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Examining the Autoimmune, Genetic, Environmental, and Microbial Aspects of the Complex Etiology of Inflammatory Bowel Diseases: A Comprehensive Review and Comparative Analysis

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Abstract

Inflammatory Bowel Disease is an autoimmune disease of the Colon and or ileum. The exact cause of the disease is unknown but there are many factors that may predispose a person, worsen or improve the condition of the patient. These include genetic, environmental, autoimmune and bacterial factors. Here we briefly discus each one of these factors. We used databases including PubMed, Google Scholar, Scopus, and Web of Science to conduct a thorough literature search for our analysis of Inflammatory Bowel Disease (IBD). Screening researches, reviews, and meta-analyses from the previous two decades was part of our methodology. Articles that provided substantial new insights into the etiology, clinical presentation, and treatment approaches of IBD were the main focus of our inclusion criteria. In order to compile the state of knowledge and new directions in IBD research, we also carefully gathered data from citations and cross-referenced them to locate more pertinent studies. Inflammatory bowel disease is an autoimmune condition the exact cause of which is still unknown. This highlights the intricate relationship that exists between the immune system, environment, and gut microbiota, as well as the need for advancements in the field to identify the precise cause of the illness under consideration and develop a treatment plan for it.

Keywords Inflammatory bowel disease, gut microbiome and IBD, Ulcerative Colitis

1. Introduction

Inflammatory Bowel Disease is an Autoimmune Disease that involve a complex interaction between intestinal microbiota and host immunity in genetically predisposed individuals. There are two types of this disease, Crohn disease and Ulcerative colitis. Crohn's disease can affect any part of the gastrointestinal tract from mouth to anus but with a propensity for distal large bowel and proximal small bowel. In Crohn disease there is transmural inflammation of the gut wall resulting in deep ulcer formation. In Ulcerative colitis the inflammation is limited to mucosa and submucosa resulting in superficial ulcer formation, this can damage the neuromuscular function of the colon leading to colonic dilation. On gross appearance the gut wall appears thick in Crohn disease and thin in Ulcerative colitis. Clinical manifestation of Crohn disease includes diarrhea, fever and right lower quadrant abdominal pain, Iron deficiency anemia, fat and vitamin malabsorption. Clinical manifestation of Ulcerative colitis includes bloody diarrhea with expulsion of sticky mucoid material and lower abdominal pain that is temporarily relieved by defecation.

The exact cause of inflammatory bowel disease is unknown but there are several factors that play role in its development, namely, environment, genetic, autoimmune and gut microbiome.

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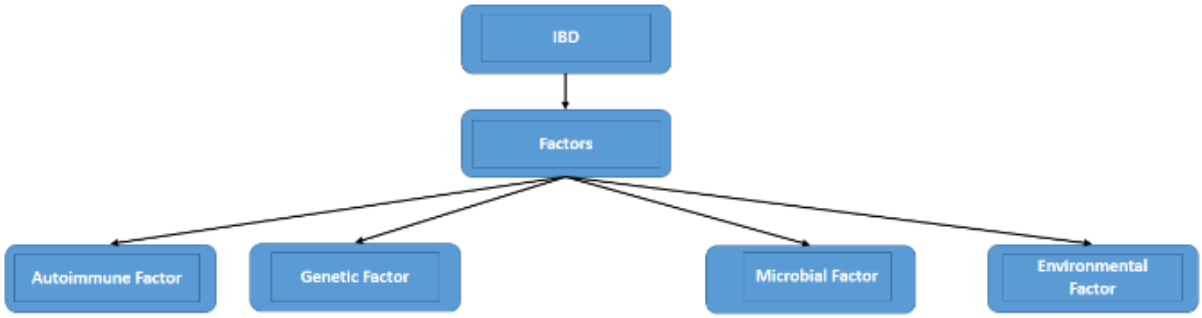

Figure 1: Diagram of the multiple components to Inflammatory Bowel Disease (IBD), including autoimmune, genetic, microbial, and environmental variables.

2. Methodology

To examine the autoimmune, genetic, environmental, and microbial aspects of Inflammatory Bowel Diseases we conducted a thorough literature search in academic databases including PubMed, Google Scholar, Scopus and Web of Sciences. We screened meta-analysis, Randomized Control Trials, and review of the past two decades. The main focus was on the articles that provided substantial insights into the of IBD.

2.1 Autoimmune Factor

Mucosal barrier of the Gut provides protection against bacterial invasion and infection. Goblet cells among intestinal epithelial cells secretes mucus that prevents bacterial infection, Paneth cells of the Gut secretes Anti-Microbial peptides like defensin that also has the same function[1]. In between Gut epithelial cells are present Dendritic cells that are a type of macrophage and will prevents intra epithelial bacterial invasion and will also serve to activate cell mediated immunity of the Gut associated Lymphoid Tissue, where eosinophils, T and B cells are concentrated. There are tight junctions like claudin in between intestinal epithelial cells that also prevent intra epithelial bacterial invasion (2). Defect of any of the above factor of innate immunity can lead to development of Inflammatory Bowel disease.

Helper T cells differentiate into Th1, Th2, Th17 and T regulatory cells depending on the type of interleukin that it comes in contact with. Th1 cell provide cell mediated immunity through macrophages, Th2 cells provide protection against parasites through eosinophils and Th17 cells inhibits T regulatory cells and also provide cell mediated immunity (1). T regulatory cells maintain a homeostasis of cell mediated inflammatory response. Interleukin 23 receptor is required for the differentiation of Th17 cells (3). Interleukin 10 is anti-inflammatory and is required for the differentiation of Regulatory T cells, Interleukin 8 is a chemokine that attracts Neutrophil[4]. Th1, Th2 and Th17 cells have play their roles in maintaining gut immunity and therefore defect of these cells or factors that downregulate or upregulate them can increase the risk for IBD.

2.2 Genetic Factor

Ashkenazi jews are the most predisposed people to Inflammatory Bowel Disease, 71 susceptible loci were identified for Corhn's Disease in a study (2). In another study 163 genes were identified, out of which 110 genes predisposed a person to both Ulcerative Colitis and Crohn's Disease, 30 genes predisposed a person to Crohn's Disease and 23 predisposed a person to Ulcerative Colitis (4). Defect in ATG16L1 gene produces defect in intestinal Goblet, Dendritic Cells and Paneth Cells, this leads to defective anti-Microbial autophagy (2, 4). Defect in PTPN22 also predisposes a person to Inflammatory Bowel Disease (5). Intestinal epithelial cells provide innate immunity against pathogens. This immunity is enhanced by NOD2/CARD15 intracellular receptors present in Intestinal epithelia cells and cells of monocytic lineage that sense lipopolysaccharides and invasive bacteria and induces NF-KB pathway. Mutation in NOD2/CARD15 genes encoding these receptors increases the risk for developing IBD (6, 7). First degree relatives of Crohn's disease affected individuals also have a risk of developing Crohn's disease as they have an increase in IBD risk alleles as compared to healthy non-related individuals (8).

2.3 Environmental Factor

Smoking has increased in the modern age. Surprisingly smoking has a protective role in Ulcerative colitis but worsens Corhn's Disease (4). In this modern age of industrialization, the production of hazardous gases has also increased. It has been found that NO_2 and SO_2 predisposes a person to inflammatory Bowel disease (9). It was found in a study that Vitamin D deficiency also predisposes a person to inflammatory Bowel disease[10]. High dietary intake of refined sugar also increases the risk for developing IBD (11). Consumption of low-Fermentable oligosaccharide, disaccharide, monosaccharide and polyol (FODMAP) decreases IBD related gut symptoms (12). Short chain fatty acids such as acetate, butyrate and propionate are produced by the action of gut microbiome on non-digestible carbohydrate (13). These short chain fatty acids regulate gut immunity (14). Acetate is produced by bifidobacteria and is responsible for maintenance of gut epithelial barrier, butyrate stimulates the differentiation of T regulatory cells, propionate prevent tumor cell growth by inhibiting HDAC enzyme. High sugar diet also decreases the concentration of short chain fatty acid produced in the gut increasing the risk for IBD development[15]. Breastfeeding has a protective role against IBD in infancy[16]. Children who are not breastfed have increased abundances of Clostridium difficile, components of breastmilk such as lysozyme, lactoferrin and immunoglobin protects against childhood infections. Such a child when receives anti-bacterial therapy may become a victim of dysbiosis which may predispose the child to IBD. Postmenopausal hormone replacement therapy and the use of Oral contraceptive pills in adult increases the risk of IBD (17). This may be due to the positive effect of estrogen on Hormone-mediated immunity.

2.4 Microbial Factor

In Gut homeostasis is maintained by suppressing excessive response to pathogen. Dysregulation may lead to inflammatory bowel disease. Normal Gut bacterial flora consist of many bacteria. Sone examples are Bacteroidetes, Firmicutes, Clostridium, Actinobacteria, Escherichia Coli, Bifidobacterial and Lactobacillus. These bacteria either have anti or pro inflammatory effect, or they produce indigestible polypeptides like butyrate, acetate and propionate that effect the gut immunity. Fecalibacterium inhibits interleukin 10 required for regulatory T cells differentiation, lactobacillus and Bifidobacterium have anti-inflammatory effect as they inhibit T regulatory cells, Clostridium promote Th17 cell differentiation (1). Short chain fatty acids can also alter transcription of DNA (18). Dysregulation of any of the above factor may predispose a person to inflammatory bowel disease.

3. Discussion

Inflammatory bowel disease (IBD) has a complex etiology that involves numerous factors, including microbial, genetic, environmental, and autoimmune. Since IBD is characterized by an abnormal immune response in which the body's immune system abnormally targets the gastrointestinal tract, resulting in persistent inflammation, autoimmune mechanisms play a crucial role. The pathogenesis of IBD heavily relies on this autoimmune component, which is what motivates continuous research into immune-modulating treatments. IBD risk is also greatly influenced by genetic susceptibility; multiple studies have shown particular genetic mutations and variants, including those in the CARD 15 gene previously known as NOD2 gene, that are closely linked to the illness. The people with a family history of IBD where more likely to develop IBD themselves, from this it is evident that IBD is an inherited disorder, this highlights the genetic effect in IBD.

The etiology of IBD is further complicated by environmental variables. The development and incidence of the condition have been linked to a number of variables, including smoking, exposure to certain bacteria, and nutrition. Given that IBD is more common in Westernized and urbanized settings, environmental variables may have a considerable impact on the disease's development. These results emphasize the need for more investigation into the role that environmental exposures and lifestyle choices play in the pathophysiology of IBD.

4. Conclusion

Inflammatory bowel disease's specific cause is still unknown. In addition to highlighting the need for research to determine the exact cause of the illness in issue and develop a treatment plan, this review emphasizes the complex relation among the immune system, environment, and intestinal bacteria.

Conflict Of Interest The author declared that they have no competing or conflict of interest.

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