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Causes and Mechanisms of Crohn’s Disease

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Chana Weis will graduate fall 2021 with a Bachelor of Science degree in Honors Biology

Abstract

Crohn’s disease and ulcerative colitis are the two most prevalent inflammatory bowel diseases (IBDs) in Jewish and Caucasian populations, affecting as many as one in 250 individuals. Nevertheless, the underlying causes of both disorders are not yet fully understood and remain unknown. However, current evidence suggests that the exaggerated inflammatory response, more commonly referred to as IBD, is believed to arise from dysregulation of the gastrointestinal (GI) immune system in genetically predisposed individuals who are exposed to environmental triggers. Recent advances have identified multiple IBD susceptibility genes; however, only a few environmental determinants of IBD have been consistently identified. The difficulty in understanding the etiology of IBD is in part due to the complex interactions between genes and the environment. Additionally, autoimmune mechanisms are believed to play a role in the development of IBDs, but the target antigens and the underlying pathways have not been sufficiently characterized and identified. IBD is commonly referred to as an “idiopathic disease;” a disease with an unknown cause (Health & Medicine, 2016; Sartor, 2006). This paper examines the possible causes of IBD, specifically highlighting Crohn’s disease.

Key Phrase
GI- Gastrointestinal Tract
IBD- Irritable Bowel Disease
CD- Crohn’s Disease
UC- Ulcerative Colitis

Introduction

Crohn’s Disease (CD) is a chronic autoimmune disease mainly affecting the gastrointestinal (GI) tract extending from the mouth to the anus; however, it’s most commonly found in the ilium, leading to the alternate name ileitis (Newman & Sminovitch, 2003). It’s characterized by thickened areas of the GI wall with inflammation extending through all four layers including the mucosa, submucosa, muscularis externa, and serosa (Politics & Government Week, 2017; Ruthruff, 2007). The inflammation is somewhat similar to that of ulcerative colitis, and commonly leads to abdominal pain, diarrhea, vomiting, weight loss, anemia and fever (Torres et al. 2017). However, some patients may experience mouth and skin sores along with joint stiffness and swelling (Creek, 2017). Unfortunately, patients suffering from CD are at a higher risk of developing other autoimmune disorders such as osteoporosis, thyroid disease, as well as colorectal cancer (Baumgart & Sandborn, 2012; O’Sullivan, 2009; Bae et al. 2014). Symptoms range from mild to severe and treatment varies depending on the severity of the disease. Typically, a doctor will perform a series of tests before confirming CD. These tests may include a physical exam, lab tests, stool samples, CT scans, MRI, endoscopy and a colonoscopy (Baumgart & Sandborn, 2012), in which a small flexible camera is inserted through the rectum to distinguish abnormalities. Together, these tests detect abnormalities which may exist throughout the intestinal track thus indicating IBD.

While there is currently no known cure for CD, treatment options are available (Akobeng, 2008; Michail et al. 2013). It is estimated that roughly ten percent of patients who undergo surgery will have prolonged clinical remission (Baumgart, 2012; D’Incà & Caccaro, 2014). The goal of treatment is to reduce inflammation and to improve the prognosis by limiting complications (Newman & Sminovitch, 2003). Noninvasive treatment options include anti-inflammatory medication, antibiotics, and immunosuppressant drugs. Anti-inflammatory medication controls and suppresses inflammation, thereby decreasing the frequency of flare ups. With proper treatment over time, periods of remission can be extended, and flare ups can be reduced. Alternatively, immunosuppressant medications, such as corticosteroids, aid by suppressing the immune system, thus allowing the intestinal tissue to heal.

However, in some instances, more invasive treatment plans are required. Despite significant progress in treatments for CD, it’s estimated that as many as seventy-five to ninety percent of patients suffering from the disease will undergo surgery to relieve symptoms at some point during the patient’s life. (Politics & Government Week, 2017; Liu et al. 2017). At times, CD creates complications that are deemed a medical emergency, such as a bowel abscess, a fistula (which may result from an unaddressed abscess), uncontrolled bleeding, or intestinal blockage, in which case surgery may be required. As an aside, patients may also require surgery as a result of previous medications having caused severe side effects, or simply because the medications have stopped working as effectively as the body adapts and immunizes itself against the medication (Torres et al. 2017).

There are several types of surgeries that can be performed, the most common one being a bowel resection. This involves the removal of all parts of the damaged intestine and is performed when parts of the small bowel are diseased or blocked (Simon et al. 2003). A partial colectomy is another type of bowel resection in which the surgeon removes the damaged parts of the colon. It can be performed openly or laparoscopically. When performed openly, the surgeon manually cuts an extensive incision; alternatively, the surgeon may prefer to work laparoscopically, making several small incisions, thereby allowing him to work outside the body. In some instances, a total colectomy is required in which the surgeon...
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removes the entire colon. This is generally required only in severe cases in which the colon is highly inflamed, and medication is ineffective (Travis et al. 2011). A colectomy often requires further procedures to reattach the disconnected portions of the digestive system, thus permitting waste to leave the body. For example, in some instances, an ostomy is performed. This surgery is categorized as a lifesaving procedure as it is performed when stool is unable to be eliminated from the body through the rectum (Travis et al. 2011). In this procedure, the colon is removed, and a stoma is created on the abdomen. Wastes are then allowed to pass through the surgically created stoma into an ostomy bag, a prosthetic bag which holds stool and can be emptied regularly.

Common risk factors of these surgeries include bleeding, bowel obstruction, infection and pulmonary embolism.

Methods

Data was collected using ProQuest and PubMed databases through Touro College's online library. Among the key-phrases used were “Crohn’s Disease”, “irritable bowel disorder”, “epigenetics”, as well as “hygiene hypothesis.”

Genetic Factors

There is a significant amount of evidence suggesting that genetic factors play a key role in the triggers of IBD. Genetic mutations lead to the body’s defective defense against microbes in the digestive system, allowing the immune system to attack the lining of the digestive tract, thereby causing inflammation indicating IBD. The genetic analysis of complex diseases, such as IBD, is difficult to identify for several reasons. First, the disease isn’t categorized into a single entity, but rather into groups of heterogeneous disorders, where environmental and genetic factors play a significant role in disease expression. Additionally, ethnic differences that may exist between patients suffering with IBD are associated with different mutations (Bae et al. 2014). Other difficulties faced include the relatively low frequency of IBD, about 1-4 percent, amongst populations (Michail et al. 2013); statistics showing that only about ten percent, first-degree relatives are affected with the same disorder (Sartor, 2006; Pena, 1998); as well as the presence of genes with minor genetic effects, are some of the difficulties faced with when identifying disease susceptibility. Nevertheless, there is an emerging understanding of the inherited aspects that predispose an individual to IBD (Newman & Siminovich, 2003).

The evidence for genetic involvement in IBD comes from ethnic e.g., Ashkenazic Jews and family-based studies on blood relatives affected with CD, associations of IBD with known genetic syndromes, diseases with known genetic predisposition such as autoimmune diseases, and more recently through genetic marker studies (Barber GE, Yajnik V, Khalili H, et al. 2016). Various genetic markers have shown different levels of correlation with IBD. Some have failed to show a consistent association with IBD, including blood groups, secretor status, a l-antitrypsin, and immunoglobulin marker genes. Studies on these markers can be divided into those in which a genetic element is proven and those in which a genetic predisposition may be present (Pena, 1998). Several polymorphisms in the genes encoding different cytokines and their receptors have been described and are potential candidates to be studied scientifically.

There are currently multiple studies being carried out to help identify the genetic mutations, causes, and susceptibility in developing IBD. In addition, technological progress in genetic testing and DNA sequencing permitted many genome-wide association studies (GWAS), which helped identify new single nucleotide polymorphisms (Loddo & Romano, 2015). Correspondingly, over the past few decades, there have been significant advances in the understanding of genetic causes linked to IBD. (Newman & Siminovich, 2003). The studies described below are population-based studies in areas that extend over a period of time, making them most likely to give fair, unbiased results. These studies have confirmed the increased prevalence of IBD in family members as compared to those in the general population. These include studies based on twins, families, and the Jewish Ashkenazic ethnic group.

The data derived from studies performed on twins powerfully supports the view that IBD is linked to a genetic component. There is a significant increase in the concordance of IBD in monozygotic twins compared to dizygotic twins, particularly with Crohn’s disease. Twin studies for CD have shown fifty percent concordance in monozygotic twins compared to less than ten percent in dizygotic twins (Loddo & Romano, 2015). Environment plays only a negligible role in predisposition for CD. Indirect evidence supporting the necessity of predisposing genes for the development of the disease in the presence of a common environment is the low prevalence in spouses of patients with IBD. Spouses who both suffer from CD, is deemed as a highly unusual occurrence, as frequent as can be expected by chance alone (Dudley, 1995).

Family-based studies consist of studying linkage analysis in sibling pairs and parental transmission in genome-wide screening using microsatellite markers. Microsatellite markers, otherwise known as simple sequence repeats (SSRs), which can be defined as segments of DNA where the nucleotide sequence repeats. Familial aggregation of IBD has been well documented in North American and European studies. It is well established that first degree relatives, particularly siblings, are at much greater risk in
developing IBD as compared to those in the general population. For example, if one parent has CD, the child has a ten percent increased risk in developing CD; and even if both parents suffer from CD, that likelihood increases to thirty-five percent (Pena, 1998). It has been shown that siblings of patients suffering from CD experience a seventeen to thirty-five times greater likelihood of developing CD (Akobeng, 2008).

Another significant study performed on ethnic populations proved that genetic variants are indeed associated with CD. People of Ashkenazi Jewish heritage have an increased risk and a higher prevalence in developing CD as compared to non-Jews (Baumgart & Sandborn, 2012; Newman & Siminovitch, 2003). Several studies have proven that CD is two-to-four times more prevalent among individuals of Jewish decent compared to non-Jewish Europeans living in the same area (NewsRX Health & Science, 2012). Currently, there are seventy-one genetic variants that have been identified in Ashkenazi Jewish ancestry that increase an individual’s risk of developing CD (Baumgart & Sandborn, 2012). In a study performed examining over six thousand individuals whose Jewish ancestry was confirmed by a large number of genetic markers, several variants were detected that are associated with the increased risk of CD. The involvement of twelve recognized CD risk variants in Ashkenazi Jews was confirmed and identified in novel genetic regions, as opposed to in non-Jewish European populations (Kenny et al. 2012). Further studies of these regions may aid in the discovery of biological pathways affecting susceptibility to CD and lead to the development of innovative and more effective treatments. This study not only proves the genetic origin of CD, but also demonstrates the value of genetic studies in secluded ethnicities, such as the Ashkenazim. Jewish heritage is an independent risk factor for developing CD. Genetic anticipation is the earlier onset of a disease in the offspring of parents with the disorder; a phenomenon featured in other genetic diseases, it has now been identified in Crohn’s (Polito et al. 1996).

While genetic studies have been highly successful at identifying the genetic risk factors for CD, these studies have proven virtually nothing about why one person will exhibit only mild symptoms of CD while another patient may require surgery to treat their condition. However, a familial link is often noticed in the symptoms of related patients. Researchers recognize that family members with CD often tend to have similar progress through treatments (NewsRX, 2017). Furthermore, researchers looked at the genome of two thousand seven hundred patients who shared similar symptoms and severity of CD. By comparing these patient’s DNA, the researchers discovered four genetic variants including FOX10, IGFBP1, MHC, and XACT that influence the severity of a patient’s condition. Strikingly, none of these genes have been shown to affect the risk of developing CD. This fact suggests that it is likely that genetics not only plays a role in the diagnosis of CD, but in the patient’s prognosis as well (Obesity, Fitness & Wellness Week, 2017).

Environmental Factors

Although the precise cause for CD is unknown, it’s believed that environmental factors also play a role in the development of the disease. Several environmental risk factors, such poor diet, as well as the side effects of breastfeeding, smoking, stress, and drugs, are believed to trigger inflammation. Additionally, childhood exposure towards an overly hygienic environment, seem to allow CD to manifest in predisposed patients.

Food is believed to promote the maintenance of gut integrity. Although the direct cause and effect relationship between the gut microbiota and IBD is unclear, targeting the intestinal microbiota allows for prevention of disease, as well as potential research concerning new treatments. Diet plays a significant role in a patient suffering from CD, as the body is unable to digest and absorb food appropriately, thereby causing malnourishment in patients with CD (O’Sullivan, 2009). Furthermore, many patients with CD are anemic, as well as deficient in vitamin D, folic acid and vitamin B12 (Torres et al. 2017; Creek, 2017). Patients are recommended to avoid certain foods such as raw fruits and vegetables, dairy, fatty, greasy, spicy, and high fiber foods, as these foods are more difficult for the body to digest and absorb, and commonly irritate the bowel (Livie et al. 2006). While it has not been proven that a poor diet is a direct cause of CD, research has shown a common thread, that a proper diet is helpful in several ways by reducing one’s predisposition to developing CD. Moreover, diet has also been used as a treatment option for CD (Akobeng, 2012). Similar research has proven that maintaining a healthy diet is equally as effective as putting a patient in remission as corticosteroid treatments, particularly in the case of children (BMJ, 1997). Nutritional repletion is effective both by affecting the gut mucosa as well as by decreasing intestinal permeability. There is some evidence that the enteral diet has a direct effect on the gut mucosa by reducing cytokine production and the accompanying inflammation, thus leading to decreased intestinal permeability (Hanaway, 2006).

Breastfeeding promotes colonization with microbiota such as Bifidobacteria by providing them with the HMOs (human milk oligosaccharides) they require to thrive. According to one study, when specific HMOs, GOs
(short-chain galactooligosaccharides) and FOSs (long-chain fructooligosaccharides), were fed to infants in the first six months of life, they later had fewer incidences of autoimmune reactions linked to gut microbiota, including recurrent wheezing, and allergic urticaria. Accordingly, Crohn's which is an autoimmune disease, may be affected similarly by breastfeeding (Torres, et al. 2017). Maternal secretory IgA, a component of breast milk has been proven to affect the composition of intestinal microbiota and the expression of genes associated with intestinal inflammation. Additionally, a negative correlation has been found between infants’ exposure to breast milk and the development of early onset IBD, suggesting breastfeeding has a preventative effect on IBD development (Stiemsma et al. 2015).

While cigarette smoking is notorious for initiating health risks such as lung cancer and heart disease, it is believed to play a role in the development of IBD as well. Although the pathogenesis for IBD is unclear, cigarette smoking is associated with IBD outcomes as it exacerbates the condition. Analysis of multiple studies has confirmed that active smokers are at increased risk for acquiring CD (Newman & Siminovitch, 2003). Furthermore, smoking has repeatedly been proven to worsen the progression of CD as it promotes a fistulizing phenotype, aggravates disease course, and produces a decreased response to medical treatment. (Ole et al. 2009). Interestingly, while smoking has negative ramifications for Crohn’s sufferers, it may have a protective effect on those with a genetic disposition towards UC. Active smokers were proven to be at a lower risk for developing UC in comparison to those who never smoked and those who quit smoking. This phenomenon may be linked to nicotinic acetylcholine receptors, which are present in mucosal epithelial cells of the bowel, as well as on T cells. However, clinical trials of nicotine replacement in IBD have only yielded a modest benefit at best; thus, nicotine alone may not be the driving factor (Ole et al. 2009).

Despite the significant consequences of smoking associated with patients suffering from IBD pathogenesis, the highest incidence of CD occurs in countries with a low prevalence of smoking such as United States and Canada (Rook, 2012). Furthermore, the majority of patients with CD are not current smokers and the majority of smokers do not develop CD, proving that smoking or lack thereof likely plays a role in the pathogenesis of only a subset of IBD patients (Torres et al. 2017). These studies display little correlation between smoking and IBD. Nonetheless, all IBD patients should be encouraged to quit smoking due to the deleterious negative health effects associated with smoking.

The role of psychological distress and personality as predisposing factors for the development of CD remains controversial. The debate concerning this matter has been ongoing for over eighty years without reaching a common ground, as attempts to investigate the role of psychological factors have unveiled conflicting results. However, over the past several years, it has become evident that psychological stress is at least associated with CD. However, that stress may be the result rather than the cause of chronic and longstanding CD. Unpredictable flare-ups and changes in body image can also lead to additional stress. This stress may precipitate an exacerbation of the disorder; thus continuing a vicious cycle of flare ups.

Multiple theories have been presented suggesting explanations on the unknown environmental exposures that may interact with the immune system and result in abnormal inflammatory intestinal response. However, the most predominant theory is the hygiene hypothesis, which explains the link between exposure to specific microbial allergies and the prevention of certain diseases. This hypothesis theorizes that when one’s childhood has had excess hygiene and a lack of exposure to enteric pathogens; the child may not develop sufficient immunity towards pollution and environmental contamination. Thus, it will inevitably impair microbial competence of the GI immune system and its ability to recognize new antigens, thereby predisposing children to immunologic disorders further on in life (Sabe et al. 2017). While the effect of lack of exposure is believed to be most profound during early childhood, the ideal timing and degree of exposure required remains unclear. The hygiene hypothesis also theorizes that multiple childhood infections and poor hygiene protects and prevents an individual from developing Crohn’s disease by allowing the host to develop tolerance or immunity to agents that may trigger Crohn’s disease later on in life (Stiemsma et al. 2015). Additionally, it is entirely probable that the impact of various exposures are not mutually exclusive; such that disease development depends on the dose-response interactions between exposures, and this reflects how strongly one’s exposure may protect or increase the risk conferred by CD susceptibility mutations) (Sabe et al. 2017).

Interestingly, the first Crohn’s disease gene identified, CARD 15(caspase-activation recruitment) also referred to as the NOD2 (nucleotide oligomerization domain gene), found within IBD1 locus is involved with the innate immune system and the response of monocytes upon perceiving a bacterial encounter. The abnormal and unconstrained inflammatory response that may occur in individuals with NOD2/CARD15 mutations is likely to be involved with the pathogenesis of Crohn’s disease. Polymorphisms in the CARD15/NOD2/IBD1 locus have been associated with the highest risk for CD.
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development. Recent evidence shows that polymorphisms cause reduced functionality of the immune system and exacerbated phenotype (Newman & Siminovitch, 2003). Counterintuitively, countries with poor sanitary conditions such as Africa and the Middle East reportedly have a relatively low frequency of Crohn’s disease (Torres et al. 2017), while more developed countries such as Canada and the United States have the highest rates of CD. It is believed that endemic parasitic infections may favorably affect the immune system as to prevent disease by stimulating T-helper type 2 (Th-2) cells, which in turn down-regulate Th-1 cells and prevent the exaggerated Th-1 response associated with Crohn’s disease. Building on this theory, the ova of Trichuris suis (eggs of a pig whipworm), have been successfully used to treat Crohn’s disease patients, as the intake of these parasites elicit Th-2 cells thereby suppressing Th-1 cells from activating (Guarnere et al. 2006; Summers, et al. 2005). Many physicians treating patients with IBD do not believe that stress or diet are direct causes of IBD. Yet, due to the lack of understanding of the etiology of IBD, no known direct cause and cure exist for the disease. The Crohn’s and Colitis Foundation and medical researchers suggest that foreign substances found in the environment or external agents such as bacteria may interact with a weak immune system, thereby producing an immune response of inflammation which the body is unable to stop (McGovern, Gardet, Törkvist, et al. 2007).

Epigenetics
It has become apparent that epigenetics plays a significant role contributing to the development of CD. Epigenetics can be defined as mitotically heritable changes in gene expression without shifting the DNA. Gene expression can be altered by changes to the structure and function of chromatin. Different cells in the body are characterized by different functions and different levels of gene expression despite each sharing the same genetic code. This variation in gene activity from cell to cell is achieved by mechanisms and processes that are collectively termed epigenetics. The main epigenetic mechanisms include DNA methylation, histone modification, RNA interference, and the positioning of nucleosomes. These epigenetic mechanisms, in particular DNA, allow the onset and reactivation of disease that’s triggered by environmental factors that rapidly break the mucosal barrier, thus stimulating an immune response or altering the balance between beneficial and pathogenic enteric bacteria. Different genetic abnormalities can lead to similar disease phenotypes; these genetic changes can be broadly characterized as causing defects in mucosal barrier function, immunoregulation or bacterial clearance. These new insights will help develop better diagnostic approaches that identify clinically important subsets of patients for whom the natural history of disease and response to treatment are predictable. Methylation appears to be of great importance in the interaction between genome and the environment. Variation in DNA methylation is a well-recognized cause of human disease and is likely to play a pivotal role in the cause of complex disorders such as CD.

Discussion and Conclusion
Inflammatory bowel disease is sectioned into two divisions, CD and UC. Both are complex multifactorial disorders characterized by chronic relapsing intestinal inflammation. However, the etiology of both diseases remains largely unknown as it is characterized as an idiopathic disease (Sartor, 2006). Understanding the causes and molecular mechanisms of CD and UC is a leading challenge in gastroenterology research, due in part to the relatively low frequency of these disorders. Although significant effort has been made to help identify genetic and environmental factors that may increase the risk of IBD, little is known about IBD-specific factors. Recent research has suggested that IBD is caused by a complex interplay between genetic predispositions of various genes, combined with an abnormal interaction with environmental factors as a result of a perceived threat. Epidemiological evidence for a genetic contribution is made apparent by twin and family studies of CD patients. Genetic variants that stimulate IBD have a substantial effect on gene function. These variants are so rare in allele frequency, that the genetic signals aren’t detected in genome-wide association studies of patients with IBD. With recent advances in sequencing techniques, roughly fifty genetic disorders have been identified and associated with IBD such as osteoporosis as well as thyroid disease. Monogenic defects have been found to alter intestinal immune homeostasis through many mechanisms. Candidate gene resequencing should be carried out in early-onset patients in clinical practice.

The evidence that genetic factors are the prime contributors to disease pathogenesis confirms the insignificant role of microbial and environmental factors. Epigenetic factors can mediate interactions between environment and genome. Epigenetic mechanisms could affect development and progression of IBD. Epigenomics is an emerging field, and future studies could provide further insight into the pathogenesis of IBD.

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