL-22 is produced by neutrophils, DCs, γδ T cells and effector αβ T cells in experimental colitis. IL-22 induces the production of antimicrobial peptides, such as defensins and regenerating islet-derived (REG) proteins, by IECs and thus influences the colitogenic potential of the microbiota and also affects intestinal barrier function. The functional relevance of IL-22 was shown by the finding that the administration of recombinant IL-22 protected mice from DSS-induced or trinitrobenzene sulphonic acid (TNBS)-induced colitis [28]. However, the pro-inflammatory effects of IL-22 were recently noted in innate immune-mediated colitis, which suggests that IL-22 may have multifaceted roles in mucosal inflammation.

T cells are implicated in the pathogenesis of IBDs because of the large number of T cells detected in the inflamed intestinal wall, the secretion of large amounts of T-cell-derived pro-inflammatory cytokines, and the need for T cells in various animal models of chronic intestinal inflammation. Interestingly, laminae propria T cells in IBDs respond poorly to T cell receptor stimulation and therefore rely heavily on costimulatory factors such as IL-6 and TNF signaling to prevent apoptosis. T_H1 cells are present in the intestinal lamina propria of patients with CD, and T-bet and STAT4 are key factors regulating T_H1 cell differentiation. STAT4 defects in T cells protect mice from experimentally induced colitis, while overexpression of STAT4 exacerbates colitis. In contrast to the lamina T cells in CD, lamina propria T cells from patients with ulcerative colitis produce the T_H2 cytokines IL-5 and IL-13 and express the T_H2-associated transcription factor GATA binding protein 3 (GATA3) [29]. Studies have shown that ulcerative colitis is associated with the presence of non-classical natural killer T (NKT) cells that have an atypical cytokine response and can secrete T_H2 cell-associated cytokines such as IL-13. IL-13 promotes

fibrosis and causes changes in IEC tight junction function and apoptosis, leading to mucosal ulceration. There are studies have shown that there is increased production of T_H17 cell-associated cytokines, such as IL-17A and IL-17F, by lamina propria T cells in both CD and UC [30]. Functionally, T_H17-type cytokines, such as IL-17 and IL-21, were found to mediate pro-inflammatory functions including the upregulation of TNF, IL-1β, IL-6 and IL-8, the recruitment of neutrophils and the secretion of matrix metalloproteinases by intestinal fibroblasts, which suggested that T_H17-type cytokines may induce tissue destruction in IBD. Consistent with this, the increased expression of the T_H17 cell-associated cytokine IL-26 has been noted in patients with Crohn's disease and this cytokine augmented pro-inflammatory cytokine production. T_H17 cells may also produce anti-inflammatory cytokines, such as IL-22, that control epithelial cell proliferation, wound healing and the production of antimicrobial proteins – such as defensins, mucins, and REG3β and REG3γ proteins by via STAT3 activation [31].

Studies using tissue from patients with IBDs and animal models of IBDs have identified cytokines as potential new targets for the therapy of intestinal inflammation. Relevant targets include pro-inflammatory cytokines, such as IL-6, IL-12, IL-23 and IL-21, as well as anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β [32] (Fig. 3).

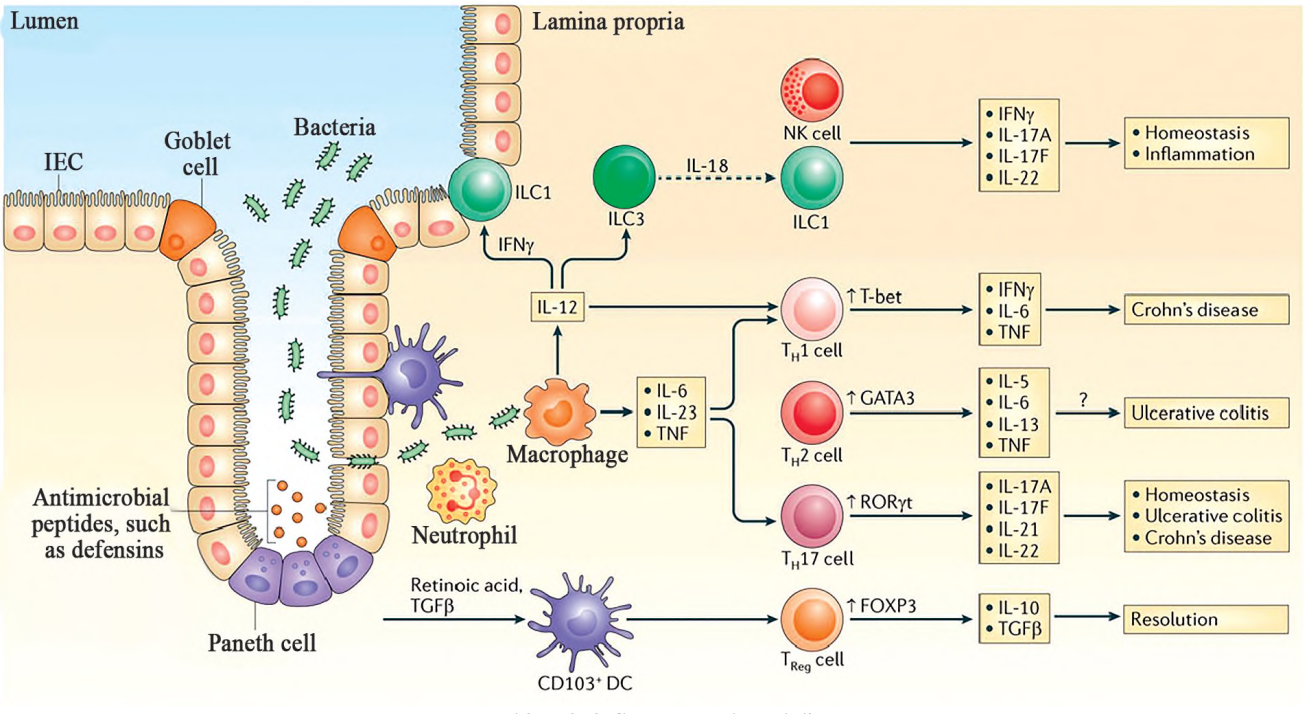

Fig. 3. Cytokines in inflammatory bowel disease [32]

The imbalance between pro-inflammatory and anti-inflammatory cytokines that occurs in IBDs impedes the resolution of inflammation and instead leads to disease perpetuation and tissue destruction.

Serological Profile of Antibodies in IBDs. In recent years, many studies have shown that fecal and serum biomarkers can be used in the diagnosis and treatment of inflammatory bowel disease. Doctors can treat patients with blood tests, radiology and endoscopy, and other tests. These diagnostic tests can be used to identify patients with IBD, determine prognosis, assess disease activity, and determine optimal treatment strategies.

A multitude of fecal markers can potentially be used to determine the likelihood that a patient has IBDs [33; 34]. In studies using a fecal calprotectin threshold concentration of 50 μg/g, the estimated sensitivity and specificity values for identifying IBD patients compared with non-IBDs patients were 89 and 81 %, respectively; in studies using a fecal calprotectin threshold concentration. In the 100 μg/g study, these values were 98 and 91 %, respectively. However, these estimates come from a combination of different studies rather than testing at different threshold levels in a single study. Lactoferrin is an iron-binding protein found in neutrophil granules and serum and secreted by the mucosa. It is resistant to degradation and proteolysis (although not as well as calprotectin), making it a useful marker of intestinal inflammation. Gisbert, et al. compiled data from multiple studies and 1001 patients. The lactoferrin test is estimated to have an average sensitivity of 80 % and specificity of 82 % in identifying patients with IBDs. Most but not all studies reported similar performance for calprotectin and lactoferrin tests [35].

Blood-based biomarkers may be superior to stool-based tests for several reasons. C-reactive protein (CRP) is one of several acute-phase proteins increased in the serum of patients with acute-phase IBDs. Studies dating back

decades found that nearly 100 % of patients with CD and approximately 50% of patients with UC have elevated CRP levels. The reason why patients with CD have higher rates of elevated CRP levels compared with UC is unclear. Furthermore, many patients with established CD do not have elevated CRP levels despite evidence of active disease, so these studies may have overestimated the sensitivity of this test in detecting CD [36].

Previous studies have found that the detection of several specific antibodies against well-defined antigens is a serologic signature of IBDs patients. Serological antibodies, including autoantibodies and microbial antibodies, arise as a result of excessive autoimmune responses, intestinal barrier damage, and loss of immune tolerance to bacterial antigens [37]. These antibodies have been shown to be useful biomarkers for the diagnosis and classification of IBDs. In recent years, some serological antibodies have been found to have clinical value in predicting disease activity or treatment response. These new findings will also be reviewed in this section.

Various serological tests have been used to try to improve the diagnosis of IBDs and differentiate between CD and UC, such as perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) tests. Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are antibodies that react with lysosomal enzymes in the cytoplasm of neutrophils and monocytes. Serum pANCA has been extensively studied and is considered to be UC specific and thus can differentiate between UC and CD. Although pANCA is currently relatively consistent in UC patients, p ANCA titers in UC patients vary with disease activity (Table 2) [38]. However, the sensitivity of p ANCA in the evaluation of patients with suspected UC is rather low [39]. pANCA was significantly increased in UC patients and CD patients with «UC-like» features. Nearly 25 % of CD patients with left-sided colitis have symptoms similar to UC and elevated pANCA levels through endoscopic or histopathological examination, which limits the application of pANCA in IBD subclassification. Neutrophil protease 3 (PR3) autoantibodies, one of ANCA, may be a useful serological marker to differentiate IBDs subgroups. The positive rate of PR3-ANCA in UC patients is 15–40 %, and the positive rate of PR3-ANCA in CD patients is 0–10 % [40].

Table 2

Serological markers in inflammatory bowel diseases

Biomarker		Association
Antibodies	pANCA	IBD subclassification (UC-specificity), lower response rate to IFX therapy
	ASCA	IBD subclassification (CD-specificity), early disease onset, fibrostenosing behavior, internal-penetrating disease behavior
	Anti-GP2	IBD subclassification (CD patients with ileum involvement)
	Anti-CUZD1	CD patients with structuring behavior
	Anti-CHI3L1	IBD subclassification (CD patients)
	Anti-GM-CSF	IBD subclassification (CD patients), aggressive disease, ileal involvement
	Anti-ACA	Diagnostic potential
CRP		Surveillance of disease activity, indicator of active disease, predicting clinical response
LL-37		Surveillance of disease activity, stricture disease in CD patients
TFF3		Surveillance of disease activity
Cytokines	IL-1β, IL-6, IL-8, IL-9, IFN-γ, TNF, CCL2, IL-22	Prediction of the response to biologics therapy and mucosal healing
	IL-2, IL-6	Disease relapse

Note. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; ASCA, anti-Saccharomyces cerevisiae antibodies; anti-GP2, anti-glycoprotein 2 pancreatic antibodies; CUZD1, CUB and zona pellucida-like domains 1; anti-CHI3L1, anti-chitinase-3-like protein 1; anti-ACA, anti-cardiolipin; TFF3, trefoil factor 3; IL, interleukin; IFN-γ, interferon-γ; TNF, tumor necrosis factor

Serological markers in UC. Many serological markers have been tested for potential correlation with UC disease outcomes. These include perinuclear antineutrophil cytoplasmic antibodies (pANCA), which are considered to be associated with a moderate prognosis for frequent relapses and a more severe course. In contrast, interleukin (IL) 1β, IL6, IL15, and serum inflammatory marker c-reactive protein (CRP) have no correlation with prognosis. Subsequent studies challenged this assumption and showed that pANCA was not a reliable predictor of overall disease outcome[71], although high levels of pANCA seemed to indicate the development of chronic pouchitis after ileal pouch-anal anastomosis in postcolectomy patients. There are similar reports of elevated serum

anti-flagellin antibodies (anti-CBir1) [41]. Furthermore, serum granulocyte macrophage colony-stimulating factor autoantibody (GM-CSF Ab) may be a promising candidate for early identification of CD and UC patients at risk of disease recurrence [42]. Mucosal TNF-alpha expression combined with histological disease activity scores at the point of diagnosis have been reported to be predictive of a severe outcome in UC with a positive and negative predicate values of 0.89 and 0.87 respectively [43]. However, such parameters are very difficult to implement in routine clinical practice and results are still pending validation in larger, independent patient cohorts.

Serological markers in CD. Over the last decades, several attempts have been made to identify serological markers prognostic of more aggressive phenotypes. Among those one of the most promising have been antibodies against Saccharomyces cerevisiae antibody (ASCA) [44]. Since then, several studies have shown ASCA to be associated with a more complicated disease course (albeit definition of 'complicated' varies as outlined above). Anti-Saccharomyces cerevisiae antibodies (ASCA) are antibodies to the mannan protein of S. cerevisiae, which have high specificity but low sensitivity in identifying CD owing to a genetic susceptibility of CD patients. The expression of ASCA is relatively low in patients with isolated colonic CD [45]. Moreover, it should be noted that the expression of ASCA varies in different ethnic populations: the prevalence and titers of ASCA are significantly lower in Asian CD patients than Caucasian CD patients [46]. Another field entirely and by definition not a serological marker is the characterization of the microbiome in IBDs patients for disease prognosis. Whereas data is still rare compared to genomic, epigenomic, transcriptomic, proteomic, and metabolomic data, first results seem to be promising. In a recent study on 143 patients for example IBD phenotype and the risk of surgery could be predicted on the basis of 16S and 18S rRNA sequencing data [47].

Other functions of biomarkers. In patients with UC or CD, mucosal healing in response to medical therapy correlates with a less severe future course of disease. There is potential to use biomarkers to assess mucosal healing following medical therapy or surgery and to predict the likelihood of relapse.

Roseth, et. al. demonstrated that patients with CD or UC who had remission following medical therapy had large reductions in levels of fecal calprotectin, (to below 50 μg/g) [48]. Several additional studies have shown similar results in response to therapy. Sipponen et al. performed one study of patients treated with anti-tumor necrosis factor (TNF) agents and another study of patients treated with other therapies. Among 5 patients that had mucosal healing after treatment with reagents other than anti-TNF agents, 4 (80 %) also had normalized levels of fecal calprotectin and lactoferrin. Among 9 patients with no mucosal improvement after therapy, 8 (89 %) had increased levels of calprotectin and 6 (67 %) had increased levels of lactoferrin [49]. Eleven patients that responded to anti-TNF therapy (based on endoscopic appearance), had significant decreases in levels of fecal calprotectin and lactoferrin, whereas 3 non-responders did not have decreased levels of these markers [50]. Despite the consistency of these results, the studies were limited by small sample sizes and an inability to define an optimal cut point for predicting mucosal healing. However, within the range of cut points tested, there does not appear to be a difference between tests for calprotectin and lactoferrin in determining treatment response.

There are limited data regarding the use of biomarkers to assess CD recurrence following ileocolonic resection; and the results for fecal biomarkers demonstrated only modest sensitivity and specificity. A possible explanation for these observations is that the initial, asymptomatic recurrence of CD results in limited mucosal injury. This small amount of injury, particularly to the ileum, is not likely to increase biomarkers to levels that can be detected in fecal samples.

Existing and emerging serum markers have been studied extensively in IBDs, thus providing valuable information into the prediction of disease course. Different kinds of antibodies against microbial components, neutrophils, and exocrine pancreas such as anti-Saccharomyces cerevisiae (ASCA), anti-outer membrane protein C (anti-OmpC), anti-neutrophil cytoplasmic antibodies (ANCA) and anti-glycoprotein 2 (anti-GP2) have been found in the serum of IBD patients. They are more likely to be detected in IBD patients in comparison with healthy controls, suggesting a possibility of differentiating IBD and controls by them [51]. One of the major goals of treatment for CD is to prevent complications such as perforation and formation of abscesses, fistulas and strictures. Biomarkers might be used to identify patients who are at high risk for a complicated disease course. Approximately 50 % of the patients with CD would be expected to have a relatively uncomplicated course during a period of 10–20 years and might be candidates for less aggressive therapy, whereas the remaining 50 % would be candidates for more aggressive therapy. The challenge is to identify these populations before the complications have occurred and to find therapies that can effectively prevent these complications.

Biomarkers might also be developed to identify patients that are likely to experience disease recurrence after treatment. Several studies have shown that in patients with quiescent disease, increased concentrations of fecal calprotectin predict disease relapse within 12 months, particularly in patients with UC [52]. Early studies reported that increased concentrations of fecal calprotectin identified patients that underwent relapse within 12 months with approximately 90 % sensitivity and 82 % specificity [53]. Costa, et al. reported that increased levels of fecal

calprotectin had a positive-predictive value of 81 % and a negative-predictive value of 90 % for relapse of UC; in patients with CD, the positive predictive value was 87 % and the negative-predictive value was 43 %.

In addition to predicting disease relapse, biomarkers might be used to predict response to therapy. For example, ASCA, pANCA and other antibodies have also been tested for their association with responses to specific therapies. Taylor et al. demonstrated a lower response rate among patients with CD treated with infliximab who had positive results from a test for pANCA [54]. Most recently, in a study of children with either CD or UC, presence of a positive test for pANCA was again associated with a lower likelihood of responding to infliximab. Results of tests for anti-I2, but not ASCA, pANCA, or OmpC, were associated with response to fecal diversion (94% response among patients with anti-I2 antibodies vs. 18 % response among those without anti-I2 antibodies).

Medical therapy does play a critical role in the treatment of patients with IBDs, and biological drugs such as infliximab, adalimumab, vedolizumab and ustekinumab targeting different signaling pathways have brought a revolutionary influence on the treatment of IBDs. To achieve the goal of precision treatment, studies regarding new therapeutic agents, optimal therapeutic targets, different disease patterns, and patients' choices are in desperate need. With the increasing understanding of the pathogenesis of IBDs, new pathophysiology has been found. What's more, considering different healthcare systems and financial structures around the world, more multidimensional prediction and monitoring tools integrating multi-omics data should be developed. Thus, an interdisciplinary collaboration between medical scientists, bioinformaticians, economists and manufacturers is encouraged. By achieving these endeavors, we are getting closer and closer to the goal of precision medicine in IBDs.

Conclusion

IBDs encompassed a variety of phenotypes that affect individuals to varying degrees. Differences in gut microbiota composition between IBDs patients and healthy individuals have been found, with reduced biodiversity of commensal microbes and colonization of opportunistic microbes in IBDs patients. Beyond innate immunity, adaptive immunity also has a direct role in the pathogenesis of IBDs. An overwhelming number of effector cells, such as Th17 cells and ILCs, induce self-destructive immunity; therefore, a cure for IBDs would involve understanding how immunological balance is controlled. Because correct IBDs management is important for disease prognosis, non-invasive serum biomarkers have been extensively investigated to discover new features for disease diagnosis, subclassification, and disease prognosis. Markers useful for monitoring disease activity and predicting treatment outcome and complications. Despite extensive research, current IBDs biomarkers are far from ideal. Since individual biomarkers lack specificity or sensitivity, the combination of different biomarkers can improve the validity of assessing disease course. On the other hand, future directions in IBDs management may rely heavily on the development of multi-omics analyses. A large number of data processing workflows require the help of artificial intelligence. Further research is needed to identify new biomarkers with lower cost and better availability. Attention should be paid to predicting complications before disease progression and assessing the risk of readmission and postoperative recurrence. Of note, methods for identifying new biomarkers and clinical trial endpoints should be rigorous and standardized. Assessment of disease activity and treatment response needs to be objective. Newly discovered markers should be confirmed in multicenter international collaborations before being used in clinical practice.

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