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Comparative study on the pathogenesis of Crohn's disease and ulcerative colitis

Yang QH *et al.* Pathogenesis of IBD

Abstract

Inflammatory bowel disease (IBD) is an incurable disease of the digestive system, however, the therapeutic methods for IBD remain limited. Pathogenesis of IBD was systematically discussed and compared in this paper, primarily comprising Crohn's disease and ulcerative colitis. This paper focused on six common aspects: (1) Dysregulated immune responses; (2) Gene function changes; (3) Intestinal microbes disorder and imbalance; (4) Microbial infections; (5) Associations between IBD and other inflammatory diseases; and (6) Other factors. In addition, pathogenesis differences between these two forms of IBD were unravelled and clearly distinguished. These unique aspects of pathogenesis provided crucial insights for the precise treatment of both Crohn's disease and ulcerative colitis. This paper aimed to illustrate the root causes and beneficial factors of resistance to IBD, which would provide novel insights on early prevention, development of new therapeutic agents, and treatment options of this disease.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Pathogenesis; Unique pathogenesis of Crohn's disease; Unique pathogenesis of ulcerative colitis; Immune responses; Gene function; Microbes

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Core Tip: Six common and fourteen unique aspects of the pathogenesis of inflammatory bowel disease, primarily Crohn's disease and ulcerative colitis, illustrate the causes and beneficial factors of resistance to inflammatory bowel disease, providing critical insights for targeted treatment of Crohn's disease and ulcerative colitis. Utilizing the main contents of this paper allows for the development of comprehensive interventions that reduce harmful influences, enhance protective factors and use an integrative approach to address the diseases for the benefit of the human being.

INTRODUCTION

Inflammatory bowel disease (IBD) is a globally prevalent disease, with incidence rates continuing to rise in the 21st century[1]. It has become a public health challenge worldwide. IBD is a systemic disease affecting the gastrointestinal tract and also multiple organs and systems. Clinically, it is classified as one of the common, multiple and currently incurable digestive system disease, characterized by severe intestinal inflammation and mucosal destruction[2,3]. Intestinal inflammation can impair mucosal healing, leading to chronic inflammation of gastrointestinal tract, which is prone to chronic relapses[4,5]. Furthermore, IBD can not only affect many organs and systems such as eyes, mouth, skin, joints, liver, gallbladder and pancreas but also lead to complications such as internal and external infection of the digestive tract and tumour, significantly increasing the risk of canceration of gastrointestinal and other organs, such as colorectal cancer, skin cancer, and cervical cancer[6,7].

The aetiology of IBD is complex and multifactorial. Pathogenesis of IBD is an area of intense research and clinical interest. In the field of international biomedical applied basic research, the breakthrough and focus are also on the pathogenesis of IBD. Insight into the pathogenesis of IBD, which provides elucidation of IBD mechanisms, is also the cornerstone for clinical therapy. However, the exact pathogenesis and mechanisms have not been fully established, posing several challenges for both fundamental research and clinical treatment of IBD. These current challenges are as follows: (1) Existing therapeutic agents cannot completely cure this disease; (2) Choice of clinical treatment; (3) Resistance to anti-tumour necrosis factor (TNF) therapy; and (4) Targeted research of new IBD therapeutic agents.

Research on the pathogenesis is vital for identifying the root causes of IBD and provides significant insights into the patient's overall condition and potential pathways for curing the disease, primarily comprising Crohn's disease and ulcerative colitis. Moreover, it aids in discovering new therapeutic targets, which can enhance clinical diagnosis, treatment and even early prevention of IBD. This is particularly crucial for

newly industrialized countries with traditionally low incidence rates, such as those in Asia, Africa, and South America. Therefore, it is necessary to study the pathogenesis of IBD.

Therefore, this paper focused on six key aspects to analyse the root causes of the two most common forms of IBD, primarily comprising Crohn's disease and ulcerative colitis. The common pathogenesis of these two forms of IBD was systematically studied and discussed. Those were: (1) Dysregulated immune responses; (2) Gene function changes; (3) Intestinal microbes disorder and imbalance; (4) Microbial infections; (5) Associations between IBD and other inflammatory diseases; and (6) Other factors. It illustrated both the causes of IBD and factors contributing to resistance against the disease. Additionally, pathogenesis differences between these two forms of IBD were unravelled and clearly distinguished. These unique aspects of pathogenesis would provide crucial insights for the precise treatment of both Crohn's disease and ulcerative colitis.

COMMON PATHOGENESIS OF CROHN'S DISEASE AND ULCERATIVE COLITIS

The two most prevalent subtypes of IBD, Crohn's disease and ulcerative colitis, have common pathogenesis. Current research on the pathogenesis of IBD concentrates on six primary aspects: (1) Dysregulated immune responses; (2) Gene function changes; (3) Intestinal microbes disorder and imbalance; (4) Microbial infections; (5) Associations between IBD and other inflammatory diseases; and (6) Other factors (Figure 1). These factors collectively contribute to intestinal damage and inflammation, leading to the onset of IBD. This section also explores protective strategies for the intestines and resistance mechanisms against IBD. Moreover, corresponding treatment strategies and feasible treatment methods are proposed.

Dysregulated immune responses

Pathogenesis of the immune system function in IBD has identified key cytokines and their functions, cytokine regulation and influence, changes in inflammatory mediators, and the relationship between intestinal mucosal immunity and intestinal epithelial cells (Figure 2). Various feasible strategies for preventing and treating IBD have also been proposed. For instance, T cell-derived interleukin (IL)-22 binding protein (IL-22BP), IL-17F, and T helper 17 (Th17) have been identified as pathogenic[8,9]. However, the IL-22, the IL-17B, the IL-15 have anti-inflammatory effects.

IL-22BP is known to induce IBD, as evidenced by experiments on mice. In IBD patients, high levels of IL-22BP are produced by CD4⁺ T cells. While cytokine IL-22 exerts a protective effect on tissues in the intestine, IL-22BP endogenously inhibits this effect of cytokine IL-22. During anti-TNF- α treatment, which is recognized as an effective IBD therapy, amounts of IL-22BP secreted by CD4⁺ T cells are reduced. Despite the inhibition of IL-22BP, IL-22 is still expressed, thereby achieving the therapeutic objective for IBD[10].

Additionally, IL-17 family (IL-17s) related members play important roles in the pathogenesis of IBD. Both IL-17A and IL-17F contribute independently to IBD. IL-17A and IL-17F activate the nuclear factor-kappa B pathway to control bacterial and fungal infections. IL-17A and IL-17F in the intestines originate from T cells and some cellular subtypes, such as CD4⁺ helper T cells, gamma delta T cells, alpha beta T cells, type 3 innate lymphoid cells (ILCs), natural killer T cells, and mucosal associated invariant T cells[11]. IL-17A and TNF synergistically mediate signal to drive the expression of inflammatory genes in Crohn's disease immunopathogenetic mechanisms[12-14]. Inhibition of IL-17F promotes the production of microbiota-mediated regulatory T cells in the colon. Treatment with anti-IL-17F antibodies reduces the severity of colitis pathology. In ulcerative colitis, IL-17B and the IL-25, both members of the IL-17s, exert opposite effects. Among them, IL-17B cytokines are protective and anti-inflammatory, whereas IL-25 is pathogenic[15]. Therefore, development of new biological therapies selectively intervening or targeting IL-17s are also prospective strategies in IBD.

Furthermore, Th17 cells' inflammation has been linked to IBD[16]. Retinoic acid, a metabolite of intestinal vitamin A, promotes the differentiation of regulatory T cells and inhibits the differentiation of Th17 cells[9]. Cytokine IL-15, secreted by fibroblastic reticular cells in secondary lymphoid organs, maintains the group 1 ILCs in Peyer's patches, thereby preventing immunopathological damage in the intestine[8]. Although ILCs accelerate virus clearance, they can cause severe intestinal inflammatory diseases, accompanied by symbiotic disorders and reduced intestinal barrier function.

The study of IBD's immune pathogenesis has led to the discovery of new treatment methods. During the episode period of IBD, some chemokines, chemokine receptors and cell adhesion molecules are upregulated in IBD mucosa. Then circulating leukocytes migrate to the inflamed gut, regulated by cell adhesion molecules, chemokines, and chemokine receptors. Disrupting this migration can improve IBD therapy[17]. For instance, inhibiting or changing the migration of inflammatory leukocytes into the gut has shown therapeutic benefits[18].

Infliximab is a therapeutic antibody directed against TNF- α to treat IBD. Infliximab has a positive effect on intestinal mucosal gene expression in patients. Before infliximab therapy, most cell adhesion molecule genes are upregulated. However, most of these genes are significantly decreased after infliximab therapy. The gene response varies depending on whether the lesion is located in the colon or the ileum. In colon IBD patients, chemokines ⁵ C-C motif chemokine ligand 20 and C-X-C motif chemokine ligand (CXCL) 1-2 continue to elevate, predisposing to IBD relapse. Meanwhile, in ileum IBD patients, several gene expressions increase before treatment, such as Mucosal vascular addressin cell adhesion molecule 1; *THY1*; *PECAM1*; C-C motif chemokine ligand 28; *CXCL1*, *CXCL2*, *CXCL5*, *CXCL6*, and *CXCL11*; *IL-8*. However, *CD58* is decreased[17]. Genes in patients with IBD of the ileum are restored to control levels after infliximab therapy[18]. Other treatment methods are used to reduce the immune response and control inflammation in the IBD, such as pro-inflammatory factor antagonists, anti-inflammatory factor mimics, cytokine inhibitors, and inhibition of inflammatory signal transduction.

The pathogenesis of immune responses to IBD offers new insight into pharmacological therapies, such as inhibiting inflammatory signaling. It also reveals that clinical parameters alone cannot sensitively stratify IBD patients, highlighting the need for more accurate analytical methods. High-resolution analytical technologies for delivering precision agents and predicting responses to specific IBD therapies can facilitate more effective and personalized treatment[19]. Promising analytical methods include immune response profiling, germline genetics, *in vivo* real-time molecular endoscopy, gut micro-biome analysis, and tissue transcriptomics.

Gene function changes

Genetic research has made substantial progress in understanding the pathogenesis of IBD. Genome-wide studies have identified susceptibility gene loci, their functions, and interrelations between genes, opening new avenues for gene therapy for IBD. Genome-wide association studies have pinpointed hundreds of gene loci associated with IBD, contributing to both Crohn's disease and ulcerative colitis, as illustrated in Figure 3[20]. For instance, variations in genes linked to IBD pathogenesis include the IL-23, the IL-23 receptor subunit (IL-23R), p40 subunit of IL-23, IL-12, p40 subunit encoding for IL-12 (IL12B), IL12B variant, TNF superfamily member 15, the *RNASET2-FGFR1OP-CCR6*, Janus kinase 2, nucleotide-binding oligomerization domain 2 (*NOD2*), signal transducer and activator of transcription 3; the homeodomain-containing transcription factor NK2 transcription factor related, locus 3 (*NKX2-3*) gene regions[21]; the susceptibility genes regulating immune function PR domain zinc finger protein 1, *REL*, Caspase-recruitment domain 9 (*CARD9*), *SMAD3*, *IL1R2*; immunity-related GTPase M (*IRGM*), *ATG16 L1*; IL-10 functional defects; Th17-IL23 pathway[22].

Encoding IL-23R is a genetic factor leading to Crohn's disease[23]. ² The *IL-23R* gene, located on chromosome 1p31, encodes a subunit of the pro-inflammatory cytokine IL-23 receptor, which is a crucial peptide for the generation of Th17 cells. *Rs11209026* (c.1142G>A, p.Arg381Gln) is an uncommon coding variant that has a protective effect against Crohn's disease. IBD is associated with IL-23R regional abnormal signal

transduction. At the same time, multiple independent signals are associated with IBD in the *IL-23R* gene region. Because of the polymorphism of *IL-23R* region, the effect on IBD is more complicated. Both the innate and adaptive immune systems contribute to IBD through the *IL-23R* region polymorphisms[24].

In addition, the homeodomain-containing transcription factor *NKX2-3* gene regions, involved in the homologous domain of lymphocyte development, differentiation and tissue, also affect Crohn's disease and ulcerative colitis pathogenesis. Susceptibility gene loci for IBD and that of mycobacterial infections are overlapped, suggesting shared human response pathways[25]. Functional variation of 45 specific genes affect IBD by high-resolution fine-mapping, including 18 associations (a single causal variant, > 95%) and 27 associations (a single variant, > 50%). These variants are as follows: Tissue-specific epigenetic marks, protein-coding changes, and transcription factor binding sites destruction[26].

Susceptibility genes for IBD vary among populations around the world, such as in Europe, America, Japan, South Korea, and China. For example, in Europe and the United States, common susceptibility genes include autophagy related 16-like 1 (*ATG16 L1*), *NOD2* defects, and *CARD9*. In Japan, common genes include *ATG16 L2-FCHSD2*, *SLC25A15-ELF1-WBP4*[27], *NUDT15 p.Arg139Cys*[28], *NUDT15 R139C*, and *NKX2-3* polymorphisms[29,30]. In South Korea, TNF superfamily member 15[22], *IL-23R*, *ATG16 L2*, *RNASET2-FGFR1OP-CCR6*[31], and *IRGM* are common, while in China, *CARD9*[32], *IL-10* gene variants[33], and *IL-17F* variants[34] are prevalent.

The concordance rates for Crohn's disease between mono-zygotic twins are 40%-50%[35]. Additionally, family inheritance proportions of IBD differ between Western and Asian countries. In Western countries, the proportion is significantly higher[36], with less than 20% for Western IBD patients and less than 7% for Asian IBD patients[37,38]. Gene interactions in IBD pathogenesis have paved the way for gene therapy, such as replacing defective genes and repairing sites in hematopoietic cells.

Intestinal microbes disorder and imbalance

IBD is associated with alterations in the composition of intestinal microbiota. The gut microbiota is indispensable for the pathogenesis of IBD, regulating the development and function of the immune system and playing both anti-inflammatory and pro-inflammatory roles. Changes in the intestinal microbes, including composition, abundance, richness, strain diversity, stability, gene variation, and function of gut microbiota, contribute to the onset of IBD[39]. In turn, oxidative and metabolic environment alterations in IBD shape the gut microbiota, leading to gut microbiota dysbiosis. The composition of intestinal microbiota in patients with IBD exhibits distinct characteristics.

The microbial composition in the intestines of IBD patients is altered. Key bacterial species associated with IBD have been identified through species and strain-level profiles, bacterial growth rates, virulence factors, antibiotic resistance, and metabolic functions[40]. Moreover, the abundance of these gut microbiota changes significantly. For instance, the abundance of *Bacteroides* are increased in the intestinal microbiota of IBD patients. *Bacteroides* are highly correlated with IBD[35]. In addition, *Bacteroides fragilis* and *Bacteroides vulgatus* are particularly elevated. Immunomodulatory molecules released by the outer membrane vesicles are produced by the gut microbe *Bacteroides fragilis*. In mouse experiments, these immunomodulatory molecules protect mice from experimentally induced colitis[35]. In patients with Crohn's disease, a deficiency in the *ATG16 L1* and *NOD2* genes induces intestinal inflammation. It is found that outer membrane vesicles mediated *ATG16 L1* and *NOD2* genes jointly protect humans from colitis. *ATG16 L1* and *NOD2* genes cause transmission mechanism problems. The release of immunomodulatory molecules from the outer membrane vesicles require the combined action of *ATG16 L1* and *NOD2* genes for patients with IBD.

In dendritic cells, outer membrane vesicles activate gene *ATG16 L1* and *NOD2*-dependent noncanonical autophagy pathways. To protect against colitis, dendritic cells triggered by outer membrane vesicles can further induce regulatory T cells in the intestine, which helps protect against IBD. The gut microbiota regulates peripheral lymphoid volume expansion and maintenance by controlling the function of RALDH(+)

dendritic cells[41]. During the early neonatal period, CD45(+)CD103(+)RALDH(+) cells in the intestine migrate to peripheral lymph nodes under the induction of symbiotic microorganisms, simultaneously inducing a substantial amount of retinoic acid locally. This mechanism promotes the differentiation of regulatory T cells and inhibits the differentiation of Th17 cells.

Additionally, the intestinal flora coordinates with the host to maintain intestinal immune homeostasis. Growth factors fibroblast growth factor 2 and IL-17 synergistically repair damage to the intestinal epithelium and maintain the immune homeostasis within the intestinal mucosal system. Growth factor fibroblast growth factor 2, which has a protective effect on the intestine, is secreted by intestinal regulatory T cells in response to an imbalance in the intestinal flora.

Enhancement of effector cell function or a decrease of regulatory cell function can lead to a dysregulated immune response to normal symbiotic bacteria[24]. Meanwhile, genetic predispositions influence the role of intestinal microflora and environmental factors within the gut[42]. In individuals with a high genetic predisposition, the immune response of the intestine to the control of symbiotic flora is dysregulated. This affects the intestinal microflora and environment, inducing changes in the colon. Intestinal homeostasis cells can promote inflammation, immune tolerance, and epithelial repair. The location of IBD within the intestine determines the composition of intestinal flora. For instance, the intestinal flora of patients with colonic type differs from those with ileal type in Crohn's disease, such as decreased alpha diversity[43]. Furthermore, certain microbial species are commonly affected in both Crohn's disease and ulcerative colitis. Four microbial species, including *Eggerthellaceae*, *Bacteroidaceae*, and *Lachnospiraceae*, are increased, while sixteen microbial species, such as *Peptostreptococcaceae*, *Eubacteriaceae*, and *Streptomycetaceae*, are decreased[40].

Studying changes in the composition and function of gut microbiota in IBD patients not only advances our understanding of the disease's pathogenesis but also broadens the potential for future research directions. Therapeutic approaches could include promoting ecological agents to correct intestinal flora imbalance, such as IL-13[44].

From a nutritional and health perspective, interventions like yogurt consumption can help reduce inflammation by enhancing the integrity of the intestinal lining[45]. Improved intestinal integrity can prevent pro-inflammatory molecules produced by intestinal microorganisms from entering the blood[46]. Further treatments for IBD are likely to focus on microbiota-based interventions. Moreover, the development of probe technologies targeting specific intestinal microorganisms could enable accurate identification and differentiation of IBD subtypes. This approach could allow for the precise distinction between Crohn's disease and ulcerative colitis by targeting key bacterial species within the gut. Additionally, there is a need to develop immunoregulatory therapeutic agents that can promote immune system activation and inhibit inflammatory response by bypassing cellular transport mechanisms, making them suitable for direct ingestion by IBD patients. Furthermore, there is an urgent need to establish a comprehensive and sophisticated treatment system for IBD that utilizes one or more intestinal flora as bio-markers. Such a system could not only deliver therapeutic agents but also facilitate accurate diagnosis and simultaneous treatment of IBD.

Microbial infection

In the study of IBD, the pathogenesis with bacteria and fungi are limited. The enteric virome is an integral part of the gut microbiota ecosystem, yet its involvement in IBD pathogenesis has been largely overlooked. The enterovirus group, comprising various DNA and RNA viruses, remains relatively understudied. Common microorganisms implicated in IBD pathogenesis include bacteria, viruses, molds, and protozoa, some of which may also trigger allergic reactions (Table 1).

Microbial infections cause inflammation directly or indirectly by a damaged intestinal mucosal barrier, imbalance of microbial homeostasis, as well as altering immune system in IBD[47]. Microbial infections also lead to shifts in the composition of intestinal flora, intestinal disorders, and increased intestinal mucosal permeability, all of which significantly elevate the risk of IBD. Moreover, there is mutual regulation and change between the intestinal microbiota and the genetic composition of the host, and between

the microbiota composition and function and the neutrophil production and function under specific environmental factors, which are linked to the pathogenesis of IBD[48,49]. The eukaryotic viruses and viromes in colon resections are different between patients with IBD and non-IBD. Colon tissue viromes and enteric viruses affect intestinal homeostasis and shape the phenotype of IBD through divergent innate immunomodulation. The immune system detects disturbances in the enterovirus group, affecting the maintenance of normal intestinal homeostasis. For IBD, the enterovirus B species of eukaryotic picornaviruses increase in colon. Additionally, genetic variations contribute to altered virome sensing, resulting in the perturbation of colon tissue viromes and the onset of IBD[50].

Oral bacteria have been observed in the intestinal mucosa of IBD patients, where they become highly enriched and colonized during the disease. For example, bacteria in the oral cavity appear and accumulate in the intestinal tract of IBD patients during periodontal disease. These oral bacteria enrich in the mucosal niche of IBD intestine, such as *Klebsiella spp.*, *Campylobacter concisus*, *Fusobacterium nucleatum*, and *Veillonella spp.*[51-53]. In Crohn's disease, *Haemophilus parainfluenzae* and *Fusobacterium nucleatum*, specific to the oral cavity, are significantly enriched in the intestinal mucosa[54]. Additionally, in the intestine of IBD patients, the number of oral-associated species *Veillonella spp.* are enriched, which are nitrate reducers[55].

Intestinal epithelial permeability is increased due to impaired mucosal barrier in the IBD patients. Oral microorganisms can not only interfere with intestinal barrier function, but also accumulate and colonize in the intestinal mucosa[56]. These microbial disturbances contribute to intestinal dysbiosis, which drives IBD pathogenesis. Moreover, the inflammatory environment within the intestine promotes the growth of oral-related bacteria and disrupts the symbiotic microbiota during IBD. During inflammation, concentrations of nitrate increase in the intestine. The *Enterobacteriaceae spp.* is increased rapidly[57-59].

The composition of oral bacterial microbiota changes significantly over time in IBD patients. In paediatric Crohn's disease, *Rothia spp.* and *Capnocytophaga spp.* are enriched

in the oral subgingival biofilm[60]. In patients with periodontitis, nitrate reductase-capable bacteria such as *Proteobacteria spp.* and *Veillonella spp.* are also increased[61]. In severe ulcerative colitis, the oral microbiota differs from that seen in Crohn's disease, with associations noted for *Campylobacter spp.*, *Haemophilus parainfluenzae*, *Veillonella parvula*, and *Veillonella dispar*[54,62].

A multistage model linking microbial and immune compartmental changes in the oral cavity and intestine has been used to assess the correlation between oral bacterial microbiota and IBD. This model suggests that oral disease-related bacteria trans-locate to the intestine, exacerbating IBD symptoms directly[63]. Additionally, oropharyngeal bacteria from the nasopharynx and mouth can migrate and colonize the stomach and intestines, leading to intestinal inflammation and malnutrition in children[64].

Non-bacterial microorganisms and viruses, including fungi like *Candida albicans*, are also present in the intestines of IBD patients[65,66]. Additionally, parasitic infections can influence IBD by triggering beneficial changes in the gut microbiota, which in turn elicit specific parasite-associated immune responses that counteract intestinal inflammation[44]. Hence, harnessing viruses or viromes unique to IBD-affected colon tissue offer the potential for developing new therapeutic strategies, bio-markers, and early screening tools based on microbial markers linked to IBD pathogenesis. In addition, oral microbial signatures enriched in the intestinal mucosa or distinctive oral bacterial microbiota could help accurately distinguish between Crohn's disease and ulcerative colitis.

Association between IBD and other inflammatory diseases

The correlation between IBD and other inflammatory diseases helps to elucidate the underlying causes of IBD. These associations stem from factors such as genetic factors, common pathogenic triggers, or the consequences of other conditions or their treatments. Compared to individuals without IBD, patients with IBD have a higher susceptibility to autoimmune diseases. Patients with one immune-mediated disease have an increased incidence of developing several other immune-mediated diseases.

Genome-wide studies have shown that chronic immune diseases tend to cluster in certain individuals. Consequently, the prevalence of multiple immune-mediated diseases is notably elevated in IBD patients. Moreover, gene loci associated with IBD are also linked to other immune-mediated diseases, including ankylosing spondylitis and psoriasis[25].

The most frequently observed concurrent inflammatory diseases in IBD patients are arthritis and asthma. Other extra-intestinal manifestations (EIMs) include ankylosing spondylitis, erythema nodosum, inflammatory eye disease, and periodontitis. Additionally, IBD patients may present with peripheral arthritis, primary sclerosing cholangitis, pyoderma gangrenosum, uveitis, and oral ulcers[67-69]. The relationship between IBD activity and EIMs varies. Some EIMs, such as uveitis and primary sclerosing cholangitis, occur independently of IBD activity, while others, including erythema nodosum and oral ulcers, are linked to IBD activity, suggesting shared pathogenic mechanisms[68,69].

IBD pathogenesis has been further explored by examining the correlation between IBD activity and EIMs[69,70]. However, the mechanisms behind most EIMs remain unclear. The pathogenesis of EIMs may arise from the following: (1) EIMs may represent independent inflammatory events triggered by genetic factors, microbial agents, or elevated inflammatory mediators and other factors[71]; and (2) EIMs may result from the extension of intestinal antigen-specific immune responses to non-intestinal sites, such as *via* microbial antigen cross-reactions and ectopic inflammation.

A large Canadian population-based study revealed that 63% of patients were diagnosed with chronic inflammatory diseases before the onset of IBD. These patients exhibited a significantly higher risk of inflammatory diseases such as bronchitis, psoriasis, and pericarditis. Ulcerative colitis patients were found to have an increased risk of chronic kidney disease and multiple sclerosis[72]. Additionally, IBD patients face an increased risk of concurrent mental health conditions, including depression and anxiety. The potential mechanisms linking IBD to psychiatric conditions include

elevated pro-inflammatory cytokines, gut dysbiosis, altered vagal nerve signalling, and changes in brain morphology and function[73].

Other factors

In addition to the previously discussed factors, alterations in colonic epithelial cell diversity contribute to IBD. Single colonic epithelial cellular subtypes have been identified, including progenitor cells, colonocytes, and goblet cells in the crypts. The positional re-modelling of goblet cells plays a key role in IBD pathogenesis. Goblet cells, which express the anti-protease molecule *WFDC2*, not only inhibit bacterial growth but also prevent invasion by commensal bacteria and mucosal inflammation[74]. Additionally, absorptive cells located at the top of the crypts, which are responsible for sensing pH, are dysregulated in IBD. These cells express the proton channel *OTOP2* and the satiety peptide uroguanylin. Furthermore, elevated levels of transforming growth factor- β 1 and nitric oxide have been detected in the saliva of both Crohn's disease and ulcerative colitis patients[75,76].

Many other non-pathological factors associated with the development of human society are closely linked to IBD. These factors include changes in the natural environment, economic development, living conditions, dietary structure, lifestyle changes, disease exposure factors, population size, increased immune-related diseases, and improved diagnostic capabilities[77]. In terms of diet, excessive consumption of high-fat and sugary foods, coupled with unhealthy lifestyle habits such as lack of exercise, smoking, antibiotic overuse, and an obsession with hygiene, have been identified as contributors to IBD[1,78]. The pursuit of excessive cleanliness has led to a reduction in exposure to intestinal worms, which are thought to play a role in host immune system training. As a result, the intestinal immune systems of some individuals may become overly sensitive, predisposing them to IBD. Additionally, the incidence of IBD has been shown to be positively correlated with population density. As the population increases, the number of patients also increases. The greater the population density, the higher the incidence of IBD[79].

Epidemiological studies comparing IBD patients and healthy controls have identified several protective factors that may lower the risk of developing Crohn's disease and ulcerative colitis. These factors include breastfeeding > 12 months, consumption of tea, vegetables, fruits, plant fibre intake, physical exercise, and pet ownership (specifically dogs) for Crohn's disease[38]. Similarly, protective factors for ulcerative colitis include breastfeeding > 12 months, consumption of tea, hot water bath, consumption of coffee, intake of vitamins C and D, and use of flush toilets during childhood[80,81]. These factors are essential not only for maintaining physical health but also for fostering mental well-being. Thus, prevention strategies for IBD should promote both a healthy lifestyle and a positive psychological construction.

PATHOGENESIS DIFFERENCES BETWEEN CROHN'S DISEASE AND ULCERATIVE COLITIS

While Crohn's disease and ulcerative colitis share some commonalities, they also exhibit significant distinctions in their pathogenesis. These two major subtypes of IBD have their own unique pathological characteristics, and the specific mechanisms contributing to the development of each have been discussed in detail. Through a comparative analysis of the pathogenesis of Crohn's disease and ulcerative colitis, the specific immune mechanisms, genetic abnormalities, and intestinal microbiota alterations that underpin these conditions have been identified, allowing a clear distinction between these two. Clinically, the pathogenesis of Crohn's disease and ulcerative colitis differ markedly, with each condition possessing its own distinctive features. Moreover, gut microbiota profiles differ significantly between patients with Crohn's disease and those with ulcerative colitis. Each condition is associated with a unique microbial environment and distinct gut microbiota characteristics. These unique aspects of pathogenesis provide crucial insights for the precise treatment of both Crohn's disease and ulcerative colitis.

The unique pathogenesis of Crohn's disease

The unique pathogenesis for Crohn's disease is manifested in the following aspects: (1) The disease is driven primarily by interferon- γ and IL-12, as observed in both patients and mouse models; (2) It causes by defects in the innate immune system. The pathogenesis of Crohn's disease is associated with genes encoding *NOD2*, *ATG16 L1*, and *IRGM*. These genes play critical roles in the innate immune system and the intracellular processing of bacterial components. In addition, *NOD2* gene is mutated in patients with Crohn's disease. The ability of *NOD2* sense bacterial peptidoglycan, activate nuclear factor- κ B, and mitogen-activated protein kinase pathways are decreased. Deficiencies in *NOD2* or *ATG16 L1* contribute to Crohn's disease susceptibility, with the functional impact being assessed through altered function of *ATG16 L1* and *IRGM* polymorphisms[24,35]; (3) Mutations in genes encoding Toll-like receptor 4, *NOD1*, and *NOD2* contribute to the inflammation in Crohn's disease, which are innate immune recognition receptors. Therapeutically, inflammatory cytokines TNF and IL-12/23 are effective in the treatment of the disease; (4) It is strongly linked to specific immune cells; (5) The gene encoding leucine-rich repeat kinase 2 (LRRK2) has been identified as a major susceptibility gene for Crohn's disease by genome-wide association studies[82,83]. LRRK2 acts as a negative regulator of the transcription factor NFAT and plays a critical role in modulating disease severity. LRRK2 protein regulates the transport and secretion of lysozyme in lysosomes, inhibits intestinal inflammation, and regulates intestinal immune homeostasis in murine cells. LRRK2 deficiency show increased susceptibility to colitis in experimental mice[84]; (6) Salivary inflammatory markers such as IL-6, IL-1 β and TNF are elevated for Crohn's disease[85]; (7) The diversity of pathogenic species, as well as pro-inflammatory flora, is notably elevated in Crohn's disease patients. This includes members of the *Enterobacteriaceae* family, such as *Escherichia spp.* and *Shigella spp.*, which are associated with colon ulceration and bloody diarrhoea. Additionally, gut microbiota alterations reveal increased levels of *Enterobacteriaceae*, *Streptococcaceae*, and *Erysipelotrichaceae* in these patients; (8) The diversity and abundance of beneficial gut microbes are markedly reduced. For instance, *Clostridia*, known to counteract inflammation through interactions with pathogenic

intestinal bacteria associated with IBD, are diminished[44]. *Faecalibacterium prausnitzii*, also referred to as *Clostridium prausnitzii*, which has anti-inflammatory properties, shows reduced levels in Crohn's disease patients[86,87]. This butyrate-producing bacterium is especially depleted in the ileum during disease onset. Similarly, the strain diversity of *Roseburia intestinalis*, which converts acetate to butyrate, is also decreased. *Bifidobacterium longum*, which provides resistance against *Shigella*-induced enteric infections, is likewise reduced. Other microbial species, including *Actinomycetaceae*, *Bifidobacteriaceae*, *Atopobiaceae*, *Prevotellaceae*, and *Firmicutes_noname*, show decreased numbers in Crohn's disease; and (9) The microbial environment within the gut of Crohn's disease patients undergoes significant alterations. The inflammatory conditions promote increased sugar degradation and quinone bio-synthesis, while fermentation pathways are diminished[40].

The unique pathogenesis of ulcerative colitis

Compared to Crohn's disease, ulcerative colitis exhibits distinct pathogenic characteristics, which are outlined as follows: (1) It is driven by natural killer T cells, which produces IL-13, as observed in both IBD patients and mouse models[24]; (2) It is caused by mutations in the coding genes of Toll-like receptor 4 and *NOD1*. These innate immune recognition receptor proteins play a role in detecting microorganisms. The inflammatory cytokine TNF are effective in the treatment of ulcerative colitis; (3) It is associated with gut mucosa. The correlation between ulcerative colitis and gut mucosa is stronger[19,26]; (4) Certain microbial species like *Bacteroides uniformis* and *Bifidobacterium bifidum* are associated specifically with ulcerative colitis. Increased gut microbiome includes *Bifidobacteriaceae* and *Acidaminococcaceae*. Conversely, reduced microbial species include *Propionibacteriaceae* and *Nectriaceae*; and (5) The microbial environment in ulcerative colitis displays increase lactate production pathways, while butyrate and acetate production pathways are diminished, which exacerbates inflammation in the intestinal environment[40].

In conclusion, the differentiation in pathogenesis between Crohn's disease and ulcerative colitis, along with the identification of highly specific markers, enables precise early diagnosis, screening, and treatment. Such distinctions offer significant potential for personalized treatment strategies for Crohn's disease and ulcerative colitis. Furthermore, the unique microbial characteristics associated with each disease subtype facilitate their accurate classification, providing a foundation for targeted treatment and advancing precision agents for IBD.

CONCLUSION

The incidence and prevalence of IBD continue to rise globally; however, effective treatment options for this disease remain limited. IBD is led by a combination of dysregulated immune responses, gene alterations, imbalances in intestinal microbiota, microbial infections, associations with other inflammatory diseases, and shifts in social and environmental factors. These immune, genetic, and environmental factors are intertwined and act synergistically, often triggering and amplifying one another in the progression of IBD. Changes in genetic, immune, and intestinal microbial factors also contribute to shaping the distinct IBD phenotype. Unique aspects of pathogenesis provide crucial insights for the precise treatment of both Crohn's disease and ulcerative colitis. Despite significant challenges in understanding the pathogenesis of IBD, research has yielded substantial insights, offering potential solutions for patients. Continued scientific efforts and exploration have shed light on the fundamental mechanisms underlying IBD, which is crucial for developing effective prevention and treatment strategies. Utilizing these main contents allow for the development of comprehensive interventions that reduce harmful influences, enhance protective factors and use an integrative approach to address the diseases for the benefit of human being.

ORIGINALITY REPORT

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