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Causes of Crohn's Disease

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ABSTRACT

Crohn's Disease is a type of inflammatory bowel disease that affects the small intestine. The causes of Crohn's Disease are not fully known, but research has shown that the main causes are an immune response due to the overproduction of signaling molecules, environmental factors and lifestyle, and a person's genetics/microbial environment. A hyper-inflammatory immune response causing immune cells to attack intestinal epithelial cells due to the overproduction of cytokines can result in discomfort for the patient and can even cause perforations in the intestinal epithelial layer. There has also been work that shows a correlation between a person's diet and the development of Crohn's Disease. Diets containing high levels of fat and sugar have been shown to negatively affect the small intestine, whereas diets high in fiber have prompted protective effects against Crohn's Disease. Additionally, smoking has been shown to have adverse effects on the small intestine since the inhaled chemicals can break down the protective mucosal layer, leaving the epithelial cells in the intestine more susceptible to damage and inflammation. Crohn's Disease has also been found in patients who have decreased biodiversity in the small intestine. Lastly, genetics have been shown to hold a significant link in the prevalence of Crohn's Disease. In this review, we will discuss the mechanisms behind the key causes of Crohn's Disease as well as discuss future research into Crohn's Disease, focusing more on finding biological cures to the disease to prevent it from being passed down.

Introduction

Crohn's disease (CD) is a form of inflammatory bowel disease (IBD) that affects over 3 million people across the United States[1]. CD affects the small intestine and can lead to ulcers, bowel obstruction, fistulas, blood clots, malnutrition, and colon cancer. These complications typically leave Crohn's patients with side effects such as diarrhea, fever, fatigue, reduced appetite, weight loss, and most commonly abdominal pain and cramping[2]. Currently, research has shown that CD is linked to several causes: an immune response due to the overproduction of signaling molecules, environmental factors and lifestyle, and a person's genetics/microbial environment[3].

The most commonly used treatments for CD patients currently include: three anti-tumor necrosis factor (TNF)-antibodies-- adalimumab, infliximab, and certolizumab, anti-CD3 antibodies, and hematopoietic stem cell transplantation[4]. Some of these treatments work by suppressing the patient's immune system and the cells creating the immune response. These drugs also attempt to block different pathways of inflammation in the small intestine to quell some of the symptoms and let the intestine heal[5]. Current treatments have their limitations, though. For example, treatments do not completely eliminate symptoms of IBD, and patients sometimes have reactions to certain treatments. Additionally, approximately 30% of patients do not respond to anti-TNF medications[6]. This highlights the need to better understand the exact mechanisms that cause CD as well as the symptoms that accompany the disease. In the future, scientists aim to have personalized treatments for patients based on their prognostic factors in order to effectively treat CD[4]. In this review, we will highlight several main causes of CD and how furthering research could lead to improved treatments for patients

Overview of the intestine and immune response in CD

The intestine is a vital organ that is responsible for the digestion of food and reabsorption of nutrients in the body. Reabsorption is made possible by the intestine's structure, which is composed of 2 main layers: the mucosal layer and the epithelial layer. The mucosal layer acts as a support layer that works by coating the top of the intestinal epithelium to provide a physical layer of protection as well as house antimicrobial peptides, which prevent epithelial damage. The intestinal epithelium is responsible for food digestion and absorption of nutrients in our body. The epithelial layer is able to accomplish this function through the presence of villi structures, which aid in the absorption of nutrients for our body by increasing the surface area for food/nutrients to come in contact with the intestinal epithelium.

One way in which CD can affect the intestine is by triggering a hyper-inflammatory immune response against the epithelium. This occurs as a result of the overproduction of cell signaling molecules known as cytokines, which ultimately lead to the body's own response against the intestinal epithelial cells. Examples of cytokines that are most commonly overproduced in the body during these inflammatory reactions include TNF-alpha and IL-1. Inflammatory responses such as this can ultimately lead to complications for patients such as ulcers and fistulas by creating perforations, or tears in the epithelial lining.

The mechanism responsible for the innate inflammation observed in CD patients is the overproduction of cytokines, such as TNF-alpha and IL-1, which promote the recruitment of lymphocytes into the intestinal tissue (Figure 1). TNF-alpha works to recruit circulating lymphocytes by binding to neighboring endothelial cells, resulting in the expression of E-selectin, which binds E-selectin ligand on lymphocytes. This binding process allows for integrin receptors on the lymphocytes to bind to ICAM-1, which is expressed on endothelial cells, leading to stable arrest of the lymphocytes. Once a state of stable arrest is reached, lymphocytes may then migrate through the endothelial layer towards the site of infection. Ultimately, this process leads to the migration of innate lymphocytes into the neighboring tissues, which is what gives rise to many of the side effects of CD. This process is also observed in adaptive immune responses where T-cells follow the same migrational path into the tissue following migration into the bloodstream from the lymph nodes.

These inflammatory responses in the intestine cause the patient extreme discomfort and in some serious cases can lead to perforations in the epithelial layer. Although atypical, these perforations result as the intestinal wall weakens, leading to the release of waste products from the intestine into the abdominal cavity. This process can result in blood poisoning and sepsis, which are life-threatening conditions.

The creation of targeted medical approaches that could minimize inflammatory responses in the intestine would prove extremely beneficial in addressing CD symptoms. As mentioned previously, an estimated 30% of patients do not respond to anti TNF medications and other anti-inflammatory medications are not specific to the intestine, limiting their efficacy.

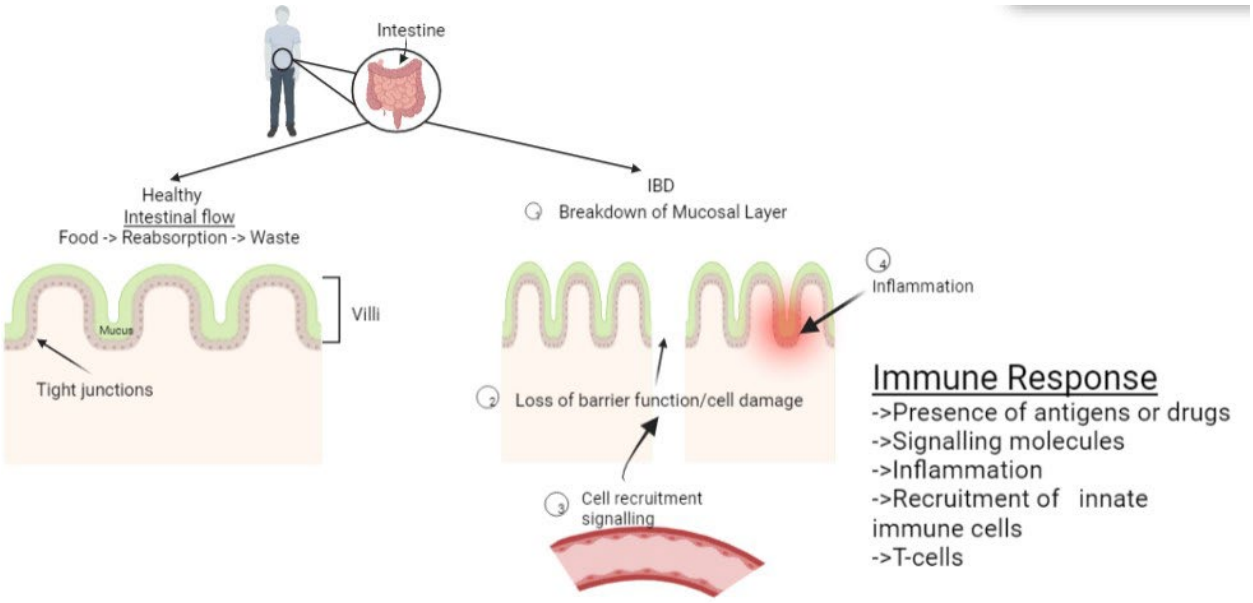

Figure 1. Impact of CD on intestine

Impact of environmental factors and lifestyle on CD

Other factors such as environment and lifestyle have been shown to play a role in CD. These factors primarily result from damage to the mucosal layer, and subsequently epithelial cell damage. Generally, people living in southern latitudes are 50% less likely to develop CD than people that live in northern latitudes. This is a result of the northern latitude community's diet and habits, which have shown to be higher in fats, sugars, and processed foods; all of which play an important role in the development of IBD[7].

It has been found that when a person's diet consists of high fat, sugar, or spice, they are more likely to develop CD (Figure 2). High fat diets adversely affect CD patient outcomes due to the buildup of fatty lipids in the intestine, leading to obstruction in the small intestine, making it unable to function correctly. Diets that are high in sugar elevate a patient's blood glucose levels, which can damage epithelial cells, leading to inflammation. This inflammation can lead to the development of CD. Additionally, diets that are high in spice can cause stomach cramps, abdominal pain, or diarrhea due to the increase in stomach acid caused by eating spicy foods. In a study performed in 2020, it was found that 53.4% of CD patients experienced a relapse of symptoms after consuming spicy food[8]. Lastly, diets that are high in fiber have been shown to prevent CD. This is because fiber increases gut motility and absorbs extra fluids in the gut, which help to alleviate diarrhea and prevent inflammation. Collectively, research on the correlation between diet and CD outcomes is important because it can lead to a better understanding of how different food groups affect patients. This in turn can translate to improved patient education for CD prevention and control.

Another factor that has been shown to play a role in CD is smoking. Active smokers have been shown to be more likely to develop CD than non-smokers, making smoking one of the most impactful environmental factors on the development of CD. Smoking in general has deleterious effects on the body, but it is enhanced in the small intestine. This results as the fumes and chemicals taken in when smoking travel through the body and break down parts of the small intestine, including the mucosal layer. The breakdown of the mucosal layer leaves the epithelial cells in the intestine more susceptible to damage and inflammation by the body's immune cells. Aside from inflammation, this also makes the small intestine more vulnerable to ulcers, making smoking one of the few confirmed risk factors of CD. Improving patient education on the impact of smoking and negative CD outcomes could have an impact on helping patients manage their CD during flare ups.

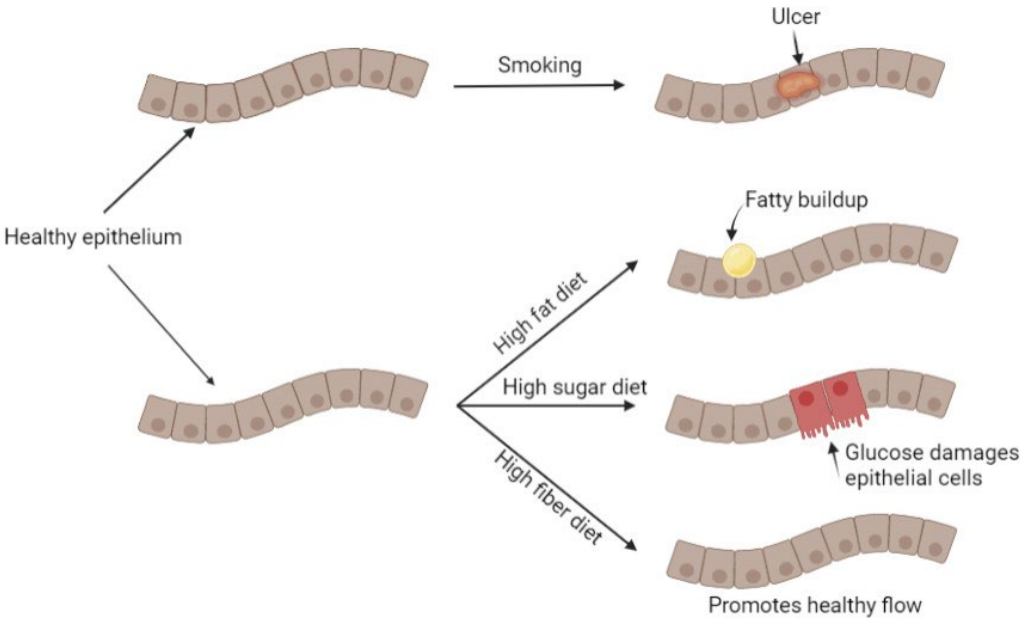

Figure 2. Effects of smoking and diet on intestinal epithelium

Microbial environment and genetics

The microbial environment plays a large role in intestinal health/homeostasis. In the small intestine, bacteria in the microbial environment have a great impact on the well-being of the intestine. Certain bacteria have been known to produce necessary vitamins, help with digestion, and protect the GI tract from pathogens. It has been shown that CD patients experience reduced biodiversity within the intestine. The decreased biodiversity leaves the small intestine more susceptible to damage as it can lead to dysbiosis, or an abnormal ratio between healthy and harmful bacteria[9]. Outside factors such as smoking and OTC/prescription drug use have been shown to play a large role in maintaining microbial homeostasis, with antibiotics representing a large problem.

Genetics have also been shown to play a significant role in CD. There was a nationwide German study done that showed over 35% of monozygotic twins, yet only 3% of dizygotic twins were concordant for CD[10]. This study highlighted the role of genetics in CD, as CD is often present in first-degree relatives of patients with CD. Research into this area has led to several advancements, with the impact of a specific mucus gene (mucin-1) laying a large role in CD outcomes[10]. As mentioned before, the mucosal layer plays a vital role in the protection of intestinal epithelial cells by providing a physical barrier against pathogens.

The breakdown of the mucosal layer can be caused by white blood cell degradation as well as genetic factors such as mucin-1 (MUC-1) deficiencies. MUC-1 deficiencies can leave the intestinal epithelial layer more susceptible to damage from factors such as bacteria and drugs (Figure 3). This deficient mucosal layer ultimately leads to epithelial damage and local inflammation, which collectively lead to the side effects of Crohn's disease. Research into understanding the specific mutations in MUC-1 that can adversely affect CD patients has led to new targeted genetic treatments that are being explored to correct this mutation.

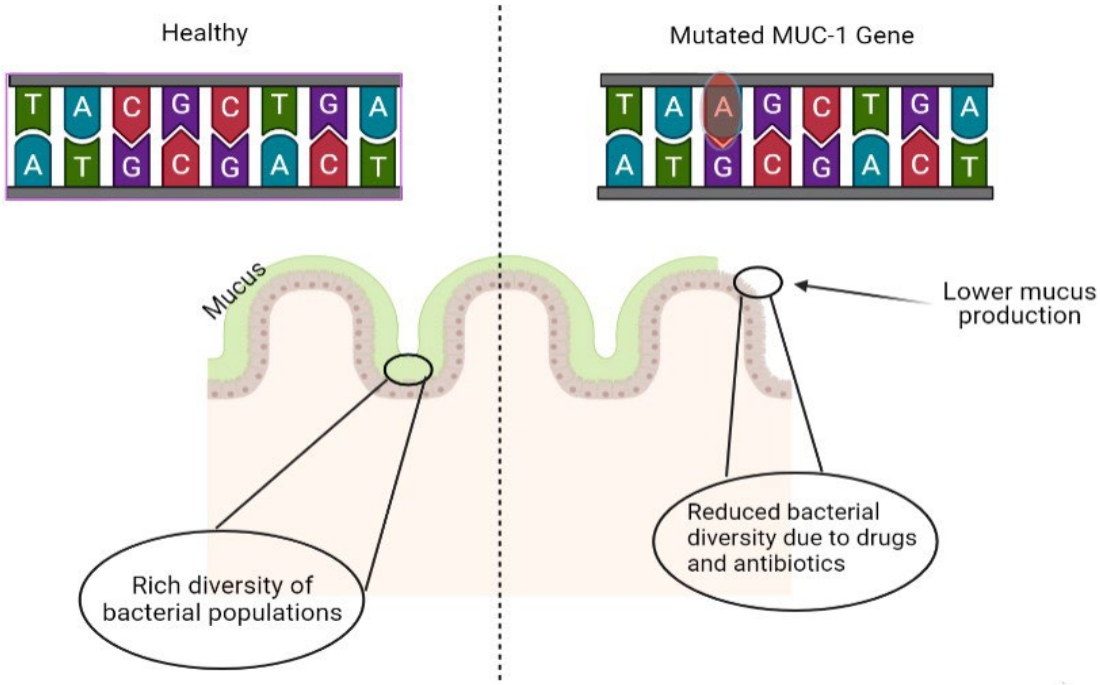

Figure 3. Mucin-1 mutations negatively impact mucus production, leaving intestinal epithelium more susceptible to damage

Conclusion

A type of IBD, Crohn's Disease affects the general function of the small intestine and can lead to many negative effects such as ulcers, bowel obstruction, fistulas, blood clots, malnutrition, and colon cancer[2]. While there are no confirmed causes of the disease currently, research has suggested that it is most likely caused by an immune response due to the overproduction of signaling molecules, environmental factors and lifestyle, and a person's genetics/microbial environment[3]. None of the current treatments for CD are able to completely eliminate the symptoms of CD. This highlights the importance of understanding the primary causes of CD in order to develop better solutions as well as educate patients as to how they can minimize their CD side effects through lifestyle changes. Research on CD in the future may be focused more towards finding a biological cure such as correcting MUC-1 mutations using genetic editing techniques to prevent CD from being passed on genetically. Additionally, as drug delivery techniques continue to advance, there is promise that future treatments may be able to address the causes/effects of CD through more accessible treatment options, such as an oral pill, rather than relying on infusion-based methods.

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References

[1] "Inflammatory Bowel Disease," cdc.gov, 2021. https://www.cdc.gov/ibd/data-statistics.htm.

[2] "Crohn's Disease," mayoclinic.org, 2020. https://www.mayoclinic.org/diseases-conditions/crohns-disease/symptoms-causes/syc-20353304.

[3] G. Roda et al., "Crohn's disease," Nat. Rev. Dis. Prim., 2020, doi: 10.1038/s41572-020-0156-2.

[4] S. Danese, M. Sans, and C. Fiocchi, "Inflammatory bowel disease: The role of environmental factors," Autoimmunity Reviews. 2004, doi: 10.1016/j.autrev.2004.03.002.

[5] L. Tsai et al., "Contemporary Risk of Surgery in Patients With Ulcerative Colitis and Crohn's Disease: A Meta-Analysis of Population-Based Cohorts," Clinical Gastroenterology and Hepatology. 2021, doi: 10.1016/j.cgh.2020.10.039.

[6] R. Mishra, P. Dhawan, A. S. Srivastava, and A. B. Singh, "Inflammatory bowel disease: Therapeutic limitations and prospective of the stem cell therapy," World J. Stem Cells, 2020, doi: 10.4252/wjsc.vl2.il0.1050.

[7] C. H. Lo et al., "Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis," Gastroenterology, 2020, doi: 10.1053/j.gastro.2020.05.011.

[8] A. Esmaillzadeh, A. H. Keshteli, M. Hajishafiee, A. Feizi, C. Feinle-Bisset, and P. Adibi, "Consumption of spicy foods and the prevalence of irritable bowel syndrome," World J. Gastroenterol., 2013, doi: 10.3748/wjg.v19.i38.6465.

[9] D. Comito, A. Cascio, and C. Romano, "Microbiota biodiversity in inflammatory bowel disease," Italian Journal of Pediatrics. 2014, doi: 10.1186/1824-7288-40-32.

[10] D. C. Baumgart and W. J. Sandborn, "Crohn's disease," 2012, doi: 10.1016/S0140-6736(12)60026-9.