Crohn's Disease Pathogenesis: Is It More than Just Genetics?

Mckenzy Klocker

Department of Biology, University of Minnesota Duluth

Abstract

About 1.4 million American's suffer from Crohn's disease, a relapsing, systemic inflammatory disease of the gastrointestinal tract. Despite ongoing research, the etiology of Crohn's disease remains uncertain and Crohn's disease has continued to be on the rise. However, research in genetics, microbial dysbiosis, and environmental influences have provided new insights on disease development. Studies have identified that affected patients have an impaired intestinal barrier associated with NOD2/CARD15 gene, reduced antimicrobial activity, and various environmental factors, all of which may trigger Crohn's disease. These studies indicate that those who are genetically susceptible must also be influenced by various environmental and immune factors. Future studies should aim toward identifying risk factors in order to reduce flare ups and develop more effective treatment. Understanding the pathogenesis of Crohn's disease can help lead to more efficient diagnosis, prevent permanent damage, and help choose the best form of treatment for each patient.

INTRODUCTION

Irritable Bowel Disease (IBD) is a term used to categorize idiopathic conditions relating to recurrent immune response and gastrointestinal (GI) tract inflammation. IBD is characterized by loss of tolerance in the intestinal immune system, resulting in overactive immune activation. This overactive response leads to chronic inflammation and tissue damage (Russo et al. 2012). Crohn's Disease (CD) is one subtype of IBD. As CD diagnosis increases among the U.S. population, loose ends in its etiology remain. Many observations support the idea that genetics influence changes to the microbial composition in the gut (Oberc and Coombes 2015).

The most recent findings provide increasing evidence that CD emerges in genetically susceptible people who develop a relapsing inflammatory response to their intestinal microbiota. Progression of the disease is thereby influenced by environmental stimuli, contributing to the rapid increase in CD diagnosis (Uhlig et al. 2014).

This review will provide an overview on the symptoms and mechanisms of CD. Additionally, this review summarizes clinical studies to demonstrate the relationship between pathogenesis and genetic predisposition. These studies seem to come to a similar conclusion that environmental exposures may increase the risk of disease, especially for those with genetic predisposition (Peloguin et al. 2016). However, there have yet to be any advances made in defining such environmental exposures. With that, I will suggest 1) an aim for future studies on the impacts of such factors and 2) how a better understanding of the microbial component of CD may be useful for treatment, in order to prevent risk exposures to susceptible individuals, eliminate harmful microbes, and restore a functional and protective gut barrier.

Corresponding Author:
Mckenzy Klocker
klock051@d.umn.edu

WHAT IS CROHN'S DISEASE? AN IN-DEPTH LOOK AT THE DANGEROUS SYMPTOMS

As previously stated, Crohn's Disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract. Effects of the disease may be seen on any part of the GI tract, but are most common in the ileum of the small intestine. Symptoms may vary depending on the patient or severity, but typically include "flare-ups" of inflammation, abdominal pain, nausea, diarrhea, weight loss, or even growth impairment in adolescent cases. If left untreated, necrosis of the intestinal tissue may ultimately result (Batra et al. 2012).

Although drug treatments are available to delay flare-ups, no drug treatments are available for curative effects of the disease (Rath et al. 2015). Treatment of CD typically involves the use of anti-inflammatory, non-steroidal drugs (NSAIDS) that aim to alleviate side effects. Consumption of certain dietary fibers and probiotics may be recommended as a therapeutic approach, in order to amplify butyrate production in the colon of CD patients (Russo et al. 2012). Surgery or fecal transplant may be required in severe cases to attempt restoration of the microbiome; however, this approach is still not curative.

The small intestine is critical to nutrient absorption, and many people with CD do not digest and absorb nutrients properly. Specifically, the ileum of the small intestine has been shown to be associated with alterations in carbohydrate metabolism and bacterial-host interactions, as well as in human host secreted enzymes (McKee 2015). Cells that line the small intestine are composed of enzymes responsible for aid in digestion. When these enzymes become deficient, unpleasant symptoms similar to those seen in CD, may result due to the alternative pathway of undigested particles. This enzyme deficiency is the reason behind the production of gas, bloating, or cramps (Mckee 2015).

Since CD is a disease pertaining to the immune system, it is medically classified as an autoimmune disorder. In other words, the body's own immune system is working against itself (Rath et al. 2015). Again, this is the cause for inflammation of the GI tract. The sharp rise in CD indicates that genetics alone does not fully explain disease development, suggesting environmental risk factors may be a precursor to CD. Research has suggested that environmental risk factors result in the loss of butyrate production inside the gut (Oberc and Coombes 2015). Such factors include smoking, use of NSAIDS, hygiene, and caesarian section births. An additional factor may be diet similar to those adopted in westernized countries. Moreover, these factors are thought to be attributed to the increased incidence of CD in young people (Peloguin 2016). With nearly 30,000 cases diagnosed annually, about 25% of these cases are people under the age of 20 years (Rath et al. 2015).

Overall, the most widely accepted hypothesis on CD development is that symptoms are attributed to overactive immune response by T-cells to bacterial agents in the gut lumen (Bandzar et al. 2013). Normally, apoptosis, or cell death, is the controlling factor of T-cell lymphocytes within the body (Bandzar et al. 2013). The molecules that begin the body's immune response are called antigens. Apoptosis plays an important role following antigen-specific lymphocyte activation. This activation causes a majority of these T-cells to undergo apoptosis. Without this apoptosis of T-cells through lymphocyte control, the development of lesions in the mucosal lining may result. Thus, mucosal lesions are commonly seen in prolonged cases of CD (Bandzar et al. 2013).

GENETIC SUSCEPTIBILITY

A vast amount of CD research is dedicated to the area of genetics and family history of CD, which commonly involves in the body's immune response. This research has been

important for understanding the genetic components of CD. Genome-wide association studies have found nearly 100 loci that are specifically associated with CD, compromising various genes and mechanisms within the gut. These mechanisms include microbe loss, lymphocyte activation, cell signaling, and intestinal barrier function (Cho and Brant 2011).

The first susceptibility gene for CD was discovered in 2001 (Cho and Brant 2011). This gene, known as NOD2/CARD15, is an intracellular protein in the pro-inflammatory nuclear factor kappa B (NFkB) pathway. It is responsible for cell apoptosis and signaling the production of defensins (Ogura et al. 2011). Variations in NOD2, as described in CD patients, may disrupt the ability of cells lining the small intestine to respond appropriately to bacteria, thus leading to inflammation and the digestive dysfunctions that are characteristic of CD (Batra et al. 2011). At least one mutation in NOD2 is present in nearly 30-40% of CD cases, as compared to 6-7% present in non-diseased controls (Anderson 2014).

Since the discovery of NOD2, research has continued to identify and confirm multiple susceptibility loci for CD that also play an important role for autophagy in immune response. Similar to NOD2, these genes have been correlated to an increased risk of CD (Cho and Brant 2011).

In addition to susceptibility loci, research in CD family history has provided evidence to suggest that having an affected relative is an important risk factor to the onset of CD. Those who have a first degree relative with CD have a 20% greater risk of developing the disease themselves (Loddo and Romano 2015). Moreover, an increased incidence of CD diagnosis in adolescents has been observed, with nearly 25% of patients being diagnosed before the age of 16 (Peloguin 2016). To demonstrate the relationship between susceptibility loci and disturbed pathways of the intestinal immune system, Buhner et al. (2006) performed a clinical study using an allele-specific PCR assay to a type 3020insC frameshift mutation in NOD2/CARD15. They examined patients with dormant CD and compared first degree relatives (CD-R), non-related household members (CD-NR), and healthy controls.

These findings (Buhner et al. 2006) showed that CD-R displayed overall increased intestinal permeability in contrast to CD-NR and control groups. Additionally, the presence of NOD2/CARD15 3020insC mutation was consistent in CD patients, and CD-R, and was higher than that of controls. Finally, a greater mucosal permeability and the presence of the NOD2/CARD15 3020insC mutation were significant in CD-R (Table 1). These results support the idea that increased gut permeability is partly due to genetic predisposition.

This study concluded that increased intestinal permeability is associated with variations in the NOD2/CARD 15 gene, therefore supporting the hypothesis of genetic predisposition to CD. However, the complete description of NOD2/CARD15, like other genes associated with CD, is far from complete. Many of these genes require further confirmation of their association with CD, as their significance in influencing disease course remains uncertain.

Table 1: Prevalence of NOD2/CARD15 3020insC mutations (Buhner et al. 2006).

Genotype	Control	CD	CD-R	CD-NR
3020insC	n=62	n=121	n=106	n=50
Heterozygous Mutant	2%	18%	22%	10%
Homozygous Mutant	0%	4%	1%	2%

MICROBIOME

Although genetics may be the most understood component, genes are only one factor of how CD emerges. The intestinal microbiota is a key component to CD pathogenesis (Cruz

et al. 2015). In the human body, the intestinal microbiota has an incredibly large impact on overall health, participating in metabolic, nutritional, physiological, and immunological processes. It plays a key role in defense against pathogens by the production of antimicrobial compounds. Additionally, the microbiota is responsible for maintaining the GI tract's mucosal immunity (Gerritsen et al. 2011).

The composition of the intestinal microbiota is acquired before birth and is shaped throughout development. Perinatal factors (including caesarian sections, diet, and environment) are factors that may influence microbes that colonize the gut (Rodriguez et al. 2015). From a persons birth, microbiome diversity will both expand and converges to a more-so established composition by the age of 5 . Once composition is established, the microbiome remains fairly stable, unless alternately influenced by infection, antibiotics, diet changes, poor lifestyle, etc. (Rodriguez et al. 2015).

Throughout the last decade, a role for gut microbes in the development of CD has been indicated by a number of studies. It is thought that the gut microbiota is an essential component to the development of mucosal lesions, a common symptom of CD (Manichanh et al. 2012). Inflammation of the intestine is generally believed to be associated with reduced complexity of bacterial species diversity. Individuals with CD typically exhibit a decrease in the phylas *Bacteroidetes* and *Firmicutes,* and an increase in *Proteobacteria*, which commonly includes *Escherichia coli*, *Salmonella*, *Helicobacter* and *Vibrio* (Gevers et al. 2014).

Culture-independent studies conducted by Manichanh et al. (2012) have compared the intestinal microbiota of CD patients with that of healthy individuals. Studies such as this have provided evidence that butyrate-producing bacteria, particularly those belonging to the phylum *Firmicutes*, exist in smaller numbers within CD compared to healthy individuals. This lack of butyrate producing bacteria initiates microbiome dysbiosis, which is a common trend in CD pathogenesis (Manichanh et al. 2012).

Butyrate is a short-chain fatty acid (SCFA) produced by bacterial fermentation of undigested dietary carbohydrates from the small intestine (Wexler 2007). It is present in high concentrations within the lumen of the large intestine, and serves as an energy supply via anaerobic fermentation. Among many functions, butyrate also plays a regulatory role in GI tract mucosal inflammation and oxidative stress. Butyrate production also maintains the epithelial defense barrier (Figure 1) (Wehkamp et al. 2011). The ability to produce butyrate is particularly important to CD, as butyrate decreases pro-inflammatory cytokine expression by inhibiting NFkB activation and maintaining homeostasis (Canani et al. 2011).
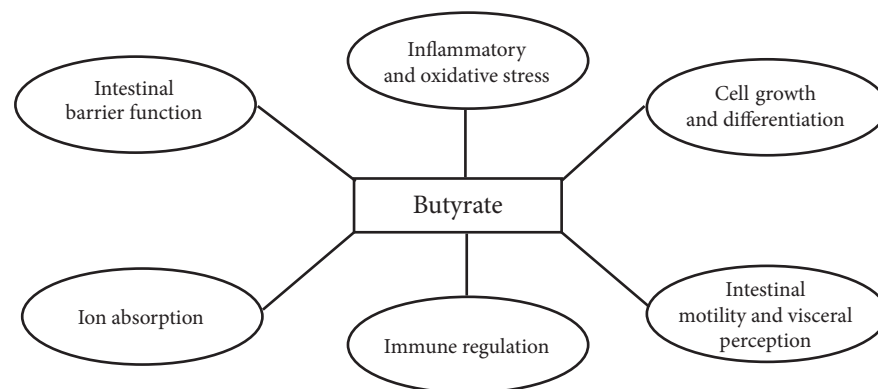
Figure 1: The roles of Butyrate production within the microbiome. The pathways which butyrate producing bacteria play a role in various processes in the gut.

To demonstrate the importance of butyrate production, Joossens et al. (2011) conducted a study on families with at least three members affected with CD. Fecal sample compositions were observed between CD patients, unaffected first-degree relatives of CD patients, and healthy controls. Results did indicate that both CD patients and unaffected first-degree relatives display altered composition of predominant microbiota in comparison to healthy controls. However, difference between CD patients and the healthy controls came down to the presence/absence of the butyrate producing bacteria (Figure 2) *Faecalibacterium prausnitzii* (Joossens et al. 2011). Overall, the role of butyrate supports the idea that genetics alone are not in fact primarily responsible for CD, as reduced butyrate production is required in order to express the disease.
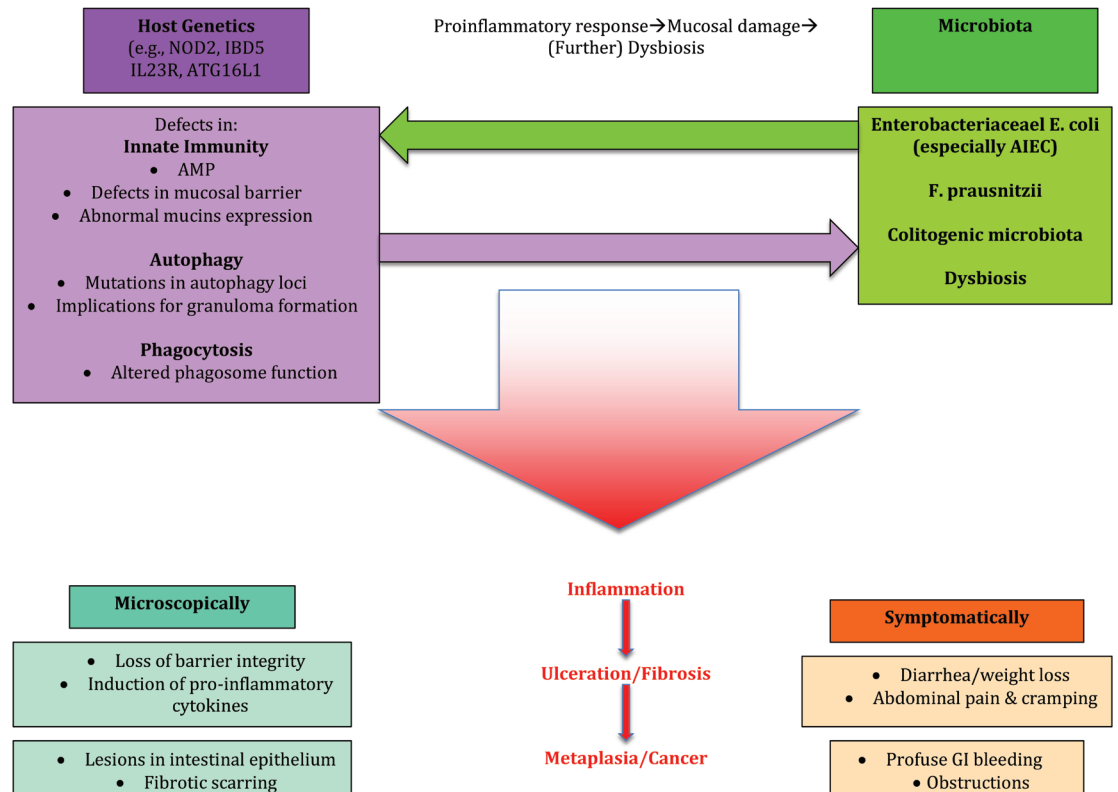
Figure 2: The role of the microbiome in CD. An interplay between the host microbiota and genetics (plus external factors not included in this figure). The result is prolonged inflammatory damage due to inflammation.

REDUCED ANTIMICROBIAL ACTIVITY

The intestinal tract comprises a large surface inside of the human body and harbors the complex microbial community that plays a central role in human health. Our gut contains an estimated 1000 bacterial species and 100-fold more genes than found in the human genome (Qin et al. 2010). It is constantly being exposed to microorganisms from the environment and to an indescribable amount of bacteria. Paneth cell defensins are a key player for regulation of the microbiome in spite of this exposure to various microorganisms (Wehkamp and Stange 2011).

Paneth cells reside in the small intestine and serve as host defense by producing antimicrobial peptides (AMPs) that are essential for barrier function. In the healthy intestine, there is a balance of host AMPs and intestinal microbes. CD patients, on the other hand, possess a comprised antimicrobial barrier function as a result of reduced expression by these peptides (Stankovic et al. 2015). This insufficient expression and function of AMPs

allows intestinal microbes to invade, provoking the inflammatory response, thus inciting CD (Wehkamp and Stange 2010).

This inflammatory defense by NOD2 plays a role in promoting the expression and secretion of defensins in the paneth cells by inducing the NFkB pathway that ultimately leads to the expression of α-defensins. As described above, NOD2 is over-expressed in CD. Mutations in NOD2 display insufficient NFkB activity, clarifying the decreased α-defensins expression in CD (Wehkamp and Stange 2010).

To demonstrate the effects of loci such as NOD2 to paneth cells, a retrospective analysis of fecal samples by CD patients were collected and analyzed, where the phenotypes of paneth cells were classified as normal or abnormal (VanDussen et al. 2013). Similarly, this study concluded that a greater proportion of reduced paneth cells are associated with CD patients exhibiting a mutation in NOD2 (VanDussen et al. 2013).

IMPACTS OF THE ENVIRONMENT

Environmental factors have been tied to the destruction of the mucosal barrier function in the small intestine. Environmental factors contribute to dysbiosis of the microbiome residing in the human gut and are necessary contributors to CD development (Figure 3) (Manichanh et al. 2012). Dysbiosis is hypothesized to arise from a response by the microbiome to environmental stressors. However, advances in identifying which environmental factors have yet to be made and confirmed.
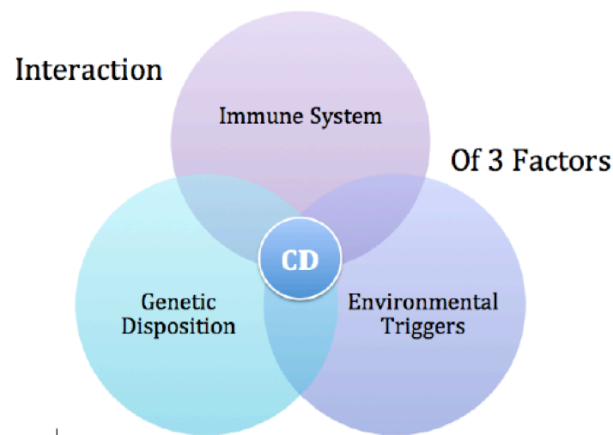
Figure 2: The role of the microbiome in CD. An interplay between the host microbiota and genetics (plus external factors not included in this figure). The result is prolonged inflammatory damage due to inflammation.

Genetic studies have identified various genes that may predispose for CD. However, this alone cannot be responsible for the sharp rise and increased incidence of CD in younger ages. Furthermore, it is known that genetic predisposition must occur in conjunction with a poor microbiome in order to express CD (Marchesi et al. 2016). The next questions to ask are how are we contributing to our microbiome? Could the lifestyle habits in more developed countries be linked with microbial colonization foreshadowing disease pathogenesis?

Environmental factors that may be linked to CD arise from the Western lifestyle and have been suggested as a predisposition to CD (Durchschein et al. 2016). These factors include smoking, hygiene, diet, and use of NSAIDs. Antibiotics are a common form of treatment for CD; the main antibiotics being corticosteroids, anti-metabolite agents, or antibodies directed against immune proteins with the intent of chronic immunosuppression. Furthermore, many CD patients incorporate dietary modifications as part of their

therapeutic management (Durchschein et al. 2016). According to Sartor et al. (2012), one factor that has changed significantly in parallel with the increased incidence of CD is diet. This assumption is evident based upon changes in microbiome composition when using a controlled feeding study of a high-fat/low fiber or low-fat/high fiber diet. High dietary intake of total fats and meat has been associated with increased risk of CD (Wu et al. 2011). In addition, the long term intake of dietary fiber has been linked to a decreased risk of CD (Wu et al. 2011).

Among these environmental factors, diet would seem to be most easily modified, making it a potential target for disease prevention and treatment. Diet is a critical component to human health, partly by modulating gut microbiome composition (Wu et al. 2011). Within the past few decades, the consumption of milk products has increased greatly. Various mouse models have demonstrated that dietary milk fat accelerates CD symptoms (Durchschein et al. 2016). Additionally, fructose intake continues to rise due to the abundance of processed food consumption. These examples suggest that dietary factors play an important role in disease development. This development is due to the interaction of particular nutrients and metabolites which influence host-microbiome interactions, thus exacerbating inflammation (Albenberg 2014).

Various therapeutic strategies exist in order to avoid disruption of the microbiome. Among these strategies, dietary modifications aim to preserve the "good" bacteria within the microbiome, such as the butyrate producers discussed earlier. Another therapeutic method recommended is limiting the use of antibiotics, as they may influence the microbial imbalance in the microbiome to be more pronounced (Durchschein et al. 2016).

CONCLUSION

Crohn's disease is a chronic, relapsing systemic inflammatory disease of the GI tract. The development of CD involves correlation between genetic predisposition and environmental influence. In other words, a genetically susceptible person needs to be influenced by environmental factors, along with dysbiosis of the microbiome, in order to express CD. Although drug treatments are available to delay flare-ups, no drug treatments are available for curative effects of the disease (Rath et al. 2015).

We currently know that CD may arise due to various susceptibility loci such as NOD2, or a reduced complexity of bacterial species diversity among the microbiome, particularly by a loss of butyrate producers. In addition, reduced antimicrobial activity may result due to mutations in NOD2 causing insufficient NFkB activity. In connection to all of this, environmental factors have been tied to destruction of the mucosal barrier function and dysbiosis between bacterial species residing in the human gut (Manichanh et al. 2012). The most important environmental factors are thought to be diet and the use of NSAIDs, which have arisen from a more modernized, western lifestyle (Durchschein et al. 2016).

It remains largely unknown whether severity of dysbiosis in the gut is a cause of, or a response to, the disease. Additional studies would not only be beneficial, but necessary in order to define environmental factors more concisely. Additionally, evidence suggests that the microbiome is over looked in terms of its significance to the contribution of CD. If the content of our microbiota is indeed determined by more than genetics alone, then the aim to integrate an individual's microbiome is necessary in order to better understand CD pathogenesis. This may lead to more efficient diagnoses, prevent permanent damage, and help choose a proper method of treatment for each patient.

BIOGRAPHY

Mckenzy Klocker is a senior at the University of Minnesota Duluth. She is working to complete her Bachelors of Science in biology with a minor in chemistry, and an emphasis on health education. From there, she hopes to pursue a career in dentistry. In her free time, she enjoys spending time with friends and family, fishing, reading, running, and cooking.

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