Inflammatory Bowel Disease: Pathobiology

43

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Key Concepts

- The pathophysiology of IBD is incompletely understood but thought to be multifactorial and a complex interaction between genetic, environmental, microbial, and immune factors.
- While hundreds of susceptibility genetic loci have been identified to increase the risk of disease, all identified loci individually contribute only a small percentage of the expected heritability in IBD.
- The significantly increasing incidence of IBD in developing urban countries worldwide lends strong evidence that environmental factors may play the dominate role in its pathogenesis.
- The composition of the gut microbiota is significantly different in patients with IBD and has increased colonization of *Fusobacterium* and members of the Proteobacteria phylum and decreased colonization of Firmicutes and Bacteroidetes. Yet, no single organism has been identified to be solely responsible for the development of IBD.

Introduction

Inflammatory bowel disease (IBD) is a disorder characterized by chronic relapsing intestinal inflammation. The incidence of both Crohn's disease and ulcerative colitis has gradually increased since the Second World War, especially in northern Europe and North America, where the highest incidence rates have been reported. Other areas with traditionally low disease prevalence, such as Asia and Africa, have reported increasing numbers in more recent years.

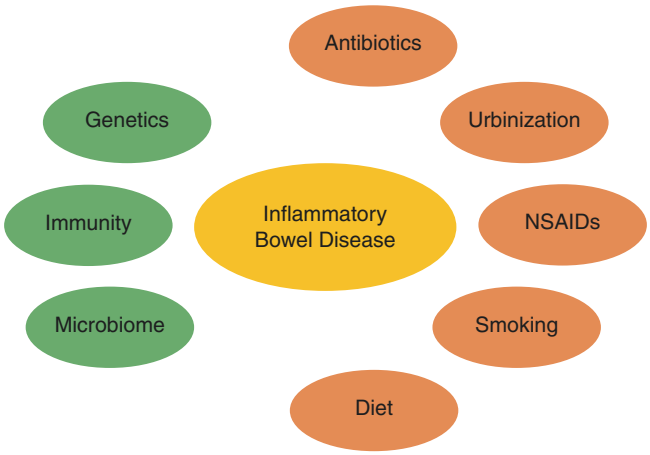

Fig. 43.1 The pathophysiology of IBD consists of host factors (green) and environmental factors (orange)

These shifts in the risk of developing IBD within a relatively short time period provide evidence for the importance of exposure to environmental factors in disease pathogenesis. The greater risk for CD in Ashkenazi Jews regardless of geographic location or time period suggests ethnic differences in the genetic predisposition to IBD.

Various theories have been espoused as to the underlying cause of IBD. A complex interaction between genetic, environmental, and microbial factors, which promote the associated immune responses in susceptible individuals, appears responsible for the pathogenesis (Fig. 43.1). Advances in genetics and immunology have allowed the identification and delineation of contributory mechanisms in IBD.

These factors variably influence the development of IBD as well as its manifestations. While Crohn's disease and ulcerative colitis behave differently, they have some similarities and differences in phenotypic manifestations. This is congruent with the underlying genetic and immunologic mechanisms involved, which also demonstrate similarities and differences in their characteristics. Environmental factors

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such as urbanization, diet, and smoking, as well as medications such as NSAIDs, may also have an impact. In this chapter, we will review the current evidence on the pathobiology of IBD including both host and environmental factors.

Host Factors

Genetics

Population-based studies suggest that genetic factors contribute to IBD. There is an eight- to tenfold greater risk of IBD among relatives of UC and CD [1]. 15% of patients with Crohn's have an affected family member with IBD, and twin studies for CD have shown 50% concordance in monozygotic twins compared to <10% in dizygotics. In contrast, the concordance rate in monozygotic twins is 10–15% in UC. Thus, non-genetic factors may have a more important role in UC than in CD. Similarly, family studies suggest that a child has a 26-fold increased risk for developing CD when another sibling already has the condition while the risk is increased 9 times in the case of UC [2].

Most cases of genetic susceptibility are polygenic, but there is a spectrum of rare genetic disorders that can contribute to early-onset IBD. Monogenic defects have been found to alter intestinal immune homeostasis through many mechanisms. While a variety of genetic factors have been identified in IBD, there remains an important role for microbial and environmental factors. Epigenetic factors can further mediate interactions between environment and genome and could affect the development and progression of IBD. Epigenomics is an emerging field, and future studies could provide new insight into the pathogenesis of IBD.

Conventional IBD is a group of polygenic disorders in which hundred(s) of susceptibility loci contribute to the overall risk of disease. While genetic components are important factors involved in disease pathogenesis, identified genetic factors account for only a small proportion of the disease variance: 13.1% for CD and 8.2% for UC. More than 50% of IBD susceptibility loci have also been associated with other inflammatory and autoimmune diseases.

Monogenic defects are rare but can lead to early-onset (younger than 5 years) and very early-onset (younger than 2 years) CD and cause severe disease manifestations. These defects lead to disruption of the epithelial barrier and the epithelial response, as well as reduced clearance of bacteria by neutrophil granulocytes and other phagocytes. Other single-gene defects induce hyperinflammation or autoinflammation, or disrupted T- and B-cell selection and activation, due to defects in IL-10 signaling or dysfunctional regulatory T-cell activity. Defects in IL-10 or one of the subunits of its receptors cause extensive inflammation of the colon and perianal region. Next-generation sequencing (NGS) through whole exome sequencing (WES) has allowed the identification of single variants in very early-onset IBD.

Progress in genetic testing and DNA sequencing has allowed many genome-wide association studies, which have identified new single-nucleotide polymorphisms (SNPs). Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) was the first susceptibility gene for CD that was discovered in 2001. This gene codes for a protein that acts as an intracellular receptor for bacterial products in monocytes and transduces signals leading to NFkB activation. The activation of NOD2 with muramyl dipeptide induces autophagy in dendritic cells. Dendritic cells from CD patients with NOD2 gene defects are deficient in autophagy induction and also show reduced localization of bacteria in autophagolysosomes. Two other autophagy-related genes, *IRGM* and *ATG16L1*, may have an important role in immune responses in IBD. Genetic variants that have been found to confer an increased risk of CD indicate the importance of innate immunity, autophagy, and phagocytosis in its pathogenesis. Other genes, like *IL23R* and *PTPN2*, are also associated with autoimmune disease, suggesting another aspect of Crohn's disease pathogenesis.

Epigenetics refers to mitotically heritable changes in gene expression via changes in structure and function of chromatin without alterations in DNA sequence. DNA methylation, histone modification, RNA interference, and the positioning of nucleosomes are some epigenetic mechanisms and are important in the interaction between environment and genome. Hypermethylation of gene promoters is associated with IBD patients; differences in DNA methylation status between normal and inflamed tissues from CD and UC patients have been identified.

MicroRNAs (miRNAs) are endogenous small non-coding single-stranded RNA molecules acting as post-transcriptional regulators of gene expression. MiRNAs have an important role in the development, regulation, and differentiation of the innate and adaptive immune system and are strongly implicated in the pathogenesis of many common diseases, including IBD. A lot of miRNAs have been discovered, but little is known of their function. In the intestinal tract, miRNAs are involved in tissue homeostasis, intestinal cell differentiation, and the maintenance of intestinal barrier function. CD and UC patients have unique miRNA expression profiles in their target organs as well as peripheral blood. Thus, identification of distinct miRNA expression profiles may provide an early method to determine a patient's disease course and a target of future treatments.

Immunity

The mucosal immune system is essential for establishing and controlling intestinal inflammation and injury. The role of

immunity in the causation and development of IBD is still evolving. The normal intestinal milieu consists of a complex interplay of genetic, microbial, and environmental factors that lead to mucosal immune and nonimmune responses. At rest and even in non-diseased states, there exists controlled mucosal inflammation regulated by a delicate balance of cytokines Th1, Th17, Th2, Th3, Th9, and Treg cells. In IBD, there is an imbalance whereby the adaptive immune system responds to self-antigens, leading to chronic inflammation and damage. Defects in innate immune functions of the epithelial barrier, pathogen recognition, and autophagy as well as adaptive immune dysfunction, particularly in T-cell activation, differentiation, and function, have all been implicated.

The first layer of defense against pathogens in the intestinal mucosa is the epithelium that faces the luminal surface. Paneth cells, which produce antimicrobial peptides, are located in this layer. Next is the lamina propria, where macrophages and dendritic cells are located and are responsible for the innate immune response. Dendritic cells have cytoplasmic extensions interdigitated among the epithelial cells to sample the luminal contents and then present antigens to T cells in the lamina propria and underlying lymphoid follicles. T and B cells and Peyer's patches form the adaptive immune system.

In the normal physiological state, gut-associated lymphoid tissue (GALT) constituted by Peyer's patches, lymphoid follicles, and mesenteric lymph nodes provides local intestinal immunity. Since there are a disproportionate number of microorganisms in the normal gut, a delicate balance of the innate and adaptive immunity is critical to avoiding an immune response, and a loss of this balance may be responsible for IBD. Alterations in autophagy, which is a cellular process related to the degradation of intracellular pathogens, antigen processing, regulation of cell signaling, and T-cell homeostasis that results in reduced clearance of pathogens, may contribute to the onset of inflammatory disorders in susceptible subjects [3, 4]. There is some evidence that problems with tolerance to self-antigens in the intestinal mucosa may lead to IBD [5, 6].

Macrophages and dendritic cells identify the molecular patterns of microorganisms by using pattern recognition receptors (PRR), such as toll-like receptors (TLR) and nucleotide-binding oligomerization domains (NOD). NOD2 is an intracellular microbial sensor that acts as a potent activator and regulator of inflammation. Mutations in the caspase recruitment domain-containing protein 15 (CARD-15) gene encoding the NOD2 protein have been identified in CD. Deficiency in NOD2 impacts the immune response in the lamina propria leading to chronic inflammation.

An internal imbalance in the cytokines in the intestinal mucosa has also been described in IBD. Such an imbalance may impact the intensity and duration of the inflammatory response in susceptible individuals. Various cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β) are implicated. UC is often described as Th2-mediated disease and CD as a Th1 condition, but the underlying mechanisms may be interrelated and more complex. Recent data suggest that IL-17 and IL-22, cytokines that initiate and amplify the local inflammatory signs and promote the activation of counter-regulatory mechanisms targeting intestinal epithelium cells, are related to the induction of colitis.

IL-2, released by macrophages and dendritic cells in the intestinal mucosa, activates signal transducer and activator of transcription (STAT) 4 in memory T lymphocytes, stimulating the production of IFN-γ. IFN-γ triggers the production of inflammatory cytokines in cells of the innate immune system, contributing to the increase of the inflammation present in colitis. IL-9 that regulates intestinal epithelial cells has also been implicated. The role of the other cytokines in IBD is as follows: IL-1 activates T cells to produce IL-8 and IL-6; IL-6 helps differentiate Th17 and Treg cells; IL-12 promotes the differentiation of Th1 cells; IL-23 stimulates the production of IL-17 and TNF-α and IL-6, while TNF-α acts on Th2 surface receptors promoting the proliferation of macrophages and inhibits Treg cells.

Intestinal Microbiome

Over the last decade, the importance of the intestinal microbiome in health and disease has become very apparent. The introduction of 16S rRNA next-generation sequencing has allowed researchers the ability to investigate how perturbations of microbes may lead to disease. Not surprising, there has been an abundance of research investigating the role of intestinal bacteria on the development of IBD.

It has been well shown that the composition of the gut microbiota in IBD patients significantly differs from healthy controls. As a whole, the microbiota of IBD patients shows less diversity and richness [7]. Increased abundance of certain pathogens is also found in patients with IBD. For example, *Fusobacterium* and members of the Proteobacteria phylum (Enterobacteriaceae, *Escherichia coli*) are commonly found to be increased in IBD patients compared to controls [8–10]. Conversely, patients with IBD have been consistently found to have decreased members of the Firmicutes (e.g., *Faecalibacterium prausnitzii*, *Ruminococcus*, *Oscillibacter*) and Bacteroidetes phyla [7, 11].

In addition to microbial composition, metagenomics has been used to provide insight into the functional characteristics of the microbiome. Interestingly, the dysbiosis seen in IBD patients is not seen in unaffected twins and relatives, suggesting that these changes are related to the disease state or environment effects, rather than underlying genetics [12, 13].

Table 43.1 Microorganisms associated with the development of IBD

Bacteria	Viruses	Fungus
Enterobacteriaceae	Caudovirales	*Saccharomyces cerevisiae*
Mycobacterium avium	*Synechococcus* phage S	*Candida albicans*
Escherichia coli	*Retroviridae* family	
Faecalibacterium prausnitzii		
Ruminococcus spp.		
Oscillibacter spp.		
Bacteroidetes		

Although cultivation of single organisms has been associated with active IBD, there is limited evidence that implicates individual organisms as the sole driver of IBD (Table 43.1). For example, *Mycobacterium avium* can induce granulomatous enteritis in animals and has been investigated as an inducer of Crohn's disease [14]. However, a clear link between *Mycobacterium avium* inducing granulomas and IBD in human patients remains unproven [15]. Colombel found that adherent-invasive *E. coli* strains colonized ileal lesions in patients with Crohn's disease. These strains demonstrated a cytolytic effect in cell culture by production of alpha-hemolysin and were hypothesized to promote Crohn's disease by increasing intestinal permeability. Yet, the fact that these strains were found in 33% of healthy controls demonstrates that they alone are not sufficient to cause disease [16].

Global metabolic changes associated with bacterial compositional alterations likely play a role in the development of IBD. Metagenomics has shown an increased prevalence of certain virulence factors in IBD patients, such as endotoxins and hemolysins [17]. Morgan analyzed both the compositional and functional differences in 231 patients with IBD compared to healthy controls [18]. They reported that while only 2% of the bacterial composition was different (at the genus level), 12% of the metabolic pathways were different between IBD patients and controls. Patients with IBD had increased virulence and secretion pathways as well as major oxidative stress pathways. Other studies have demonstrated significant decreases in microbial metabolism such as short-chain fatty acids and amino acid production [19].

The role of viruses and fungi in the pathogenesis of IBD has been receiving increasing attention. Similar to bacteria, certain patterns have emerged in patients with IBD compared to healthy controls. A comprehensive analysis of the virome in IBD patients has been performed [20]. The authors demonstrated significant expansions of certain virions including Caudovirales bacteriophages. Others have found associations of *Synechococcus* phage S and the *Retroviridae* family of viruses in IBD patients [21]. Interestingly, some studies have shown these virome changes are independent of IBD-associated bacterial composition changes. In a similar fashion, Sokol characterized the fungal microbiota in 235 patients with IBD [22]. They found increased abundance of multiple fungal species including *S. cerevisiae* and *C. albicans*. Additionally, they reported that *Basidiomycota* abundance was associated with IBD flares.

While these microbiota changes have consistently been demonstrated in patients with IBD, whether they are driving the disease or are a consequence of inflammation remains uncertain. For example, inflammation decreases the oxygen tension of the intestinal mucosa, preventing the growth of aerotolerant taxa [23]. Alternatively, the changing oxygen level can promote anaerobic microorganisms and dysbiosis [24]. Further studies are needed to understand the interplay between dysbiosis and inflammation and determine which may be driving the pathogenesis of IBD.

Antibiotics

Antimicrobial agents have a strong influence on the composition and diversity of gut microbiome. Multiple studies have demonstrated that within the first few days following antibiotic administration, there are a profound and immediate decrease in diversity and significant shift of the bacterial community structure [25]. While the microbiome begins to reconstitute to its initial state after antibiotics are stopped, in some cases the microbiome remains altered [26].

Given this large influence of antibiotics on the microbiome, researchers have investigated if antibiotic exposure is a risk factor for the development of IBD. In a Canadian case-control study, 294 children diagnosed with IBD were compared to 2377 controls [27]. The authors found that patients who were diagnosed with otitis media (a proxy for antibiotic use) were 2.8-fold more likely to have IBD (95% CI 1.5–5.2; $p = 0.001$) compared to controls. In a similar study, antibiotic prescriptions were significantly associated with both the development of ulcerative colitis and Crohn's disease [28]. In a recent meta-analysis, 8 case-control and 3 cohort studies including 7208 patients with IBD were analyzed. Antibiotic exposure was significantly associated with Crohn's disease (OR 1.74, 95% CI 1.35–2.23), but not with ulcerative colitis (OR 1.08, 95% CI 0.91–1.27). While all antibiotics, except for penicillin, were associated with Crohn's disease, metronidazole and fluoroquinolones were most significantly associated with IBD overall. Taken together, the evidence strongly supports antibiotics to be a risk factor for the development of IBD, further implicating the microbiome as a major driver of IBD.

Environmental Factors

Urbanization

Since its discovery in the late 1800s, IBD has long been thought to be a disease of Caucasian people of European descent; IBD continues to be most prevalent in wealthy Western countries, with a prevalence of ~0.5% in North America and Europe [29, 30]. Because of new diagnoses and the low mortality rate in IBD patients, the prevalence of IBD in these countries is increasing [31]. While IBD was rare in developing nations during the twentieth century, the emergence and increasing incidence of IBD in developing countries in Asia, Africa, South America, and the Middle East is now well documented (Fig. 43.2) [32]. For example, in Brazil the incidence of ulcerative colitis increased to 4.5 cases per 100,000 people in 2005 from 1.0 per 100,000 between 1986 and 1990 [33]. Similarly, in the 1960s–1980s, IBD was barely recognized in Hong Kong, while now the incidence ranges from 1.3 to 2.1 per 100,000 patients [34].

Industrialization and urbanization in developing countries is associated with a multitude of factors including changes in lifestyle, diet, smoking habits, pollution, and healthcare delivery. In fact, Benchimol found that growing up in a rural environment was significantly protective of later development of IBD (IRR 0.58, 95% CI 0.43–0.73). Thus, the emergence and increasing incidence of IBD in these developing countries worldwide provides strong evidence that environmental factors play a large role in pathogenesis. While it is not possible to isolate all environmental changes associated with urbanization, herein we will review the influence of certain lifestyle changes on the development of IBD.

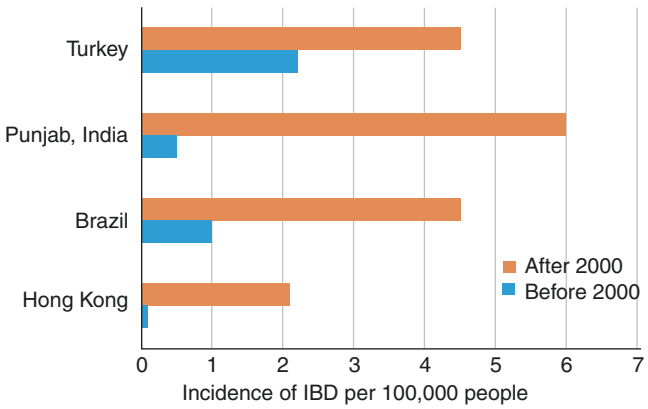

Fig. 43.2 The incidence of IBD is significantly increased over the last two decades in developing countries

Smoking

The divergent findings of smoking as a risk factor for Crohn's disease, yet potentially protective for ulcerative colitis, have been appreciated since the early 1980s. Both passive and active smoking is associated with a twofold increased risk of development of Crohn's disease (OR 1.76; 95% CI 1.4–2.2) [35]. Additionally, smoking portends a significantly increased risk of fistula formation, strictures, and need for surgery [36]. On the other hand, it is well accepted that smoking is protective against ulcerative colitis. In a meta-analysis of 13 articles investigating the association of smoking on IBD, the authors reported that current smokers have a significantly lower incidence of ulcerative colitis compared to controls (OR 0.58; 95% CI 0.45–0.75) [35].

How smoking promotes IBD is unclear. Smoking changes the microvasculature, which can contribute to inflammation via decreased perfusion and recruitment of immune cells. This can increase oxidative stress which subsequently affects gut barrier function, mucus production, and microbiome changes [37, 38]. How these molecular changes promote Crohn's disease but protect against ulcerative colitis is uncertain. Ananthakrishnan studied nicotine metabolism in 634 patients with Crohn's disease and 401 with ulcerative colitis. They found that certain genetic polymorphisms in nicotine-metabolizing enzymes, such as CYP2A6, and GSTP1, were associated with the development of Crohn's diseases and protection against ulcerative colitis [39]. Thus, a genetic predisposition may exist as to the effects of smoking on the pathophysiology of IBD.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been associated with the development or exacerbation of IBD, although the literature shows conflicting results. Long recently retrospectively studied 791 patients from a prospectively collected database with IBD patients that were in remission [40]. They reported that Crohn's disease patients with NSAID use more than five times per month had a greater risk of active disease (RR 1.65; 95% CI 1.12–2.44), while no effect was seen in patients with ulcerative colitis (RR 1.25; 95% CI 0.81–1.92). Ananthakrishnan reported that NSAID use at least 15 times per month increased the risk of development of both Crohn's disease and ulcerative colitis [41].

Low-dose NSAID does not appear to promote IBD. In 426 Crohn's disease patients and 203 ulcerative colitis patients, low-dose NSAID (<200 mg/day and used less than daily) was not associated with an increase in disease activity. High-dose NSAID use was associated with a higher numeri-

cal disease activity score in Crohn's patients, but was not associated with an increase in disease flares in Crohn's or ulcerative colitis patients. Takeuchi studied the effect of NSAIDs in patients with quiescent IBD. Patients were given either acetaminophen, naproxen, diclofenac, or indomethacin for 4 weeks and then assessed for recurrence [42]. The authors reported a 17–28% recurrence rate in both Crohn's disease and ulcerative colitis patients within 9 days of administration of NSAIDs, but no recurrence was seen with acetaminophen.

Given these mixed results, a recent systematic review and meta-analysis of publications between 1983 and 2016 examined the association between acetaminophen and NSAIDs on the risk of disease exacerbation [43]. Pooled analysis of 18 publications found that NSAID use was not associated with exacerbation of Crohn's disease (OR, 1.42, 95% CI, 0.65–3.09) or ulcerative colitis (OR, 1.52, 95% CI, 0.87–2.63). Similar findings were observed with acetaminophen.

Multiple mechanisms have been suggested as to how NSAIDs can promote IBD. NSAIDs inhibit cyclooxygenase (such as COX-1 and COX-2) and prevent accumulation of prostaglandins. Cyclooxygenases and prostaglandins play a critical role in epithelial wound healing, mucosal defense, and immune modulation within the colon [44–46]. For instance, using a model of dextran sulfate sodium (DSS)-induced colitis, inhibition of COX-1 and COX-2 resulted in significantly decreased amounts of mucosal prostaglandins and exacerbation of DSS colitis [47]. Of the many pathways impacted by COX inhibition, increased mucosal permeability has most often been suggested as the main pathogenic factor. Animal models of IL-10-deficient mice (a common animal model for colitis) given 4 weeks of NSAID treatment had a 75% reduction of PGE_2 and developed colitis, with infiltration of the lamina propria by macrophages and CD4+ T-cells [48]. Collectively, while the literature is mixed, there is a biological basis to support the notion that NSAIDs influence the pathobiology of IBD.

Diet

A recent Cochrane review concluded that the effects of dietary interventions on Crohn's disease and ulcerative colitis are uncertain [49]. However, observational studies have shown associations between dietary patterns and the risk of being newly diagnosed with Crohn's disease and ulcerative colitis, as well as the exacerbation of symptoms. Greater consumption of meat and animal products has been associated with the onset of Crohn's disease and ulcerative colitis, whereas greater consumption of fruits and vegetables had a lower incidence. Some hypotheses used to explain the impact on diet on IBD suggest a direct alteration of the microbiome. Dietary antigens may also influence the immune response of the gut. Alternatively, diet may directly affect the mucosal barrier or indirectly affect immune function by influencing the composition of gut enzymes, bile acids, and hormones. Some diet-based therapies have been shown to impact IBD, particularly in CD. Studies are underway to further elucidate the role of diet on the pathogenesis of IBD.

Pouchitis Pathobiology

Pouchitis is a common complication in patients who undergo restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). The incidence of pouchitis depends upon the indication for surgery; pouchitis occurs in approximately 50% of patients with ulcerative colitis but rarely if ever it occurs in patients with familial adenomatous polyposis [50–52]. While the pathogenesis of pouchitis remains unclear, the finding that the incidence is dependent upon the primary diagnosis strongly suggests an underlying genetic component. Carter found that patients who carried the +2018 single-nucleotide polymorphism in interleukin-1 were at a significantly higher risk for the development of pouchitis (relative risk 3.1; 95% CI 1.2–7.8) [53].

Similarly, Sehgal investigated the association of NOD2 mutations to the development of pouchitis [54]. They reported that mutations in NOD2 were significantly higher in patients with severe pouchitis compared to either asymptomatic IPAA patients or patients with IPAA complications such as abscess or fistula. Genetic changes have also been linked to immune alterations in patients with pouchitis. Increased expression of toll-like receptors 2 and 4 is seen in patients with pouchitis [55]. Additionally, aberrant expression of defensing-1 and increased expression of defensing-5 is expressed in IPAA patients when compared to normal ileum [56, 57].

The reservoir function of an IPAA promotes fecal stasis, leading to adaptation and metaplasia of the mucosa from small bowel to colon-like mucosa [58]. Similarly, the pouch bacteria move closer to a colonic-like microbiome after pouch creation [59]. Because fecal stasis promotes bacterial overgrowth, the influence of microbiome changes on pouchitis has been investigated. McLaughlin investigated the colonizing bacterial community of the pouch in patients with ulcerative colitis and familial adenomatous polyposis [60]. Interestingly, they found a significant decrease in Bacteroidetes and significant increases in Proteobacteria in patients with ulcerative colitis compared to polyposis patients. Additionally, bacterial diversity, which is a marker of bacterial health, was significantly increased in polyposis patients, compared to ulcerative colitis patients.

Functional characteristics of the host in relation to microbiome changes have also been studied in IPAA patients. Investigators have found that the most strongly microbe-associated transcriptomic pattern is enrichment with activation of the interleukin-12 pathway and complement cascade

genes. Collectively, the investigations to date suggest that pouchitis is a multifactorial disease resulting from immune and microbial changes in a genetically susceptible host.

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