The Relationship Between the Gut Microbiome, Genetic Mutations, and Anti-TNF Treatment in Inflammatory Bowel Disease

Eric Wu

Abstract:

Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), are thought to be autoimmune disorders in which the body's immune system mistakenly attacks the intestinal tract and other parts of the body. IBD has around 2.4 to 3 million patients in the US. Most patients are in early adulthood, with the highest rates among White individuals. IBD is more common in industrialized regions. Many of the genetic mutations associated with IBD are related to immune function and, specifically, interactions between the immune system and the microbiome. The composition of the gut microbiome varies among people, with factors such as ethnicity, environmental factors, age, diet, gender, and lifestyle contributing to its uniqueness. In IBD patients, gut dysbiosis is characterized by decreased proportions of beneficial phyla, such as Bacteroidetes and Firmicutes, and increased proportions of Proteobacteria and Actinobacteria; patients may also harbor potentially harmful bacteria, such as *adherent-invasive E. coli* (AIEC) and diffusely adherent *E. coli* (DAEC). Genetic mutations associated with IBD, including those in NOD2 and ATG16L1, may impair immune invasion, immune response regulation, autophagy, and bacterial recognition. These impairments can weaken the intestinal barrier and promote excessive inflammatory responses involving TH1 and TH17 cells and inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). Anti-TNF therapies reduce inflammation by preventing TNF-α from binding to its receptors. These treatments promote symptom relief, disease remission, and mucosal healing in IBD patients. Treatments were also associated with short-term changes in the intestinal microbiota of CD patients, with a significant reduction in the prevalence of E. coli after 1 and 3 months of treatment with adalimumab, an antibody that targets TNF-α, compared with the amount measured before the patients started adalimumab treatment, and identified Firmicutes as the main phylogroup recovered after 3 months of treatment. This research examines the relationship and interaction between genetic mutation, dysbiosis, TNF-α-mediated inflammation, and anti-TNF treatment in IBD. A lot of research is still needed to fully understand IBD and the precise role of microbiota in this disease.

The Role of the Microbiome in the Human Body:

The human microbiome comprises bacteria, archaea, viruses, and eukaryotes that reside within and outside our bodies, with the large intestine containing the highest and most dense commensal bacteria. These organisms impact human physiology, both in health and in disease, contributing to the enhancement or impairment of metabolic and immune functions (Ogunrinola et al.). It is estimated that 10 different phyla are thought to contribute to the functional role of the gut microbiome, with Bacteroidetes and Firmicutes being the most dominant phyla. In the gastrointestinal system, the density of microbiota is inversely proportional to the acidity in the region. The acidic environment of the stomach has a sparse microbiota (101 bacteria/g) compared to the estimated 103 bacteria/g found in the less acidic small intestine, which is the

main site of drug absorption. The neutral pH or weakly basic environment found in the large intestine is the most densely colonized area of the gastrointestinal tract (GI tract), with an estimated 1012 bacteria/g (O'Hara and Shanahan, 2006). People are born with a unique microbiome composition due to delivery mode, infant feeding method, and maternal factors, which is further influenced by various factors including age, ethnicity, gender, environmental factors, diet, and lifestyle (Walsh et al.). Commensal bacteria live in harmony with the host, while pathogenic bacteria cause disease because pathogens possess specialized genetic traits called virulence factors that allow them to invade tissues, damage cells, and hide from the immune system (Peterson).

Introduction to Inflammatory Bowel Disease:

Inflammatory bowel diseases are thought to be autoimmune disorders in which the body's immune system mistakenly attacks the intestinal tract and other parts of the body, although this is unproven (“Arthritis Associated with Inflammatory Bowel Disease”). It has around 2.4 to 3 million patients in the US. Most patients are in early adulthood, with the highest rates among White individuals due to certain gene changes linked to IBD that are more common in people of European descent. IBD has a higher occurrence in industrialized regions. It consists of two forms: ulcerative colitis and Crohn’s disease. Ulcerative colitis (UC) mainly affects the large intestine and rectum, while Crohn’s disease (CD) can affect any part of the digestive tract.

Symptoms of IBD in the intestinal tract include: bloody diarrhea, crampy abdominal pain, and fever. People with the arthritis of IBD have pain, swelling, and stiffness in the joints that are inflamed, particularly in the morning, which is called an extraintestinal manifestation (“Arthritis Associated with Inflammatory Bowel Disease”). The joint symptoms often correlate with the bowel symptoms. In other words, the joints tend to be more painful and swollen when the gastrointestinal symptoms are worse.

Some people with IBD have a type of arthritis similar to rheumatoid arthritis (RA). However, there are important differences. In arthritis associated with IBD, inflammation tends to involve only a few large joints, as it is an asymmetric reaction triggered by gut inflammation and does not involve both sides of the body equally. For example, it might affect the knee on one side and the ankle on the other. In rheumatoid arthritis, more joints, especially the small ones in the hands and wrists, are involved, and joints on both sides of the body tend to be affected equally because circulating immune autoantibodies systematically target matching tissues throughout the body (“Arthritis Associated with Inflammatory Bowel Disease”). The bowel problems caused by inflammatory bowel disease usually appear before the arthritis develops. Occasionally the arthritis appears first, and the inflammatory bowel disease is diagnosed months or even years later (“Arthritis Associated with Inflammatory Bowel Disease”).

The phyla Bacteroidetes and Firmicutes dominate the gut microbiota of healthy humans. Conversely, CD and UC patients exhibit dysbiosis consisting of decreased proportions of

Bacteroidetes and Firmicutes and increased proportions of Actinobacteria and Proteobacteria, or elevation of specific pathogenic organisms, such as adherent-evasive Escherichia coli (Ciccia et al.).

As well as decreased bacterial diversity, patients with IBD also present with an increase in colonization of the mucosal surface compared with healthy subjects.

Extra-Intestinal Manifestation:

Extra-intestinal manifestations are illnesses that affect body parts outside the gastrointestinal tract, which primarily affect the joints, skin, and eyes, with less frequent effect on the liver, kidney, and pancreas. This manifestation occurs in up to 40% of patients with IBD, yet predicting who may develop them is difficult (Alizadeh et al.).

Cause of Extra-Intestinal Manifestation:

Beneficial and potentially harmful bacteria normally exist in balance. Diet, lifestyle, infections, and antibiotic use can disturb this balance, causing dysbiosis. For example, diet disturbs the balance of gut bacteria by altering nutrient supplies, reducing microbial variety, and promoting harmful microbes. An unbalanced diet causes dysbiosis through high sugar intake, excess saturated fats, and processed food additives (Mansour et al.). The intestinal lining normally protects the body by keeping bacteria and harmful substances inside the gut; however, dysbiosis can disrupt this barrier and cause it to be more permeable (Petersen and Round). As a result, harmful substances such as bacterial toxins, metabolites, and bacterial components can cross the intestinal lining to other tissues (Petersen and Round).

Cause of IBD:

Many of the genetic mutations associated with IBD are related to immune function and, specifically, interactions between the immune system and the microbiome. These genes include nucleotide oligomerization domain 2 *(NOD2)*, autophagy-related 16-like 1 *(ATG16L1)*, caspase recruitment domain–containing protein 9 *(CARD9)*, and C-type lectin domain family 7 member A *(CLEC7A)* (Glassner et al.).

NOD2:

NOD2 is a gene expressed in intestinal epithelial cells that codes for a cytoplasmic innate immune receptor. This receptor interacts with peptidoglycan found in bacterial cell walls. Upon sensing invading or infectious bacteria, NOD2 triggers antibacterial autophagy, a cellular recycling and cleaning process; promotes cell survival and tissue repair; and stimulates the

secretion of antimicrobial peptides (Véronique Ancey). It functions as a protective factor against intracellular bacteria and helps recognize and regulate harmless bacteria that live in the gut.

Humans with an NOD2 mutation are characterized by a decreased level of IL-10, an anti-inflammatory cytokine, and increased abundance of mucosal associated bacteria. Patients also have a decreased abundance of Faecalibacterium species and increased abundance of Escherichia species.

Bacteroides vulgatus has been associated with alterations in mucosal barrier function and the expression of inflammatory genes in NOD2-depleted mice. Eliminating this bacterium restored mucosal barrier function and decreased inflammatory cytokine levels (Glassner et al.). Although this relationship remains unproven, researchers believe that certain *E. coli* strains, such as adherent-invasive *Escherichia coli* (AIEC) and diffusely adherent *E. coli* (DAEC), may influence inflammatory bowel disease. These strains may contribute to the disease by adhering tightly to epithelial cells, entering and multiplying within them, and triggering immune cells to produce large amounts of cytokines.

ATG16L1:

ATG16L1 is a gene that helps control autophagy, a cellular recycling and clearing process. NOD2 interacts with ATG16L1 by recruiting ATG16L1 to the plasma membrane at the entry site of invasive bacteria (Glassner et al.). A mutation in either NOD2 or ATG16L1 in CD patients will impair their interaction, which will interfere with both bacterial elimination and antigen presentation.

T300A:

T300A is a particular version of the ATG16L1 gene in which the amino acid threonine at position 300 is replaced by alanine. This variant is associated with an increased risk of CD. The T300A change in the ATG16L1 gene is a missense mutation—a single substitution of a DNA base that results in a different amino acid in the protein. This mutation leads to lower levels of full-length ATG16L1 protein and reduces the cell's ability to perform a specific type of autophagy.

In one experiment, researchers studied two groups of mice: one group carried the normal ATG16L1 gene, while the other carried the T300A variant. The researchers transplanted fecal microbiota from patients with inflammatory bowel disease into both groups of mice. When the fecal microbiota came from patients with active CD, mice carrying the T300A variant developed greater levels of *Bacteroides* bacteria and greater numbers of TH1 and TH17 T cells in the intestinal lamina propria.

TH1 and TH17 T cells are specific types of T cells, which are essential white blood cells involved in the adaptive immune response. TH1 cells help fight pathogens that live inside cells,

while TH17 cells help fight pathogens found outside cells, particularly at the body's barrier surfaces. Although these cells help coordinate immune responses, excessive activity can promote inflammation. Therefore, the T300A variant appears to create an intestinal environment in which certain bacteria become more abundant and the immune system becomes more inflammatory.

Normally, *Bacteroides fragilis* is a harmless gut bacterium that can help prevent inflammation. It interacts with $CD4^+$ $Foxp3^+$ regulatory T cells, or Treg cells, causing them to produce IL-10. IL-10 is an anti-inflammatory cytokine that tells the immune system to desensitize. However, human immune cells carrying the T300A variant did not properly promote regulatory T-cell development after exposure to *B. fragilis*. Therefore, the normal protective pathway may be weakened (Glassner et al.).

Tumor Necrosis Factor as a Cause of Inflammatory Bowel Disease:

TH1 Cells produce tumor Necrosis Factor-alpha (TNF-α). TNF-α is a cytokine that regulates the inflammatory response and is involved in the pathogenesis of several inflammatory autoimmune diseases. Structurally, TNF-α is a homotrimer protein consisting of 157 amino acids, mainly generated by activated macrophages, T-lymphocytes, and natural killer cells. TNF-α triggers inflammation by binding to cell receptors, primarily tumor necrosis factor receptor 1 (TNFR1), on immune and structural cells. This binding activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κ B) and mitogen-activated protein kinase (MAPK) signaling pathways, which command cells to release secondary inflammatory cytokines (like IL-1 and IL-6) and increase blood vessel permeability (Jang et al.). In patients with active inflammatory bowel disease, TNF-α levels are often elevated because immune cells become excessively activated in response to gut bacteria and damage to the intestinal lining. The increased TNF-α further promotes inflammation and contributes to ongoing intestinal tissue damage (Souza et al.).

Anti-TNF:

Anti-TNF biosimilars are biologics, a biological medication that is highly similar to an existing original biologic drug. Anti-TNF therapy targets TNF-α. It blocks TNF-α from binding to its receptors. Anti-TNF drugs have shown strong results in inducing pain relief, mucosal healing, and disease remission in patients with chronic inflammatory and autoimmune diseases. Current clinical guidelines recommend anti-TNF agents for patients who are refractory to other treatments. Patients have also been reported to reduce the need for surgery and hospitalizations among patients with moderate-to-severe IBD and contribute to better disease control with a reduction in (late) complications of the disease and improved quality of life. Unfortunately, a considerable proportion of patients fail to respond to anti-TNF induction therapy

and are categorized as primary non-responders. In addition, up to 50% of patients who initially respond to anti-TNF therapy show a loss of response (LOR) over time (i. e., secondary LOR), which often leads to discontinuation of treatment (Ciccia et al.).

Anti-TNF's Influence on Intestinal Microbiota:

One study found that dysbiosis in IBD patients was linked to changes in the Firmicutes and Proteobacteria phyla. The researchers also examined the relationship between microbiome variance and medical treatment. They found that medical treatment, such as anti-TNF agents, was independently associated with changes in the gut microbiome.

Another study investigated the short-term intestinal microbiota changes in CD patients who were treated with adalimumab. The results show a significant decrease in the abundance of E. coli after one and three months of treatment compared to the amount before the treatment. The study also identified Firmicutes as the main bacterial group recovered after three months of adalimumab treatment.

Conclusion:

In conclusion, inflammatory bowel disease is a complex illness constituted by the interaction between genetic mutations, the immune system, and the gut microbiome. Bacteroidetes and Firmicutes dominate the healthy microbiome, but IBD patients often experience dysbiosis and increased levels of harmful bacteria such as Escherichia coli.

Anti-TNF therapies can reduce inflammation by preventing TNF from binding to its receptors. They may promote symptom relief, mucosal healing, disease remission, and improvements in microbiome composition. For example, adalimumab treatment has been associated with decreased levels of *E. coli* and the recovery of Firmicutes in patients with CD.

Other therapies used to treat inflammatory bowel disease besides anti-TNF agents include vedolizumab, ustekinumab, and Janus kinase inhibitors. These treatments may help reverse dysbiosis by increasing overall microbial alpha diversity; promoting the growth of beneficial, short-chain fatty acid-producing bacteria, such as Lachnospiraceae and *Blautia*, that nourish the intestinal lining; and reducing active tissue inflammation. Reduced inflammation decreases the production of oxygen- and nitrate-rich byproducts that pathogens such as *Escherichia* and *Enterococcus* use to multiply, thereby reducing their populations in the gut ("Changes in Gut Microbiome Associated With Biologic Therapy in Inflammatory Bowel Disease - Gastroenterology Advisor").

Much about inflammatory bowel disease remains unknown. Further research is needed to clarify the precise role of the microbiome in its development and progression.

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