



The Role of Epigenetic Mechanism in the Pathogenesis of Inflammatory Bowel Disease

Gontar Alamsyah Siregar¹, Darmadi Darmadi^{1*}, Riska Habriel Ruslie²

¹Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; ²Department of Child Health, Faculty of Medicine, Universitas Prima Indonesia, Medan, Indonesia

Abstract

Inflammatory bowel disease (IBD) is a chronic inflammation of the intestine due to interaction between inappropriate immune response and environmental factors. It consists of ulcerative colitis and Crohn's disease. The incidence of IBD is increasing globally and disrupts patient's quality of life and causes heavy economic burden. Several risk factors are involved in IBD including genetic, environment, lifestyle, and socioeconomic status. Antigen enters host's gastrointestinal tract and triggers an immune reaction. In subject with IBD, the immune reaction is hyperactive. Some conditions such as intestinal barrier disintegration, gut microorganism imbalance, molecular mimicry, and abnormal autophagy trigger chronic inflammation and end with IBD. Genetic predisposition plays a central role in IBD. NOD2, IL23R, and ATG16L1 have the most significant association with IBD. With the presence of epigenetic mechanisms, patients with genetic predispositions have higher probability for suffering from IBD. The most common epigenetic mechanisms in the pathogenesis of IBD are DNA methylation and non-coding RNAs. The epigenetic mechanisms lead to changes in T-cell activity, cytokine production, intestinal epithelial integrity, autophagy activity, and innate immunity response. All of those cause chronic inflammation as the main characteristic of IBD. Genetic aspect can be a promising approach in managing IBD. The field of genetic may be applied in diagnosing, treating, and predicting disease outcomes. However, this topic still needs further investigations.

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***Correspondence:** Darmadi Darmadi, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
E-mail: ign.darmadi@yahoo.com
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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammation of the intestine, which arises from a complex interplay between a dysfunctional host immune response and environmental triggers [1], [2]. IBD consists of two subtypes which are ulcerative colitis (UC) and Crohn's disease (CD) [1], [3], [4]. UC was firstly identified as a discrete entity in 1858 by Samuel Wilks while CD was firstly described by Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer in 1932 [2], [4], [5]. Later in the 1950s, the concept of immunity in IBD was proposed since the symptoms relieved by steroid administration [4]. The common symptoms of IBD are recurrent abdominal pain, diarrhea, bloody purulent stool, and weight loss [6], [7]. The incidence of IBD is continuously increasing globally during the recent five decades [3], [7], [8]. IBD has the highest prevalence in Western countries [3], [7]. Around 1.4–1.6 million people in America suffer from IBD [4], [5], [7]. Industrialization and westernized lifestyle have increase the incidence of IBD in other parts of the globe [2], [5]. Even though IBD has a low mortality rate [5], it impairs patient's quality of life and causes heavy economic burden, reaching USD 6.3 billion per year [3], [5], [6], [9].

There are several risk factors for IBD including diet rich in saturated fat, sedentary lifestyle, poor air quality, improved socioeconomic status, and appendectomy. Genetic is also an important risk factor even though it can not be the only presenting risk factor for the disease to occur [3], [5], [8], [10]. The fact that no case of IBD found in Pacific island people and lesser cases in Maori and non-Caucasian ethnic supports the fact [8]. Extensive antibiotic utilization along with nonsteroidal antiinflammatories impair the balance of gut microorganisms and cause increased risk of IBD [3], [4], [5], [7], [8]. In contrast, vegetarian diet [3], [4], [5], [10] and breastfeeding during infancy [3], [5], [8] were protective factor for IBD. Interaction between several risk factors is required to result in disease manifestation [8], [10]. In addition, there is a controversy regarding smoking as a risk factor for IBD. Some studies found that smoking is not associated with the incidence of IBD [3], [4], [5], [8], [10], while other studies reported contradictive results [1], [3], [4], [5].

The management of IBD, including diagnosis and treatment, is difficult. There is no single protocol which can be applied to all IBD cases. Classic diagnosis of IBD is confirmed by history taking including drug utilization and family history of IBD, physical and

rectal examination, laboratory parameters and stool examination, endoscopy, imaging, and histologic examinations. Genetic analysis is a potential modality not only for diagnosing but also predicting and treating IBD. However, it still needs further study before being extrapolated to general population [6], [7]. In this article, we will discuss about genetic aspect in IBD.

Review Methodology

We conducted this review based on a question: Does epigenetic mechanism have significant role in the pathogenesis of IBD? We did a literature search from Pubmed and Google Scholar. We used keywords as following: “epigenetic”, “genetic”, “IBD”, and “pathogenesis”. All types of literatures, including review, from the recent 10 years were included. An exclusion criterion was literatures which were not in English. The summary of all literatures was presented in Table 1.

Table 1: Summary of reviewed literatures

Citation number	Authors	Publication year	Main finding
1	Greuter <i>et al.</i>	2019	Genetic predisposition is associated with the occurrence of extraintestinal manifestations of IBD
4	Malik	2015	Hereditary factor is one of the risk factors for IBD
6	Zeng <i>et al.</i>	2019	Genetic predisposition affects the incidence of IBD. Epigenetic mechanism is important in patient with genetic predisposition for IBD. Without epigenetic mechanism, IBD will not occur
8	Geary <i>et al.</i>	2010	Family history and Caucasian ethnicity are associated with the increased incidence of IBD
9	Huang <i>et al.</i>	2017	There are 18 gene loci associated with the incidence of IBD with more than 95% certainty. Epigenetic mechanism is required for the susceptible gene to elicit the disease
10	Amarapurkar <i>et al.</i>	2018	Family history is one of the significant risk factors for IBD
13	McGovern <i>et al.</i>	2015	Epigenetic mechanism results in the appearance of coding and noncoding genes that associated with the risk of IBD

IBD: Inflammatory bowel disease.

Epidemiology of IBD

The annual incidence of UC and CD in Europe are 24.3 and 12.7 per 100,000 persons per year, respectively [10]. In the USA, the incidence of UC and CD are 12.2 and 10.7 per 100,000 persons per year, respectively [3]. The incidence of IBD is stable or even decreasing in North America and Europe [2]. In Asia, the incidence of IBD is ranging from 0.5 to 3.4 per 100,000 persons [10]. The incidence of IBD tends to increase by time globally, particularly in Asian countries [2], [3], [5]. Besides the shift of socioeconomic status, improvement in diagnostic and epidemiological methods contribute to the increasing incidence [5]. Most IBD cases are diagnosed in patients aged 30s [3], [4], [5]. The second

peak is observed in the age of 40s. In Western countries, gender predilection for IBD is not significant with slight female predisposition while in Asian countries, males are dominant [3].

Pathogenesis of IBD

The hallmark of IBD is chronic inflammation from inappropriate immune responses toward external and internal antigens. Genetic predisposition and environmental factor collaborate to induce the disease [3], [6], [7]. Immune mechanism underlying the pathogenesis of IBD is mediated by T cell. T-cell activity is amplified in CD, mainly T helper (Th)1 and Th17 thus increasing proinflammatory cytokines such as interleukin (IL)-17, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α . In UC, Th2 activity is increased leading to B cell and natural killer activation. Innate immunity is also involved in the IBD [7]. Antigen-presenting cells in the intestinal mucosa, including macrophage and dendritic cell, are hyperactive and permits antigen translocation from intestinal lumen [4], [7]. The amount of human leukocyte antigen (HLA) is also increased in patient with IBD. This facilitates antigen processing and presentation [4]. Antigens from the environment enter host's body and are presented by antigen-presenting cells through HLA to T helper cells. This initiates broad immunological responses. Macrophages are activated and produce proinflammatory cytokines including TNF. TNF triggers caspase activation which leads to cell apoptosis. TNF also orchestrates inflammation by enhancing other cytokines production [1].

Hygiene theory is thought as one of the underlying pathogenesis of IBD. The increased hygiene status is followed by increase in the incidence of inflammatory disease [4], [5], [8]. Improved hygiene decreases exposure to environmental antigens and alters balance between Th1, Th2, and regulatory T-cell which ends with immune dysregulation and IBD [3]. Fewer exposure to antigens in early life results in abnormal immune response toward antigen exposure in advanced age [4], [5], [8]. The intestinal barrier, involving the interaction between enterocytes, goblet cells, neuroendocrine cells, Paneth cell, and M cell, plays a significant role in the pathogenesis of IBD [7]. Intact intestinal epithelial barrier is important in the context of physical defense against microorganism invasion and colonization, toxin translocation, and immune regulation. Epithelial damage increases intestinal permeability and makes those antigens able to enter host's body [6], [7]. This condition triggers inflammation like observed in IBD [7]. Gut microorganism imbalance causes decreased production of short-chain fatty acid, impaired T-regulatory cell activity, and hampered epithelial function [4], [7]. Anti-inflammatory

cytokines such as IL-2, IL-10, transforming growth factor- β , and TNF- β are downregulated [4]. The combination results in inappropriate immune response of IBD [4], [7], [11], [12]. Inflammation itself leads to impaired intestinal epithelial barrier and further exposure of antigen which triggers chronicity [6].

Molecular mimicry of foreign antigens with self-antigens is also suggested as the pathogenesis of IBD. Foreign antigens trigger immune activation, and when their structures have similarity with self-antigens, the immune response remains persistent and create a chronic inflammatory state. Among foreign antigens, gut microorganisms attract the interest of study regarding IBD pathogenesis [1]. Autophagy is another process involved in the pathogenesis of IBD. Autophagy is a process to recycle abnormal cytoplasmic component including pathogen clearance thus affecting inflammatory response [5], [6], [7], [13]. Activated gut lymphocytes by antigen exposure may translocate systemically. They will trigger inflammation in the extraintestinal organs and result in the presence of extraintestinal manifestations [1].

Clinical Manifestations of IBD

The abdominal pain is often chronic and colicky in characteristic. It is aggravated by bowel movement and localized in the right lower quadrant of the abdomen. Diarrhea can be just watery or bloody. Its chronic and intermittent in fashion. The weight loss itself results from chronic diarrhea, malabsorption, and anorexia [7]. Fistula and obstruction may appear later in time [3], [7]. IBD may also develop to colorectal cancer. Patients with IBD have a 2.4 times higher risk for developing colorectal cancer [3], [6]. Other literature even reported a higher risk which lies between 10 and 25 times [4]. Besides having gastrointestinal symptoms, IBD may also present with extraintestinal manifestations in 6% to 47% cases [1], [3], [10]. Joint manifestations are the most common extraintestinal manifestation reported, followed by ocular manifestations [3].

The Role of Epigenetic Mechanism in IBD

Approximately 15% of patients with IBD have a first-degree relative with a history of IBD [4]. A study reported that a family history of IBD increases the risk for having UC and CD with odds ratio of 4.51 and 3.97, respectively [10]. This result is confirmed by a study by Gearry *et al.* They found that family history of IBD will increase the odds of UC and CD as many as 2.52 and 3.06 times, respectively [8]. Other literature

reported a higher risk for first-degree relatives of IBD patients, which is five times compared to normal population [7]. Using genome-wide association studies, there is a lot of genetic predisposition associated with IBD identified [3]. Many genetic predispositions have been identified for the incidence of IBD. NOD2, IBD1-9, TNFSF15, IL23R, ATG16L1, IRGM, PRDM1, and NDP52 are susceptible loci of gene for IBD [1], [3], [5], [9], [13]. Among them, NOD2, IL23R, and ATG16L1 have >95% probability of association with IBD [5], [9]. The genetic predispositions are found across the globe even in different ethnicities [13].

Epigenetic mechanisms are the result of the collaboration between genetic predisposition and environmental factors. Epigenetic modifications are changes to gene structure and heritable phenotype that can't be explained by altered DNA sequences [6]. Some epigenetic mechanisms identified as risk factors for IBD are DNA methylation, non-coding RNAs, histone modification, and the positioning of nucleosomes [6], [7], [13]. Genetic predisposition without epigenetic mechanisms can not induce IBD since the heritability of UC and CD are only 8.2% and 13.1%, respectively [6].

DNA methylations in THRAP2, FANCC, GBGT1, DOK2, and TNFSF4 loci are associated with increased risk of IBD [6], [7]. Furthermore, hypermethylation in GBGT1, IGFBP4, and FAM10A4 plus hypomethylation in IFITM1 are associated with the incidence of CD. Methylation in several loci such as PAR2, MDR1, CDH1, CDH13, and GDNF are associated with progressive disease course. The methylation causes PAR2 activation that leads to intestinal myofibroblast proliferation and stricture formation. PAR2 activation also stimulates T-helper cell type 1 to produce cytokines such as TNF- α , IL-1, and IFN- γ . Methylation of RUNX3 gene, which causes its downregulation, makes T-cell over-responsive and overstimulated which ends with an excessive inflammatory response leading to IBD. Other methylations involving TRAF6, IL12B, HLA-DOB, IL16, IGHG1, and THY1 genes are associated with the development of T-cell and B-cell, antigen processing, and cytokine response which contribute to the pathogenesis of IBD [3], [6]. Several genes including CHD1, LAMB1, HNF4A, and MYO9B act as epithelial barrier regulators by maintaining epithelial tight junction. Methylations in those genes are associated with IBD [6].

The non-coding RNAs including microRNAs (miRNAs) alter T-cell differentiation, IL23/Th17 signaling pathway, and autophagy [3], [5], [6], [13]. Overexpression of miR-155 supports Th1 differentiation while loss of miR-155 favors Th2 differentiation. Th1 and Th2 are associated with the incidence of CD and UC, respectively. In addition, overexpression of miR-155 increases proinflammatory expression such as TNF- α , IL-6, IL-12, IL17, and IFN- γ [3], [6]. miR-21 is also associated with IBD. Its overexpression promotes Th2 cell differentiation, T cell-mediated immune responses, IL23/Th17 axis, and the disruption of the intestinal epithelial barrier.

Th17 is a proinflammatory cell associated with intestinal inflammation in CD by increasing proinflammatory cytokines and chemokines [6]. miR-146a affects the modulation of T regulatory cells, dendritic cells, and natural killer cells, along with signaling pathways related to NOD2 and toll-like receptors (TLR). NOD2 stimulates the production of proinflammatory cytokines via nuclear factor kappa B (NF- κ B) and caspase3 signaling pathways, maintains intestinal mucosal barrier, and regulates innate and adaptive immunity of intestine [5], [6], [7], [13]. TLR itself will increase proinflammatory cytokines production via NF- κ B signaling pathway after binding with lipopolysaccharide. On the other hand, miR-21 and miR-200b also plays important role in epithelial integrity. The presence of miR-21 damages tight junctions and increases intestinal permeability while miR-200b has protective effect and down-regulates IL-8 and TNF- α [6]. Some genes regulating autophagy are identified such as ATG16L1, NOD2, and IRGM. The presence of micro RNA such as miR-142-3P, miR-106b, and miR-196 decrease the autophagy activity while miR-93 acts contrary [3], [5], [6], [7], [13]. miRNAs may also be utilized to monitor disease activity of IBD such as miR-124, miR-877, and miR-595 [6].

The role of HLA is important in the pathogenesis of IBD. HLA is a recognition molecule that play important role in the early phase of immune response. Variations in HLA gene will increase the risk of inflammatory diseases. For extraintestinal manifestations of IBD, the presence of HLA-B8/DR3, HLA-B35, HLA-B44, HLA-B58, and HLA-DRB1*0103 are found to increase their incidence [1].

Several approaches for the management of IBD from genetic perspective have been proposed. Anti-methylation and micro RNA antagonists have been proven effective in study animal. However, those agents have poor efficiency when being applied to patients due to their poor chemical stability, low specificity, and prominent side effects [5], [6], [13]. On the other hand, the cost of pharmacogenetic is high and nearly unaffordable in developing countries [5]. Genetic markers are gaining place in the diagnosis of IBD. A combination of genetic, serological, and inflammatory evaluations gives higher accuracy in discriminating IBD. However, this method can't be applied yet for general population due to limited resources. In addition, genetic testing alone is neither sensitive nor specific in diagnosing IBD. Other genetic predispositions are being investigated, especially IL23R and TNFSF15, in association with IBD outcome [13].

Conclusion

IBD is increasing in global incidence. It is not a disease of Western countries anymore. It impairs

patient's quality of life and carries heavy economic burden. IBD has complex pathogenesis involving several risk factors including genetic. NOD2, IL23R, and ATG16L1 are genes with the strongest association with IBD. The presence of genetic predisposition along with epigenetic mechanisms, particularly DNA methylation and non-coding RNAs, lead to the occurrence of IBD. Further direction regarding the role of genetic in IBD may aid in the disease diagnosis, management, and outcome. However, this topic needs further investigations.

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