Immunology Presentation - Group 9

Topic: Ulcerative Colitis

Group members:

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Outline:

Part I: Introduction

1. Discovery (The morbid appearance of the intestine of Miss Banks)
2. Definition (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4539174/)
3. Symptoms (https://medlineplus.gov/ulcerativecolitis.html)
4. Related Diseases [1] (https://www.healthline.com/health/crohns-disease/crohns-ibd-uc-difference#overview1)
5. Epidemiology [2] (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563787/)

Part II: Causes (https://en.wikipedia.org/wiki/Ulcerative_colitis#Causes)

1. Genetic factors
2. Environmental factors (https://emedicine.medscape.com/article/183084-overview#a2)
3. Autoimmune disease
4. Molecular Basis [3] (https://www.embl.de/aboutus/communication_outreach/media_relations/2007/070314_monterotondo/)
5. Other Theories

Part III: Treatments

(https://www.webmd.com/ibd-crohns-disease/ulcerative-colitis/ulcerative-colitis-topic-overview#1)

1. Mild-antidiarrheal medication
2. Enemas or suppositories that contain medicine
3. Aminosalicylates, steroid medicines, or other medicines that reduce the body's immune response
4. Immunomodulator medicines or cyclosporine, strong medicines that suppress the immune system to prevent inflammation
5. Biologics that block the inflammatory response in the body and help reduce the inflammation in the colon, microbiome
6. Severe - surgery to remove the colon

Part IV: Current Research

1. Understanding the markers of UC (https://www.intechopen.com/books/ulcerative-colitis-from-genetics-to-complications/research-of-immunology-markers-of-uc)
2. Specific Immunotherapy ameliorates UC (https://aacijournal.biomedcentral.com/articles/10.1186/s13223-016-0142-0)
3. UC increases infection risk in patients undergoing stem cells transplant (https://www.healio.com/internal-medicine/gastroenterology/news/online/%7Bef4184f3-eaf6-4080-9cca-85f9d802b611%7D/latest-crohns-ulcerative-colitis-research-from-aibd-2015)
4. Biologics for UC (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4282853/)
5. Genetics initiative (http://www.crohnscolitisfoundation.org/science-and-professionals/research/current-research-studies/genetics-initiative.html)
6. Links between the appendix and UC (http://www.nature.com/ajg/journal/v111/n2/full/ajg2015301a.html?foxtrotcallback=true)

Notes:

1. Primary Sclerosing Cholangitis (PSC causes scarring of the bile ducts that drain bile from the liver to the intestine.). Fatty Liver Disease (It occurs when fat builds up in the liver, either from a problem with fat metabolism in the liver or excess fat in the body.), Autoimmune Hepatitis(Autoimmune hepatitis is caused by chronic inflammation of the liver rather than an infection by a virus), Gallstones, Pancreatitis.
2.
    a. The annual incidence is 10.4-12 cases per 100,000 people. The prevalence rate is 35-100 cases per 100,000 people. Ulcerative colitis is 3 times more common than Crohn disease.
    b. It is more common in developed, more industrialised countries, pointing at urbanisation as a risk factor.
3. The epithelial cells line the intestinal surface and they protect us from the harmful bacteria present in the gut, helping with digestion. NF-κB is a signaling molecule that helps cells cope with stress, in the intestinal epithelium. Researchers generated a mouse model that does not express NEMO, a protein needed to activate NF-κB, in intestinal epithelial cells. As a result, these mice developed severe chronic intestinal inflammation very similar to Colitis in humans. Without the NF-κB molecule, epithelial cell functions are disrupted and they die. This results in holes on the intestinal surface which allow bacteria to penetrate. Below the epithelial layer is the immune system which detects the penetrating bacteria and produces a concoction of signals which in turn leads to inflammation. Inflammatory signals reach epithelial cells which due to lack of NF-κB molecules leads to their destruction causing wider gaps in the gut. This leads to chronic inflammation and Inflammatory bowel diseases.

4. Some more links:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723519/#B2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653902/#ref3
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563787/
http://www.nejm.org/doi/full/10.1056/NEJMra1102942
https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis (Pretty basic info regarding the disease for all topics. Builds on what we have here so far)
https://medlineplus.gov/ulcerativecolitis.html (This page has some links we can use for further research)

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Immunology 4323
Mehmet Sen MW 1:00 - 2:30
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Group #9

Overview of Ulcerative Colitis

What is Ulcerative Colitis and What Causes it - Glenn

Ulcerative colitis is a chronic disease which causes inflammation and the formation of open sores called ulcers in the inner lining of the large intestine first observed around 1859 by Sir Samuel Wilks. This disease is categorized as a type of inflammatory bowel disease (IBD) which is confined to the large intestine. Symptoms include abdominal cramping, loose stools, bloody stools, a feeling of urgent bowel movement, fatigue, loss of appetite, and, in some severe cases, anemia. Ulcerative colitis is also sub-categorized into five unique types. Acute severe ulcerative colitis is a rare form of the disease that causes eating disorders. Left-sided colitis affects the descending colon and rectum. Pancolitis affects the entire colon and causes the patient to have persistent bloody diarrhea. Proctosigmoiditis affects the lower colon and rectum. Ulcerative proctitis only affects the rectum and is considered the mildest case of the disease.

Generally, ulcerative colitis affects someone gradually. Over periods of time, symptoms may become worse. In addition, people who suffer from ulcerative colitis may experience periods of remission where symptoms seem to disappear from days, weeks, months, or even years. Despite this, symptoms always come back as there is no known cure for the disease at this given time. Thus, the aim of modern-day treatment of the disease is aimed to keep patients in the remission state to ease suffering and improve quality of life.

This disease can happen to any person of any age. However, ulcerative colitis is more common in people between the ages of 15 to 30 as well as people over the age of 60. Men are at a higher risk of obtaining ulcerative colitis at later ages. People with a family history of IBD have a higher risk of contracting the disease. Also, people of Jewish descent are at higher risk of contracting ulcerative colitis.

While there is no known exact cause of the disease, researchers suspect that genetics, environmental factors, overactive intestinal immune responses, and molecular interactions are all factors that may explain why one has ulcerative colitis.

The disease is known to be linked to genetics as ulcerative colitis is passed down from generation to generation in some families. Research regarding the genetics of ulcerative colitis has shown that those who suffer from the illness may have abnormal genes. Scientists still have not found a clear link between abnormal genes and ulcerative colitis, but ongoing research is still underway.

Albeit rare, some studies have shown that ulcerative colitis may be the result of being around certain environmental factors. The intake of nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and oral contraceptives may increase the odds of developing ulcerative colitis. In addition, diets that are high in fats may cause someone to get ulcerative colitis. Depending on the person, certain foods can also worsen symptoms of ulcerative colitis. Lastly, it is speculated that stress may cause someone to obtain the disease, but further testing is needed to validify this statement.

Abnormal immune reactions in the intestines may cause someone to contract ulcerative colitis. Generally, the immune system protects an individual by targeting pathogens. However, in a case where the immune system is abnormal, researchers believe that sometimes bacteria and viruses cause the immune system to attack the inner lining of the large intestine. Naturally, the immune system will trigger the inflammatory response. This further cascades into symptoms of ulcerative colitis.

Research on molecular factors also show that the expression of NF-κB may play a role in the initial stages of the disease. Scientists experimented with mice that did not express NF-κB, a signalling molecule that helps intestinal tissue cope with stress. As a result from their abnormality, the mices' large intestine began to inflame. This is because the epithelial tissue that protected the gut lining was damaged. Thus, bacteria could penetrate the intestinal wall and continue to hurt the patient.

Ulcerative colitis is one among the many forms of inflammatory bowel diseases. Others include Crohn's disease, microscopic colitis, diverticulosis-associated colitis, collagenous colitis, lymphocytic colitis, and Behcet's disease. Common like ulcerative colitis, Crohn's disease causes inflammation of the GI tract anywhere from the mouth to the anus but usually is localized to the small intestines. Common features of Crohn's disease are the presence and prevalence of Peyer patches, which are clustered lymphoid follicles, fistulas, and rectal bleeding. The causes of Crohn's disease are also unknown.

Molecular basis of Ulcerative Colitis: (Sushmithaa)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882124/#!po=11.2500

The epithelial cells line the intestinal surface and they protect us from the harmful bacteria present in the gut, helping with digestion. NF-κB (nuclear factor kappa light chain enhancer of activated B-cells) is a signaling molecule that helps cells cope with stress, in the intestinal epithelium. It controls transcription of DNA, cytokine production and cell survival. It also plays a key role in regulating immune response against infection. Researchers generated a mouse model that does not express NEMO, a protein needed to activate NF-κB, in intestinal epithelial cells. As a result, these mice developed severe chronic intestinal inflammation very similar to Colitis in humans. Without the NF-κB molecule, epithelial cell functions are disrupted and they die. This results in holes on the intestinal surface which allow bacteria to

penetrate. Below the epithelial layer is the immune system which detects the penetrating bacteria and produces a concoction of signals which in turn leads to inflammation. Inflammatory signals reach epithelial cells which due to lack of NF-κB molecules leads to their destruction causing wider gaps in the gut. This leads to chronic inflammation and Inflammatory bowel diseases.

NEMO activates NF-κB to protect epithelial cells against invading bacteria. (Alternative pathway)

NF-κB molecules are activated by NEMO which is the NF-κB essential modulator. Activation of the molecule starts when the Inhibitors of κBs (IκBs) are degraded by the IκB kinase (IKK). The IKK is a heterodimer with α, β subunits and a master regulatory protein called NEMO. The IKK phosphorylates IκB and then these proteins undergo ubiquitination and are then degraded by proteasomes. With the inhibitors out of the way, the NF-κB cells set to work and they enter the nucleus, bind to specific genes and turn on their expression. They regulate genes responsible for both innate and adaptive immunity which are involved in T-cell development, maturation and proliferation. Therefore without activated NF-κB epithelial cells in the human gut do not have immunity against invading bacteria.

NF-κB on inflammation in canonical pathway:

But the treatment for ulcerative colitis works on inhibiting NF-κB which is controversial to the above mentioned topic. This is because we are trying to eliminate the symptoms which involve inflammation. NF-κB plays an important role in the expression of proinflammatory genes including cytokines, chemokines and adhesion molecules. NF-κB regulate expression of both pro and anti-inflammatory mediators in resident tissue cells and leukocytes recruited from the blood. Currently our understanding of signaling in inflammation is obtained from studying members of the IL-1 and TNF (tumor necrosis factor) receptor families and the Toll-like microbial pattern recognition receptors (TLRs). TLRs are a nonself recognition system that are encoded by the germline and they directly trigger inflammation. However, there is some suggestion that endogenous ligands may trigger TLRs during tissue injury and certain disease states, which may cause inflammation although there is no sign of infection. TLRs are structurally different but they also undergo similar signal transduction by activation of IκB kinase (IKK) and NF-κB. The "canonical" pathway for NF-κB activation is triggered by microbial products and proinflammatory cytokines such as TNFα and IL-1 as described previously, usually leading to activation of RelA- or cRel- containing complexes. The canonical NF-κB pathway has been defined primarily in response to TNFα and IL-1 signaling, prototypical proinflammatory cytokines that have important roles in the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, and chronic obstructive pulmonary disease (COPD). NF-κB activation is also widely

implicated in inflammatory diseases and much attention has focused on the development of anti-inflammatory drugs targeting NF-κB.

NF-κB has both pro and anti-inflammatory pathways:

Although NF-κB regulates pro-inflammatory pathway and is a main therapeutic target in inflammatory diseases like Ulcerative colitis. There is a controversy because this same molecule also regulates the anti-inflammatory pathway and if there is an infection, we need B-cells to be activated to fight against bacteria and its alternative pathway helps with this process. Therefore more studies have to be performed to determine if NF-κB is the best molecule to target to treat the inflammatory bowel diseases.

Diagnosis of UC:

There are various ways for diagnosing UC. It usually starts with patients reporting the symptoms, such as abdominal pain, bloody diarrhea and are commonly associated with symptoms of rectal urgency as well as tenesmus, and the doctor ruling out other possible causes. At this point, different tests can be administered for confirmation of the diagnosis.

The first test is a simple blood test for anemia, or any major nutrient deficiency. This is based on the fact that iron and other nutrients fail to be absorbed as food passes through the intestine when UC has developed. Lack of nutrient in the blood can also result from blood lost, from the ulcerations of the intestinal mucosa, which is frequent in cases of UC. These are also often linked with antibody blood tests, since the presence of specific antibodies may indicate that the patient has UC. Iron regulation is affected by hepcidin. Hepcidin is a protein that binds to ferroportin 1, an iron transporter, causing it to be degraded. In the absence of ferroportin, iron is not transported properly across the cell. Hepcidin is also upregulated during inflammation in UC, which causes the low iron levels in the blood.

Other diagnosis methods such as colonoscopy, flexible sigmoidoscopy, X-ray, CT scan, Computerized tomography (CT) enterography and magnetic resonance (MR) enterography can also be used to identify UC symptoms. These methods rely on more physical tests by directly inspecting the inflamed area and are used less often.

Epidemiology of Ulcerative Colitis - Adelle Flores

According to Medscape, ulcerative colitis affects 1 million people in the United States. The annual incidence, or amount of people newly diagnosed with ulcerative colitis each year, is 10.4 to 12 cases per 100,000 people. In regards to race, caucasians are most affected by ulcerative colitis, followed by Asians, Hispanics, and African-Americans. In regards to gender, women are more highly affected by ulcerative colitis than men. Age of onset of ulcerative colitis peaks for both genders between the ages of 10 and 30, although the disease can develop

at any age. While every 2 in 100,000 children are affected by ulcerative colitis, one in four new cases of ulcerative colitis occur in people 20 years old or younger. Ulcerative colitis is more common in North America, Europe, and other westernized regions across the globe. Compared to Crohn's Disease, ulcerative colitis is three times as common. (Source)

Treatments and Medications - Nick

Ulcerative colitis patients suffering from low to moderate pain are usually treated with medications like aminosalicylates, an anti-inflammatory agent that suppresses the immune system locally. Aminosalicylates, whose mechanisms of action are still obscure, inhibit activation of nuclear factor kappa B (NF-κB) transcription, IL-1, platelet activating factors, and eicosanoids, molecules made from oxidized polyunsaturated fatty acids that are responsible for signaling inflammation. Furthermore by interfering with interferon binding and TNF-α, the agent is able to disrupt the signaling cascade and stop short the inflammatory response. Moderate pain is treated with corticosteroids, which also inhibits NF-κB, and severe pain is treated with cyclosporine, a cyclic peptide responsible for inhibiting T cell activation and suppressing antibody formation. Patients may need colectomy for ulcerative colitis in rare situations when present treatments fail to manage symptoms, when lacerations form in the large intestine, or when abnormal cell growth is found.

Alternative methods include the use of monoclonal antibodies that target certain proinflammatory cytokines, particularly TNF-α, in the gut lamina propria. The antibodies facilitate the induction of cell death, inhibit growth factors for Th cells, complement activation, and antibody production. Infliximab, adalimumab, golimumab are well known anti-TNF-α agents that have been shown to increase healing of the intestinal epithelium and clinical remission. Infliximab is a chimeric IgG monoclonal antibody that binds to TNF-α, both soluble and membrane-bound, and essentially disables the cytokine. The binding of infliximab to TNF-α receptors alters the complement system to induce antibody-dependent cell cytotoxicity and T cell apoptosis. Studies show that cumulative incidence rate of colectomy in infliximab groups is 7% lower than 17% seen in the placebo group. However, infliximab contains a protein sequence that is one-fourth mouse gene which can trigger human antichimeric antibody formation (HACA) that target the medicine and result in increased risk of infusion reactions and lowered drug efficacy. Intermittent administration of the drug is shown to have high incidence of HACA while regular and continuous delivery of the medicine results in low occurrence of HACA. Similar to infliximab, adalimumab binds to soluble and membrane-bound TNF-α and induces cytotoxicity and cell lysis. Adalimumab is a humanized recombinant monoclonal IgG1 antibody that can is administered subcutaneously in 2-week intervals. It is a treatment option for patients that are unable to tolerate aminosalicylates or steroids and has shown to significantly increase clinical remission rates. Targeting TNF-α, golimumab is also a humanized monoclonal IgG1 that is utilized in moderate to severe cases for diseases not limited to ulcerative colitis like psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis. The dosage range was

studied in a maintenance therapy phase III trial and found that higher dosage (100 mg vs. 50 mg) correlated to a significantly higher clinical remission rate. However, the higher dosage showed higher rates of infection and several adverse reactions when compared to the placebo and 50 mg group. Fortunately, more research approaching the issue from different perspectives have arisen in recent studies.

New Medications - Nick

Current therapies that target the migration and adhesion of leukocytes and signaling pathways are promising treatments for inflammatory bowel diseases. One such drug, vedolizumab, is a humanized anti-α4 integrin monoclonal antibody that inhibits the movement of leukocytes into the intestine by repressing the communication between the leukocyte and the gastrointestinal vessels. Specifically, it inhibits adhesion of MAd-CAM-1, a ligand that binds to α4β7-integrin on T cells which triggers extravasation, and results in the selective barrier for trafficking of inflammatory cells. Vedolizumab has been shown to increase successful remission of ulcerative colitis from 33% to 50% of cases. Alongside, another humanized monoclonal antibody by the name of etrolizumab acts as an adhesion molecule inhibitor that selectively binds to the β7 subunit of integrins α4β7 and αEβ7.

JAK (Janus-activated kinase) inhibitors take advantage of the importance of intracellular messengers and cytokines in inflammatory response. Tofacitinib is a well-known JAK inhibitor molecule that specifically targets JAK1, JAK2, and JAK3 as well as blocks cytokine receptors. The inhibition of these tyrosine kinases help monitor the signaling of interleukin receptors including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. In particular, inhibition of JAK1 by tofacitinib prevents the stimulation of proinflammatory cytokines (IL-6 and interferon γ) and inhibition of JAK2 blocks signaling to erythropoietin, a cytokine hormone with multiple functions including stimulating production of red blood cells and decreasing TNF-α production.

Ongoing Research on Immunotherapy and Genetic Initiative - Nick

https://aacijournal.biomedcentral.com/articles/10.1186/s13223-016-0142-0#Tab5

Recents studies have noted that food allergies can trigger hypersensitive reactions and is associated with the pathogenesis of Crohn's disease and ulcerative colitis. 102 patients undergoing clinical trials were split into 4 groups: specific immunotherapy (SIT), *Clostridium butyricum* (CB) capsules, SIT and CB, and placebo group. Specific immunotherapy general involves the administering of allergens in increasing dosage until an effective immunologic tolerance is reached. This process decreases the symptoms that come with hypersensitive reactions and prevents long-term recurrence of the ailment. Results indicate that SIT and CB conjunction treatments showed significant decrease in truncated Mayo scores while the other treatment groups did not. Another approach is understanding the genetic markers that result in ulcerative colitis. Scientists have identified well over 100 genes that increase the risk of IBD but have yet to discover their function in the bigger picture. One recent study discovered ADCY7, a

missense variant, that doubles the risk of developing ulcerative colitis. 1,767 patients with ulcerative colitis has their genome sequenced and analyzed, comparing them to control populations, to find an association with a 0.6% frequency in ADCY7 that constitutes increased risk of ulcerative colitis. This form of analysis can lead to whole genome sequencing that are able to detect IBD susceptibility early on.

The microbiome has been a shrouded mystical subject in the past. In recent years, a number of cross-sectional analyses of gut microbiome reveal variable as well as consistent findings. *Proteobacteria* phylum, a major phylum of gram-negative bacteria, display increased population while *Firmicutes* phylum, mostly gram-positive bacteria, show decreased population in inflammatory bowel disease patients' stools compared to non-IBD controls. The diversity of the gut microbiome is generally decreased across all studies with patients with IBD. Many subsequent studies have tested to see if the imbalance in the bacteria population was the culprit and found inconclusive evidence for cause as bacterial composition mostly changed independently of bowel inflammation. Continuous observation and long-term studies are needed to answer further questions of whether the bacterial community is a factor in the pathogenesis of ulcerative colitis and other inflammatory diseases. What is clear is that microbe effects depend moreso on the aggregate function that can cause a pathophysiological response in the host. Presence and expression of certain function pathways were observed in bacteria communities. It was seen that more pathways and protein production relating to oxidative stress, nutrient transport, and nutrient uptake were seen in IBD patients compared to control. Researchers predicted that bacteria adapted for survival in the inflammatory environments.

Sources:

- The morbid appearance of the intestine of Miss Banks
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