

Communication Gone Wrong in the Gut: Cytokines and Colitis

by

Isis D. Rivera-Walsh and Sheri L. Boyce
Department of Biological Sciences
Messiah University, Mechanicsburg, PA



Part I – Introduction and Clinical History

Skylar's long-awaited family vacation was almost cancelled after she heard a huge rumble coming from her mother's stomach. A second later, she saw her mom run to the bathroom. She came out with one minute to spare before the plane gate door closed, and all breathed a sigh of relief once they ran and made it inside the plane. Skylar had just finished an exhausting year in college, and she was looking forward to several days full of snorkeling, ziplining, and riding ocean waves in Puerto Rico. But it seemed like her mom, Angie, was going to struggle with diarrhea. Having just taken an anatomy and physiology course in college, Skylar jumped at the chance to diagnose her mom's condition based on her symptoms. She had learned that the body's immune system becomes specifically activated with every single pathogen that enters the body, and the symptoms could be indicative of her immune system at work.

Angie had also been under considerable stress during that year. She had started a new nursing job, and her work hours had been long, especially during the past six months. Angie had been taking antibiotics for a sinus infection the week before their journey, and she suspected the antibiotics were causing her to have intermittent watery diarrhea. Angie knew that it was not uncommon for antibiotics to have negative side effects. However, she decided to ignore the symptoms and finish her antibiotics, just like her doctor had recommended. She wanted to recover from her sinus infection in time for their vacation flight to Puerto Rico. However, after the airport bathroom run, it seemed like Angie's diarrhea would follow her through vacation as well.

After a conversation with Angie, Skylar suspected that her mother's immune reaction to the sinus infection could have also contributed to the dysfunction in her gastro-intestinal (GI) tract. Skylar had learned in the immunology unit of her A&P course that the GI tract is crucial for digestion and nutrient absorption but is also home to a local immune system with cells and signals that defend the body against foreign substances. When a bacterium, virus, or parasite enters the tract, the local immune system is activated through the inflammatory response when cells, like macrophages, mast cells, and neutrophils, come into contact with the invader. This encounter activates signaling events, which induce adaptive immunity, by attracting T and B cells. Adaptive immunity provides continuous protection and pathogen clearance in the GI tract. The inflammatory response, or inflammation, can happen in many sites in our bodies through the release of signaling molecules called cytokines, but it needs to be tightly regulated because it can damage healthy tissue. Skylar had also learned that diarrhea is a disruption of homeostasis in the large intestine and that her mom's diarrhea could be the result of sustained inflammation.

In midsummer, two weeks after their vacation, Angie's diarrhea continued unabated. She was having multiple watery bowel movements a day with no specific triggers. Since returning, Angie had tried everything from changing her diet to trying a variety of daily supplements, but nothing helped. Her doctor decided to order a diagnostic colonoscopy to do a deeper study into her symptoms. Tissue biopsies from the colonoscopy revealed Angie had lymphocytic colitis (LC). Skylar had heard of ulcerative colitis and Crohn's disease, the two main presentations of inflammatory bowel disease (IBD), but she was unfamiliar with LC. When she typed "lymphocytic colitis" in an internet search engine, she was able to connect lymphocytic colitis to IBD (see Figure 1, next page).

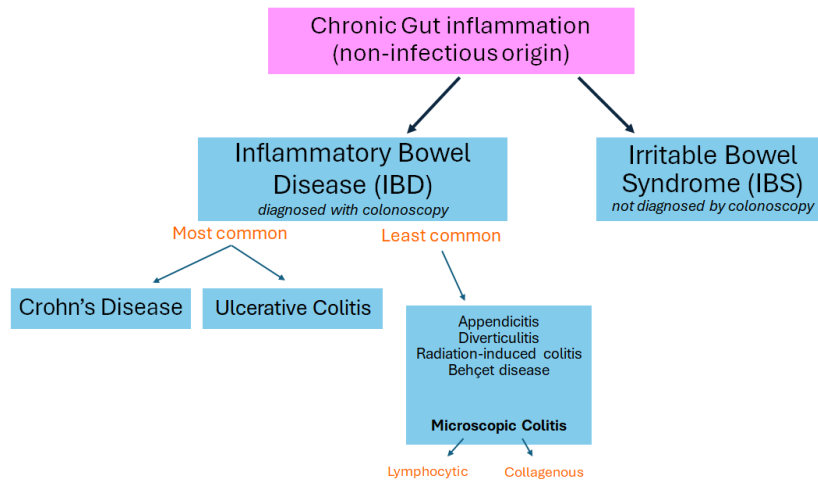


Figure 1. Irritable bowel syndrome (IBS) vs. inflammatory bowel disease (IBD).

Questions

Please answer the following questions on gut immunity with the information provided above, your textbook, or a medical database such as PubMed.

1. In a few sentences, describe the cellular events that lead to the activation of the immune system in the GI tract. In your answer, be sure to include three types of *innate* immune cells that begin the induction of this process.

2. The intestinal inflammatory response is induced when innate immune cells release molecules called cytokines. After the pathogen has been cleared, tissues return to a healthy state when immune cells then produce anti-inflammatory cytokines. Search a medical database such as Pub Med for the following:
 - a. Provide two examples each of pro-inflammatory and anti-inflammatory cytokines.

 - b. Describe the effect of high levels of IFN- γ on intestinal tissue and its functions.

 - c. Provide an example of a cytokine that could downregulate colitis when released.

3. Explain why unchecked cytokine release can lead to colitis, tissue damage, and dysfunction. Is colitis always associated with an infection?

4. Describe the major differences between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Present your answer in the form of a table and include differences between the two clinical presentations related to symptoms, links to inflammation, diagnosis, and causes.

	<i>IBD</i>	<i>IBS</i>
<i>Symptoms</i>		
<i>Links to Inflammation</i>		
<i>Diagnosis</i>		
<i>Causes</i>		

Part II – The Gatekeeper Role of the Gut

Skylar wanted to know more about colitis, so she made sure Angie discussed every detail of the colonoscopy preparation process with her. For a camera to look through Angie's large intestine, Angie had to drink about four liters of a liquid laxative that would clean her GI tract on the night before the procedure. That meant staying next to the toilet for hours. Despite this inconvenient preparation, the colonoscopy was successful in that it showed signs of lymphocytic colitis.

In class, Skylar had been fascinated by this tract and its function as a portal through which substance from outside the body passed from the intestinal lumen to tissues inside the body. The GI tract is a hollow tube that begins in the oral cavity and ends at the anus. This tube is an important site for the digestion and absorption of any substance that enters the tract. Of utmost importance, the small intestine processes nutrients, such as carbohydrates, proteins, and lipids, which are essential for the metabolism and function of all body cells.

The tissue anatomy of the GI tract contains mucosal, submucosal, muscular, and adventitial layers. The muscular layers are important for peristalsis, while the mucosal and submucosal layers monitor the entry of foreign substances that are ingested, such as medications, pathogens, or any toxic chemicals. This function provides the tract with a dual role of nutrient tolerance and protection from harmful materials. The cells involved in this monitoring function are interspersed with cells involved with nutrient absorption

and are part of the immune system. First, the epithelial layer (or mucosa) of the GI tract is the interface between the lumen (inside) of the tract and the inside of the body. In addition to serving as an absorptive surface for nutrients with epithelial cells arranged in villi structures, the mucosa also contains immune cells, such as M cells and intra-epithelial lymphocytes (IELs). Deeper in the submucosa (also known as the lamina propria), the GI tract is home to resident macrophages, dendritic cells, and Peyer's Patches (Figure 2). Macrophages and dendritic cells act as a bridge between food substances in the lumen and the gut immune system present in the Peyer's patches. Inside the patches, T and B cells, adaptive lymphocytes, communicate with gut macrophages and dendritic cells, the front line of immune defense; together, they make decisions on whether a particular food molecule is worthy of immune attack. Because of this strategic arrangement, any bacterium, virus, or parasite that enters the body is continuously checked by cells in charge of innate and adaptive immunity. Finally, this region in the GI tract also contains lymphatics that drain into mesenteric lymph nodes. The body uses lymph nodes outside of the GI tract to request immune system reinforcements if a pathogen enters the body through the gut.

In the large intestine, the anatomy of the tract changes from numerous absorptive villi present in the small intestine to mucus glands and membrane channels for absorption of electrolytes and water (mucus glands shown in left panel of Figure 3, next page). This allows the large intestine to maximize water and electrolyte absorption and to facilitate the passage of undigested material out of the body.

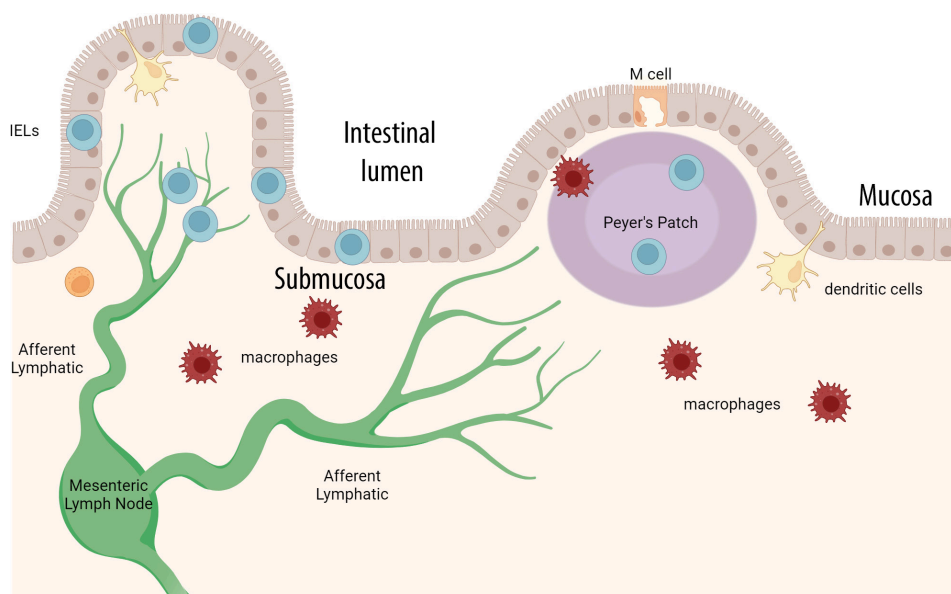


Figure 2. Immune cells and tissues that serve the gut. (IEL, intraepithelial lymphocyte).
Credit: Image created with BioRender.com.

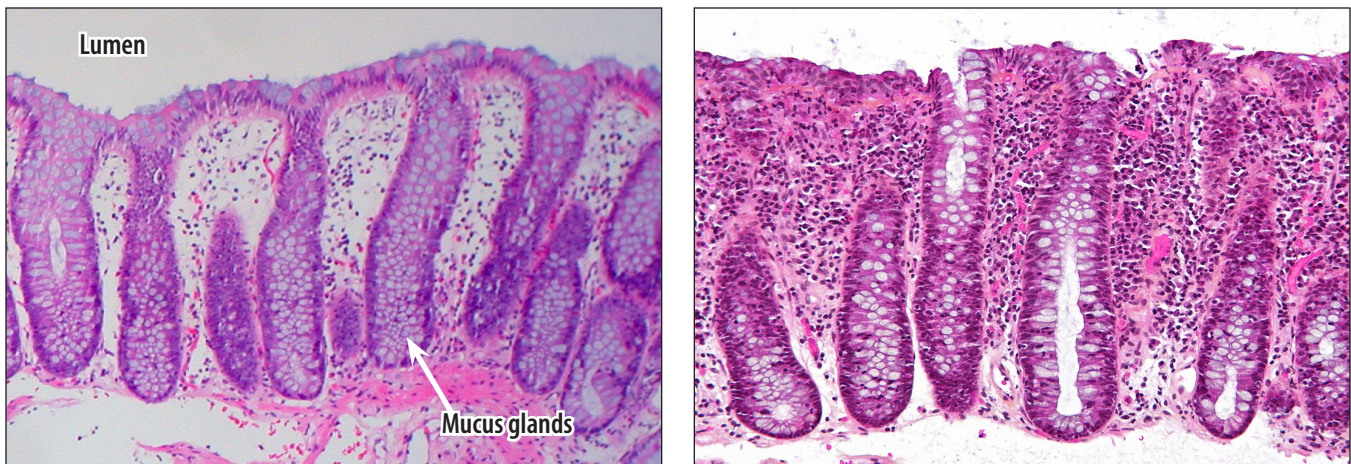


Figure 3. Diagnosis of lymphocytic colitis. The left panel shows healthy colon mucosa and submucosa. The right panel displays colon mucosa and submucosa from a patient with lymphocytic colitis; notice the abundant dark purple nuclei in the submucosal layer.

Credits: Left panel, Ed Uthman | Flickr, CC BY-SA 2.0. Right panel, Michael Bonert | Wikimedia Commons, CC BY-SA 3.0.

Colitis is diagnosed by histological examination of intestinal tissue biopsies taken during a colonoscopy. In the presence of LC, the “empty” spaces you normally see in the submucosa of healthy intestinal tissue are filled with nucleated cells (lymphocytes) with purple nuclei (Figure 3, right panel). Having learned about both immunity and gut anatomy, Skylar understood how colitis can occur, but she still did not understand how colitis can cause persistent diarrhea. She did remember the role of the large intestine in water reabsorption, so she decided to start looking more deeply into the function of the large intestine.

Questions

Search previous content or online search databases for the answers to the following questions. Online sources should be reputable in nature (belonging to a scholarly site) or journal.

1. Using your textbook and lecture content on water balance in gut epithelium, what principle drives water from the lumen of the GI tract into the tissue? What layer of the large intestine wall is involved with water balance in this section of the GI tract? You only need two sentences to answer.
2. Search for detailed images of a Peyer’s patch. When you find a detailed image, click on the source to obtain more information. What types of cells are present inside? Draw a diagram to describe their placement. In one sentence, how do Peyer’s patches contribute to inflammation?
3. In the case of LC, tissue specimens show a high number of lymphocytes present in the mucosa or submucosa of the colon. Because of these lymphocyte numbers, which of the groups of cytokines mentioned in Part I has been shown to be increased in LC? Provide examples of cytokines in this group.
4. How does an increased number of lymphocytes lead to colitis? When you connect inflammation with water movement in the large bowel, how does colitis lead to diarrhea? You should use two to four sentences to answer.

Part III – Treatment for Colitis is Multifactorial

One year later, Skylar, Angie, and the rest of the family boarded a plane to Europe for their next vacation. This time there were no loud stomach gurgles or last-minute bathroom runs that would delay them. After the LC diagnosis, Skylar and Angie tried to figure out what the initial prognosis and treatment for lymphocytic colitis would be. Fortunately for Angie, lymphocytic colitis was treatable with medication and several changes to her daily nutritional regime. She was prescribed a daily dose of mesalamine and a psyllium husk powder supplement. Angie was also told to avoid greasy foods and increase her intake of fruits and green vegetables.

One of the more interesting things Skylar and Angie learned throughout the year was that the millions of bacteria that live in the intestine, a community known as the gut microbiome, can be a factor in the progression to colitis. Probiotics and prebiotics were terms that both had heard in yogurt commercials, but they were surprised to hear that pro- and prebiotics feed the gut microbiome. After a deep dive into immunotherapy, Skylar was now interested in how bacteria can contribute to gut homeostasis, but that would have to wait for next semester in her microbiology class!

Questions

1. Investigate and briefly describe how mesalamine can be an effective treatment for lymphocytic colitis. Your answer should contain mesalamine's chemical name and the type of signaling pathway activated. Why is mesalamine considered anti-inflammatory? You need three to four sentences to answer.

2. Lymphocytic colitis is considered an acute type of colitis, and this makes it different from Crohn's disease (CD) and ulcerative colitis (UC). Lymphocytic colitis resolves with proper treatment. When treating chronic IBD like CD and UC, there are several current clinical trials that use cytokines as immunotherapy to reduce gut inflammation. Conduct a search in PubMed to briefly describe two current IBD immunotherapy approaches. In your answer, you should:
 - a. Specify the type of molecule used in the approach.
 - b. Specify whether this approach blocks a pro-inflammatory cytokine or enhances an anti-inflammatory cytokine.

3. Psyllium husk powder is a common fiber supplement. Describe two ways in which fiber is effective in treating acute colitis by restoring gut water balance.