Inflammatory Bowel Disease (IBD)

&

Laboratory Diagnosis

1-Immunopathogenesis of **inflammatory bowel disease (IBD)** including Crohn's disease (CD) & Ulcerative colitis (UC), (Dr. Khoshmirsafa, 45 min)

2- Laboratory diagnosis of IBD: biochemical and immunological findings (Dr. Sarafnejad, 30min)

3- Recent Findings and the Importance of Autoantibodies in Laboratory Differentiation between **Crohn's Disease** and **Ulcerative Colitis,** (Dr. Shekarabi, 30 min)

4- The role of laboratory and pathological methods for monitoring and follow up of patients with IBD, (Dr. Zahedifard, 30 min)

5- Conclusion and group discussion (15 min)

Immunopathogenesis of **Inflammatory Bowel Disease**

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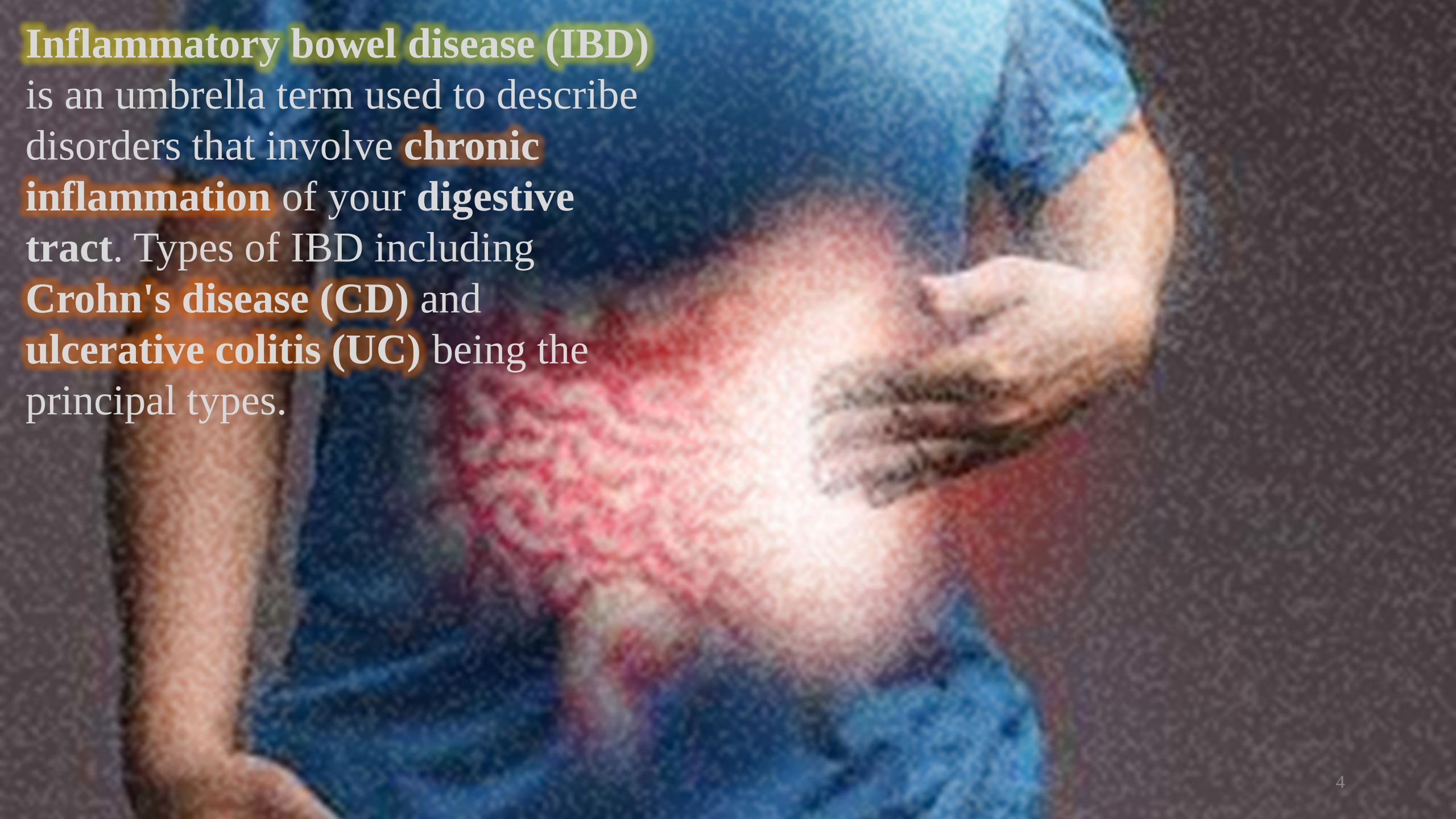
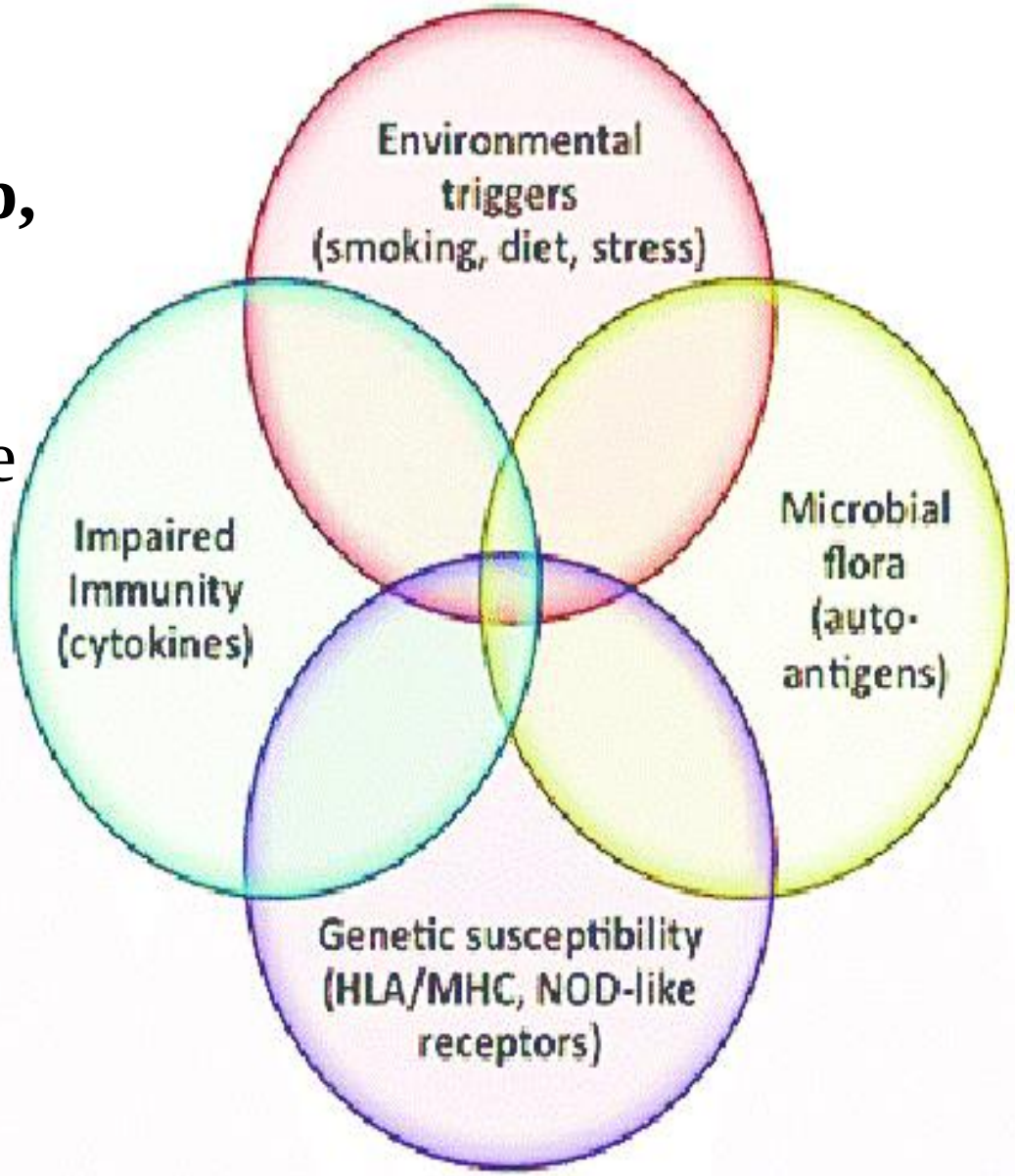
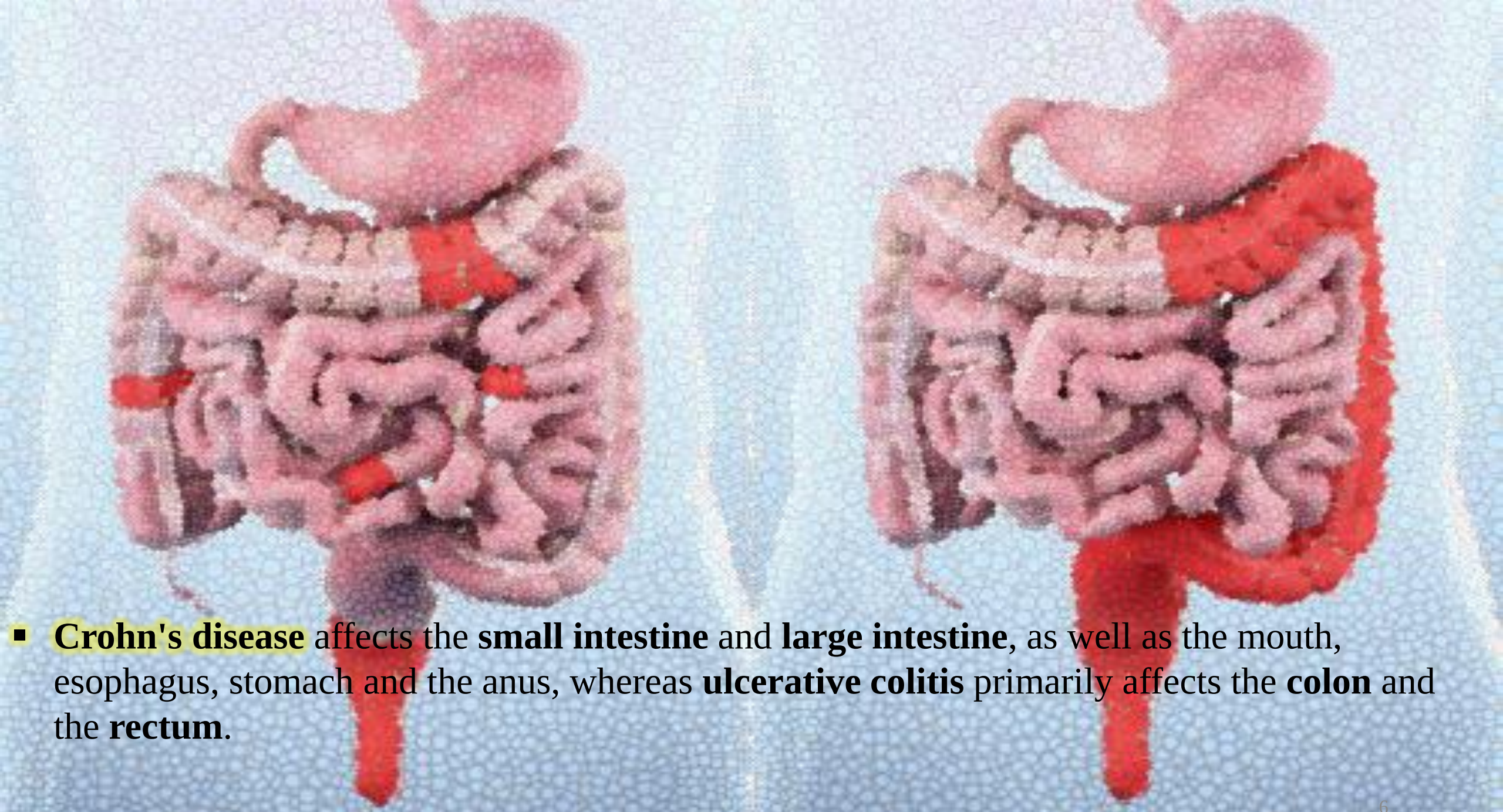


Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that involve **chronic inflammation** of your **digestive tract**. Types of IBD including **Crohn's disease (CD)** and **ulcerative colitis (UC)** being the principal types.

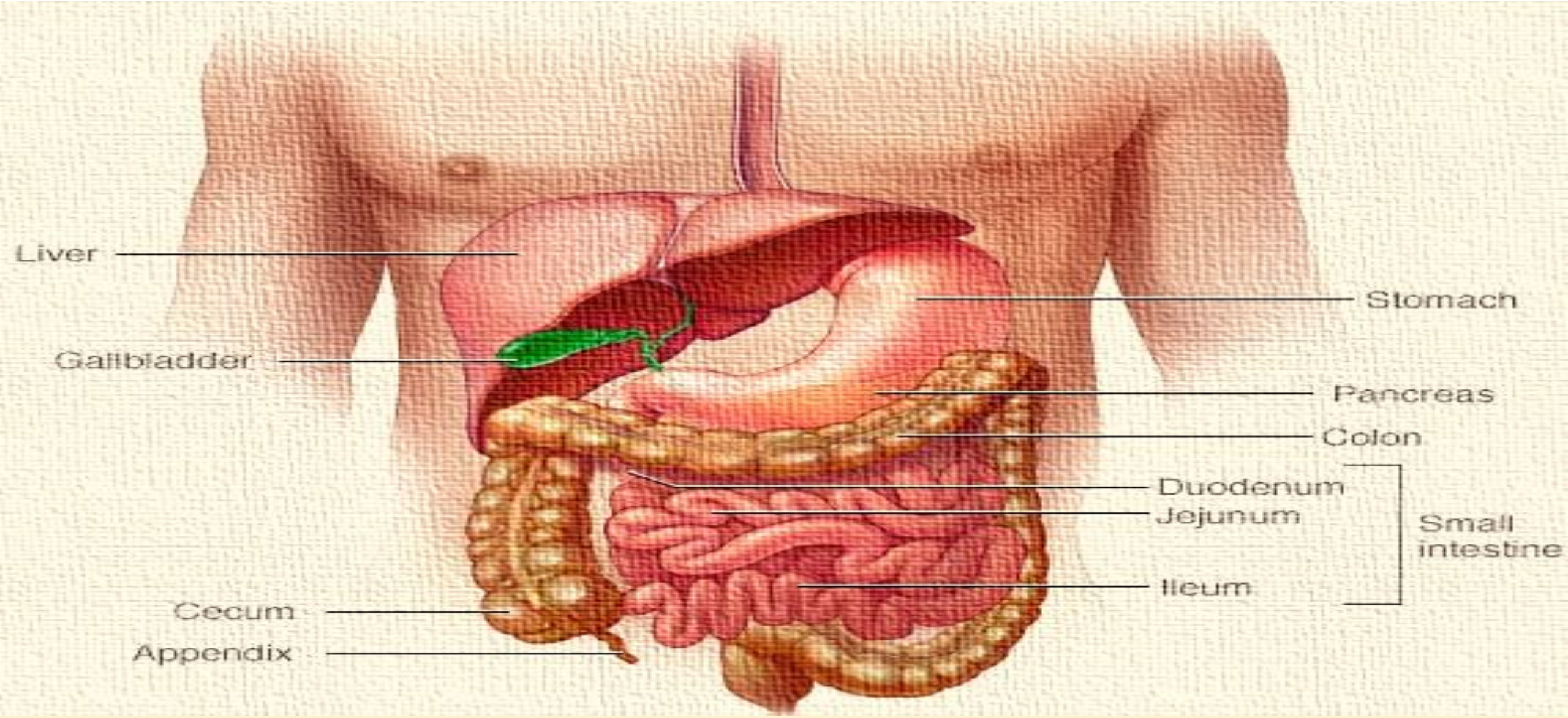
Pathophysiology of Inflammatory Bowel Diseases

- IBD is thought to arise from a combination of **environmental components, genetic make up, gut microbiota,** and the **immune system**.
- **Chronic inflammation** is, ultimately, a **dysregulated immune response**, and therefore much of the investigation of IBD pathogenesis has been focused on **immune abnormalities**.
- IBD also occurs in dogs and cats. The term **"chronic enteropathy"** might be better to use than "inflammatory bowel disease" in dogs because it differs from IBD in humans in how the dogs respond to treatment.





- **Crohn's disease** affects the **small intestine** and **large intestine**, as well as the mouth, esophagus, stomach and the anus, whereas **ulcerative colitis** primarily affects the **colon** and the **rectum**.



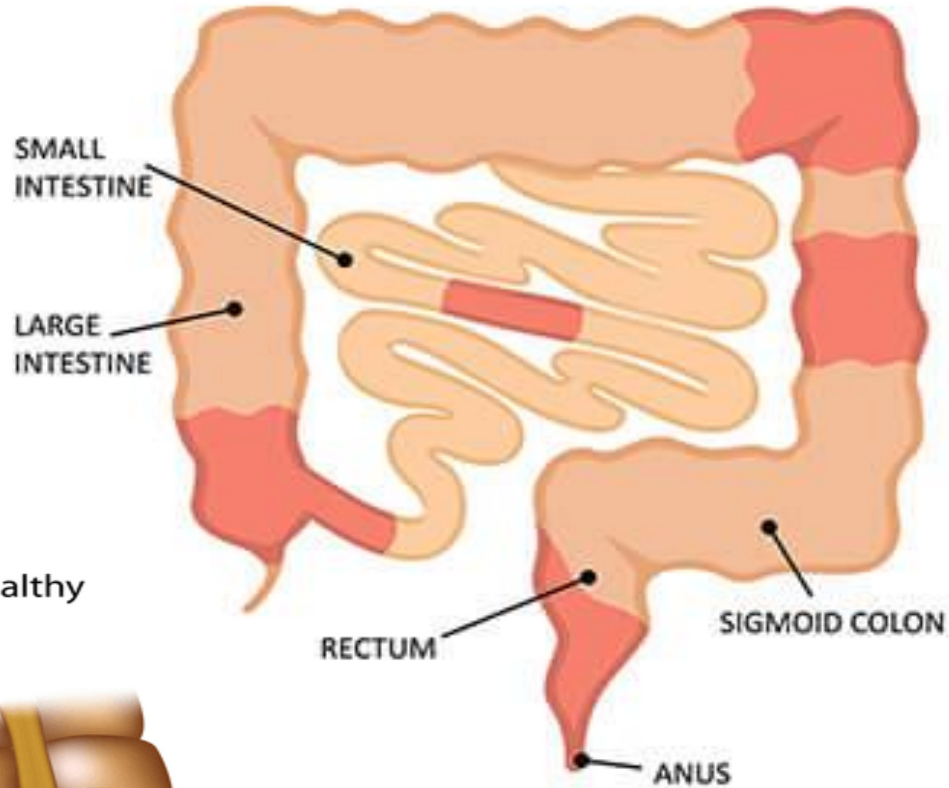
Digestive system, Crohn's disease (CD) and **ulcerative colitis** (UC) are both forms of IBD.

✓ **CD** most commonly affects the **colon** and the last part of the **small intestine** (**ileum**).

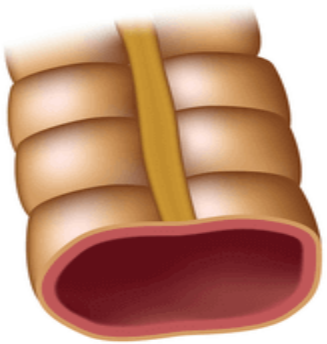
✓ UC affects only the colon.

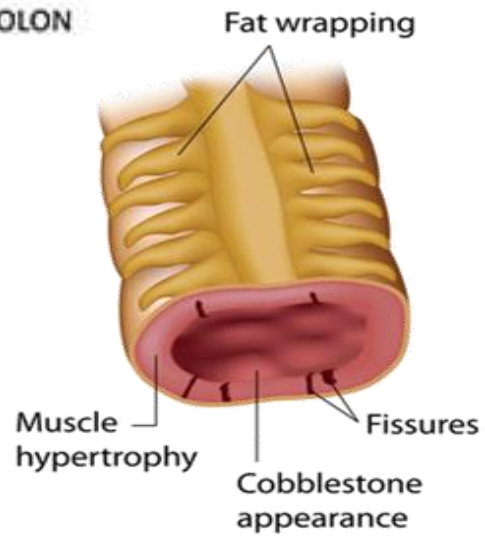
CROHN'S DISEASE

PATCHY INFLAMMATION THROUGHOUT SMALLAND LARGE BOWEL



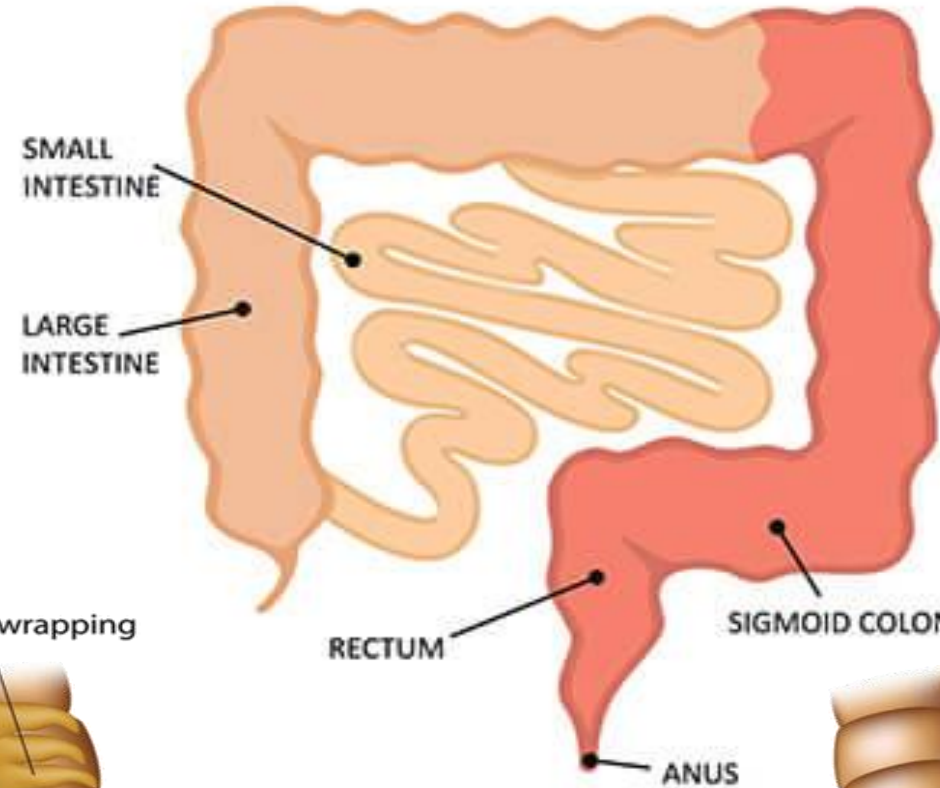
Healthy

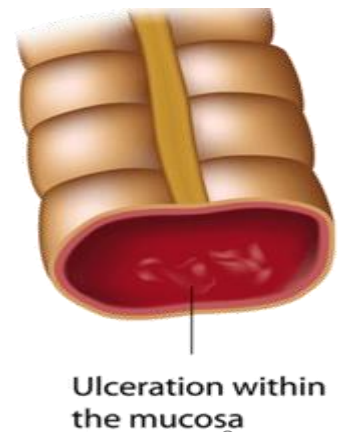




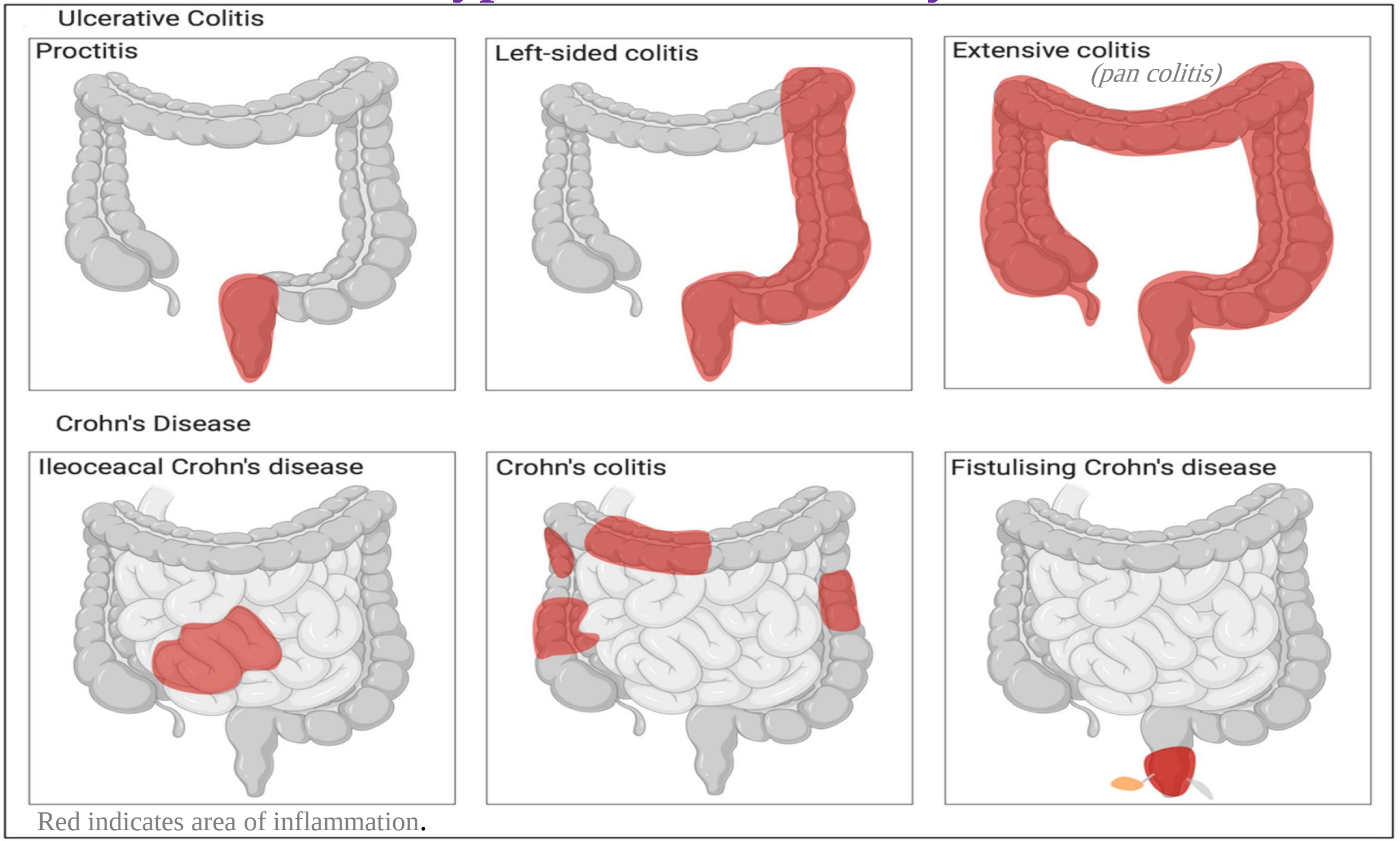
ULCERATIVE COLITIS

CONTINUOUS AND UNIFORM INFLAMMATIONIN THE LARGE BOWEL





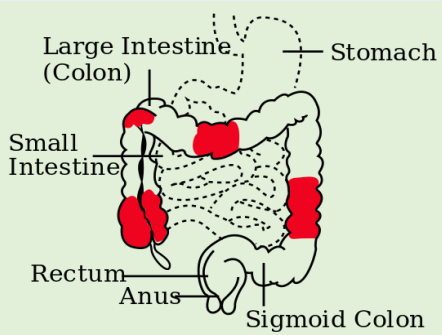
Different types of Inflammatory Bowel diseases.

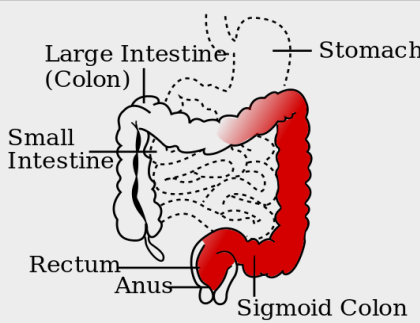


Red indicates area of inflammation.

Diagnostic Findings

	Crohn's disease	Ulcerative colitis
Terminal ileum involvement	Commonly	Seldom
Colon involvement	Usually	Always
Rectum involvement	Seldom	Usually (95%)
Involvement **around the anus**	Common	Seldom
Stenosis	Common	Seldom
Bile duct involvement	No increase in rate of primary **sclerosing cholangitis**	**Higher rate**
Distribution of disease	Patchy areas of inflammation (skip lesions)	Continuous area of inflammation
Endoscopy	**Deep geographic** and **serpiginous** (snake-like) ulcers	Continuous ulcer
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Granulomas on biopsy	May have non-necrotizing non-peri-intestinal crypt granulomas	Non-peri-intestinal crypt granulomas not seen





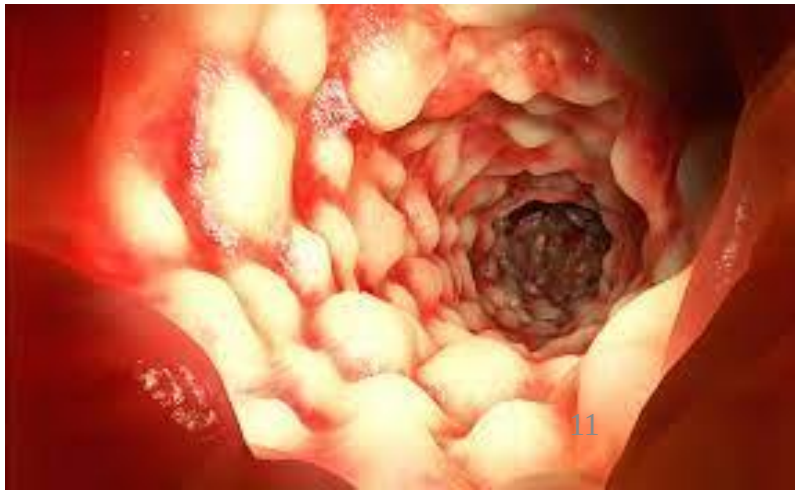
Signs and Symptoms

Defecation	Often porridge-like, sometimes steatorrhea	Often mucus-like and with blood
Tenesmus	Less common	More common
Fever	Common	Indicates severe disease
Fistulae	Common	Seldom
Weight loss	Often	More seldom

Signs and symptoms

- In spite of CD and UC being **very different diseases**, both may present with any of the following symptoms: **abdominal pain**, **diarrhea**, **rectal bleeding**, severe internal **cramps**/muscle spasms in the region of the pelvis, and **weight loss**.
- **Anemia** is the most prevalent extra intestinal complication of IBD.
- Associated complaints or diseases include **arthritis**, **pyoderma gangrenosum**, **primary sclerosing cholangitis**, and **non-thyroidal illness syndrome** (NTIS).
- Associations with **deep vein thrombosis** (DVT) and **bronchiolitis obliterans organizing pneumonia** (BOOP) have also been reported.

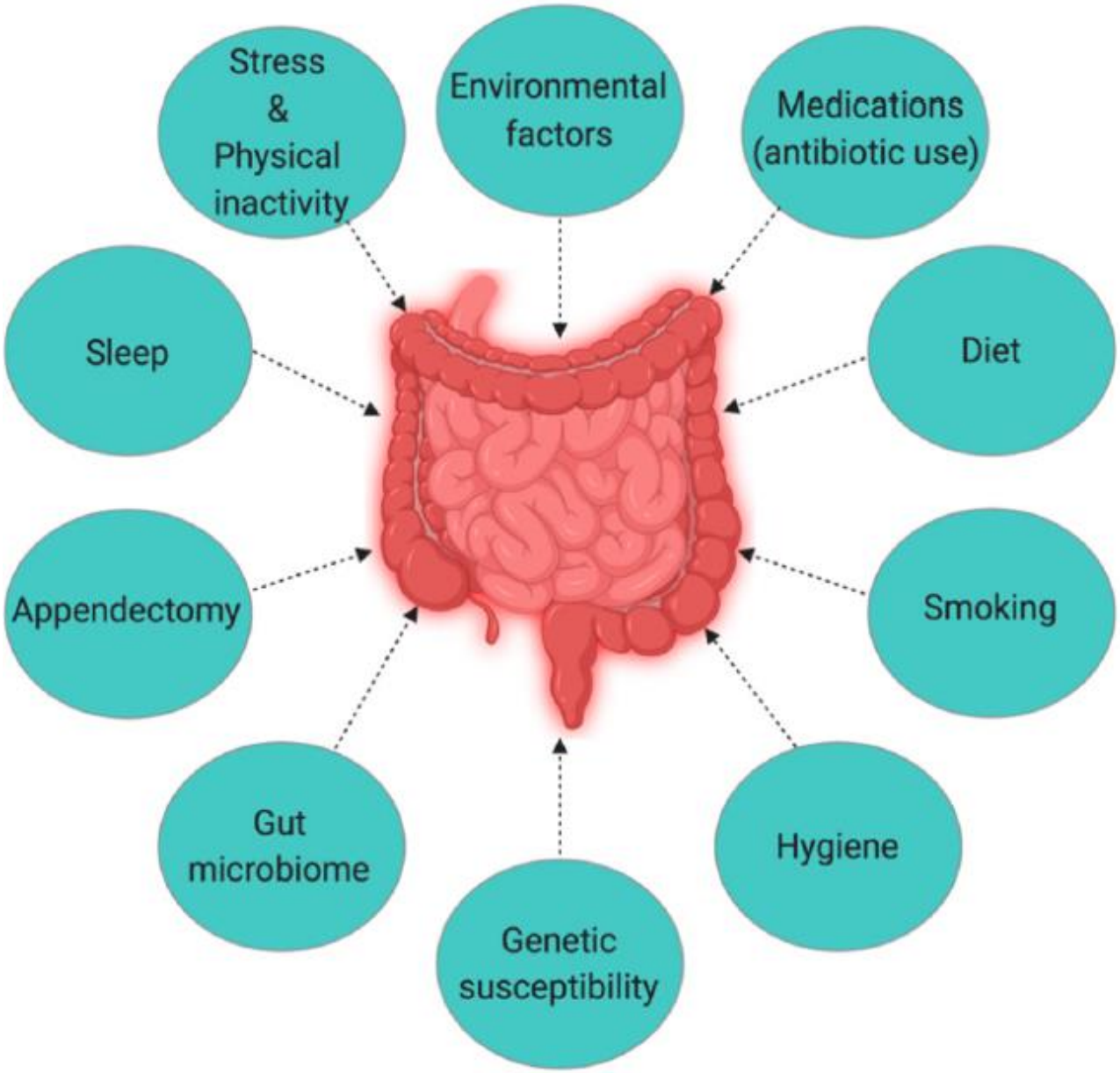
- Diagnosis is generally by assessment of serologic tests, **inflammatory markers** in **stool** followed by **colonoscopy** with **biopsy** of pathological lesions.



Immunological pathogenesis of inflammatory bowel disease

- The 2 subtypes of IBD are characterized by **chronic inflammation** in the gastrointestinal tract and **repeated** cycles of **relapse & remission**.
- Although UC and CD show differences in their clinical presentation, the **same risk factors** are implicated in the **pathogenesis** of both subtypes.
- The pathogenesis of both UC and CD involve **genetic factors**, environment, **changes in the gut microbiome**, and **immune response** including **cytokines** and **immune cells**.
- Phenotypes common to both subtypes include **chronic inflammation** and a **dysregulated immune inflammatory response**; therefore, much of the research on IBD pathogenesis has focused on the ***immune system***.

The interplay of factors causing inflammatory bowel disease (IBD)



Genetic Susceptibility → **Environment Factors** → **Gut Microbiota**

Immune Reponses

Epidemiological evidence **shows a clear** correlation between the decrease in infectious diseases, lack of parasites, use of antibiotics, vaccinations and a general improvement in food, water and housing sanitary conditions with an increase in the incidence of autoimmune and chronic inflammatory disorders. This finding forms the basis of the so-called **hygiene hypothesis**, which is supported by the fact that the microbiota is fundamental to the '**education**' of the immune system after birth.

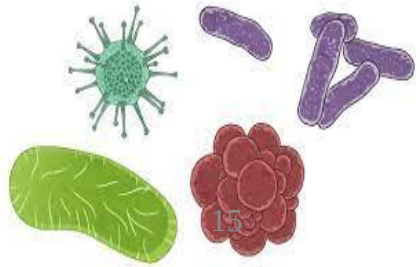
Environmental components

- Among various components of **modern lifestyle** several have emerged as modifiers of **systemic & intestinal immunity**, such as **alterations of the microbiota**, **antibiotics**, diet, smoking & vitamin D.

- Risk of IBD markedly increases in **children repeatedly** exposed to **antibiotics** in **early life** & in adults after an episode of acute **gastroenteritis**, events probably secondary to changes in the gut microbiota.

- **Western pattern diets** also modify the composition and function of the microbiota, as do smoking and ubiquitous food additives.

- Availability of **vitamin D**, an important regulator of **mucosal immunity**, depends not only on ingestion, but also on sunlight, and **low sunlight exposure** is a risk factor for CD.



- **LPS**, a ubiquitous bacterial product with **potent immunoregulatory actions**, and LPS levels are lower in house dust samples from children with IBD than from HCs.

Genetics

- The known association of **fibrostenosing CD** with **NOD2** gene variants is found primarily in patients of European or Jewish ancestry, but not in patients of Japanese or Chinese ancestry.
- The first IBD-based genome wide association study (**GWAS**) revealed that **IL23R**, a gene encoding the receptor of the proinflammatory cytokine IL-23, was associated with both CD & UC.

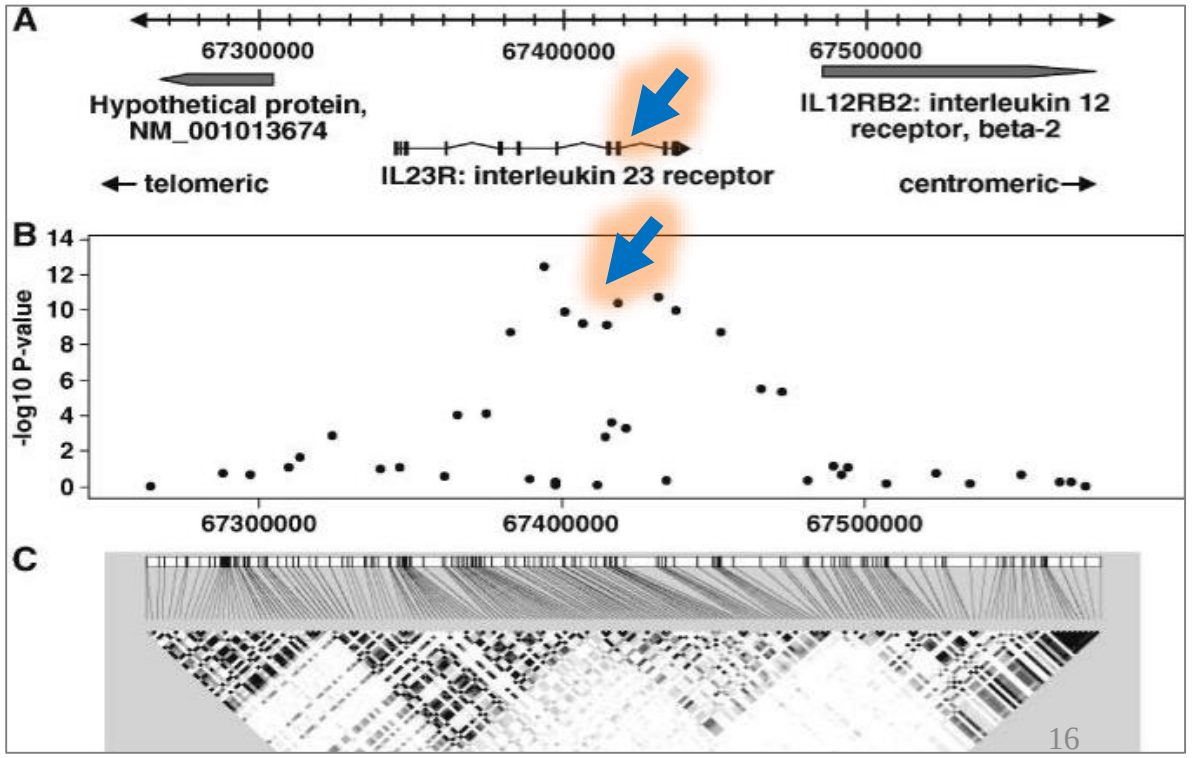
> Science. 2006 Dec 1;314(5804):1461-3. doi: 10.1126/science.1135245. Epub 2006 Oct 26.

A genome-wide association study identifies IL23R as an inflammatory bowel disease gene

Richard H Duerr [1], Kent D Taylor, Steven R Brant, John D Rioux, Mark S Silverberg, Mark J Daly, A Hillary Steinhart, Clara Abraham, Miguel Regueiro, Anne Griffiths, Themistocles Dassopoulos, Alain Bitton, Huiying Yang, Stephan Targan, Lisa Wu Datta, Emily O Kistner, L Philip Schumm, Annette T Lee, Peter K Gregersen, M Michael Barmada, Jerome I Rotter, Dan L Nicolae, Judy H Cho

Affiliations + expand

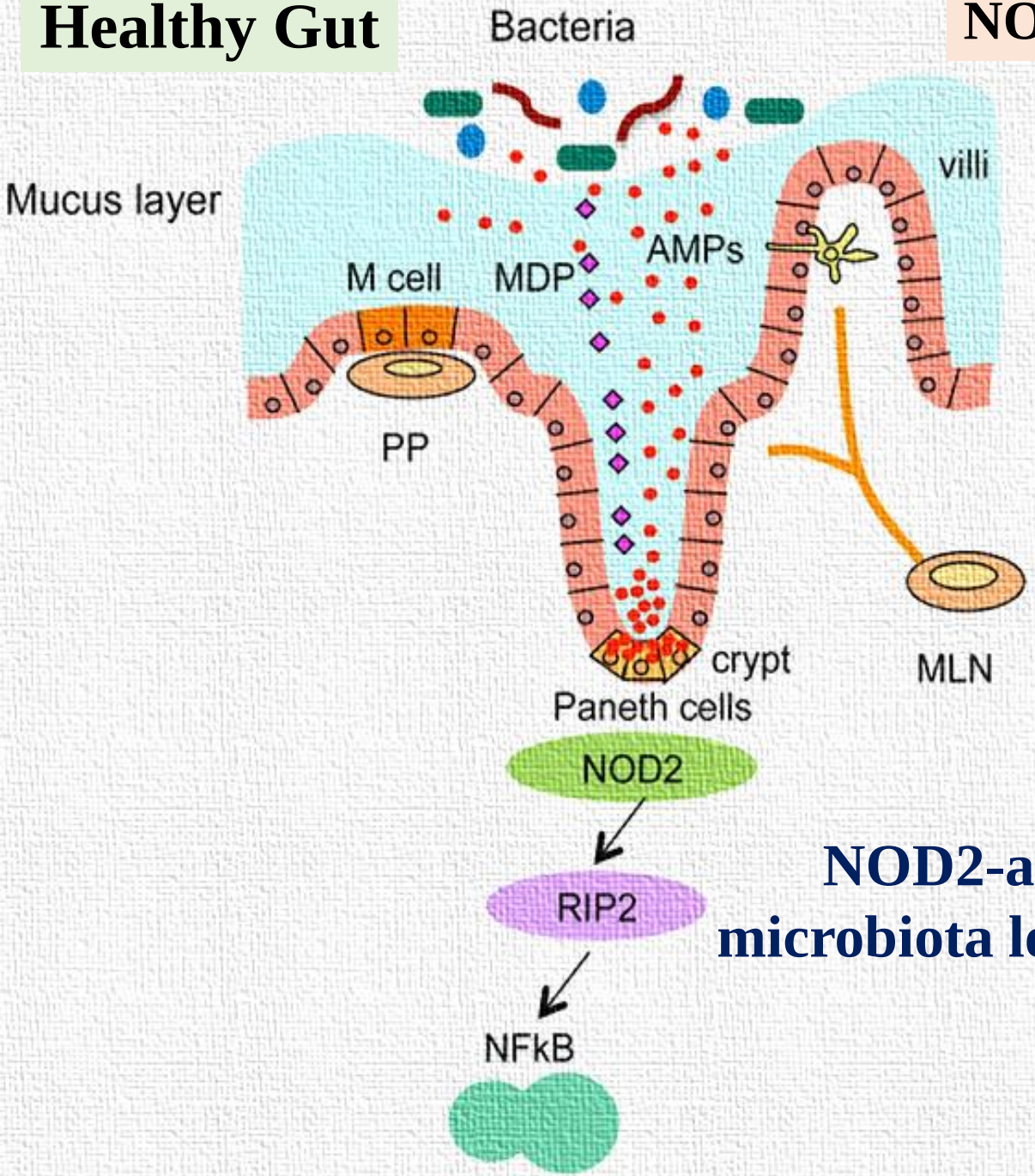
PMID: 17068223 PMCID: PMC4410764 DOI: 10.1126/science.1135245



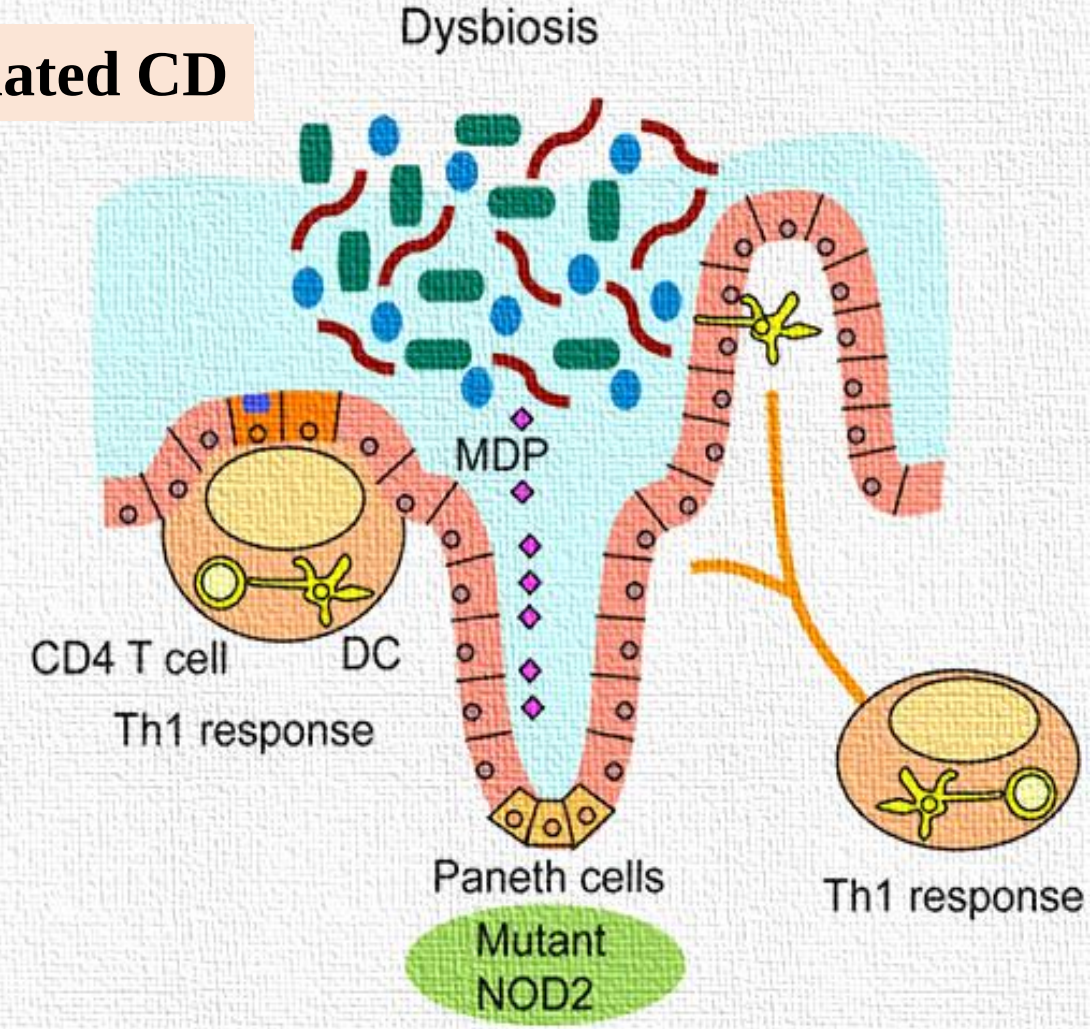
NOD2

- A member of the **NOD-like receptor (NLR) family**, NOD2 encodes the primary receptor for **muramyl dipeptide (MDP)** found in all Gram-negative & positive bacteria.
- **NOD2 signaling** is essential for bacterial recognition, making it a key player in **innate immune** responses and **regulation** of the commensal microbiota.
- Most investigators currently agree that a **loss of NOD2 function** is a **key pathogenic** event in CD, as defective NOD2 would lead to increased inflammation due to impaired bacterial clearance.
- In addition, **NOD2 variants** have been reported to **suppress** transcription of **IL-10**, a potent anti-inflammatory cytokine.
- A complete understanding of the role of NOD2 in CD is confounded by other NOD2-dependent activities, including induction of **autophagy**, alternate activation pathways and **modulation of adaptive** immunity.

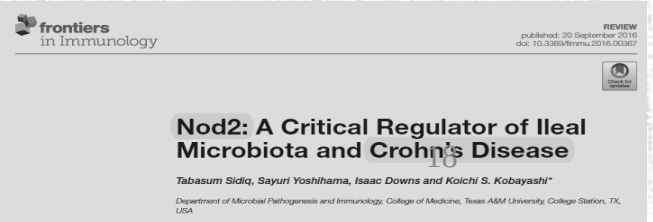
Healthy Gut



NOD2 associated CD



NOD2-associated dysregulated microbiota leads to the susceptibility of CD


frontiers in Immunology

REVIEW
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Nod2: A Critical Regulator of Ileal Microbiota and Crohn's Disease

Tabasum Sidiq, Sayuri Yoshihama, Isaac Downs and Koichi S. Kobayashi*

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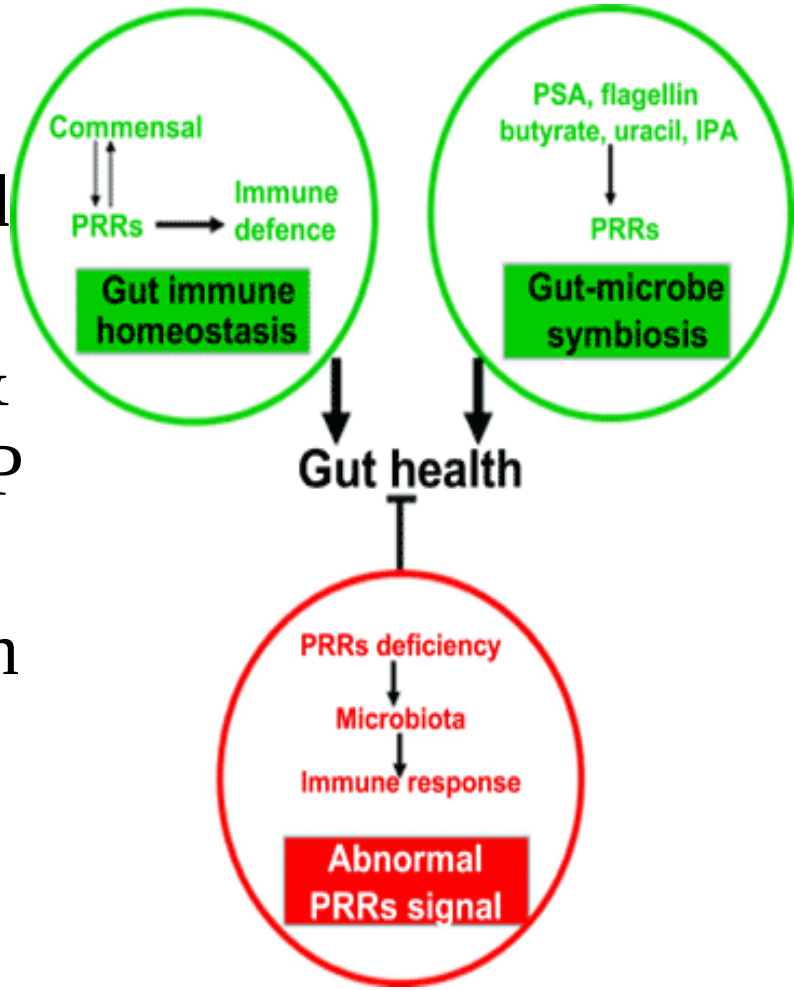
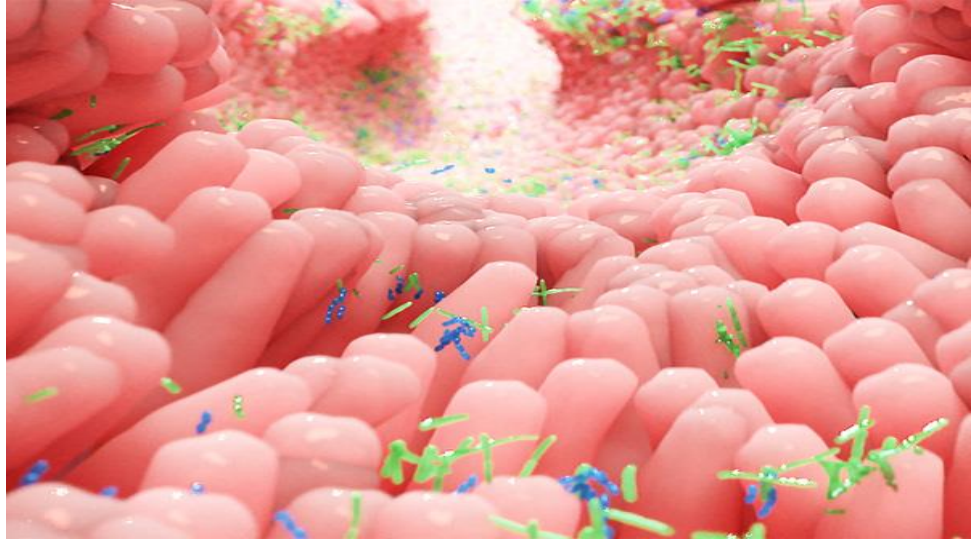
Gut microbiota and immunity

- Early environmental exposures, including **delivery mode**, **milk**, **food**, **hygiene** & **several.**
- Other factors exert a fundamental effect on shaping the **intestinal microbiota** in childhood, whilst in **adulthood** the gut microbiota is **more stable**.
- The microbiota is **controlled by** products of epithelial & immune cells, such as the **mucus**, secretory IgA, & AMP (RegIIIγ, defensins) .
- **Mucosal immunity** is regulated by the **microbiota**, with certain microbes favoring the growth of distinct T-cell subsets, such as **segmentous filamentous bacteria**, **Clostridia** and **Bacteroides fragilis** promoting the induction of TH17, Treg cells and TH1 cells, respectively.

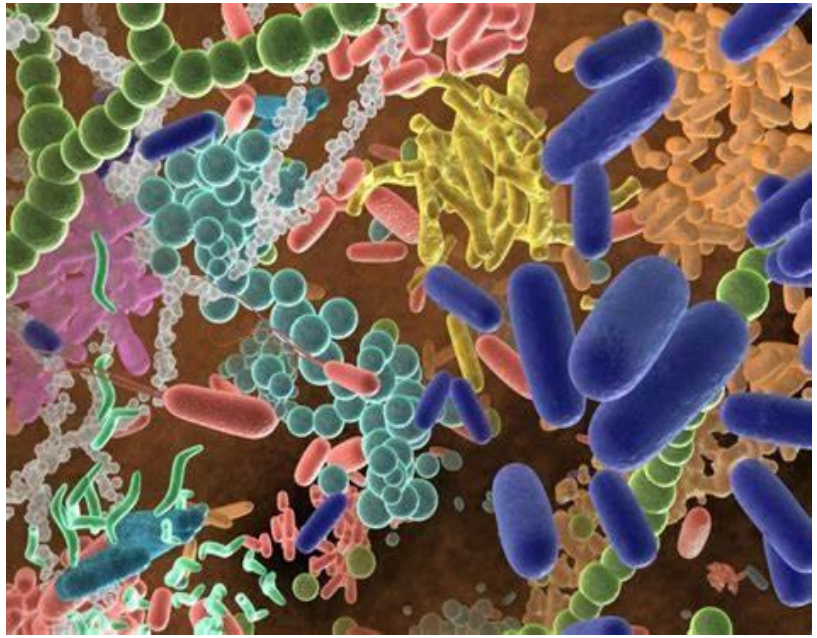


Gut microbiota in IBD



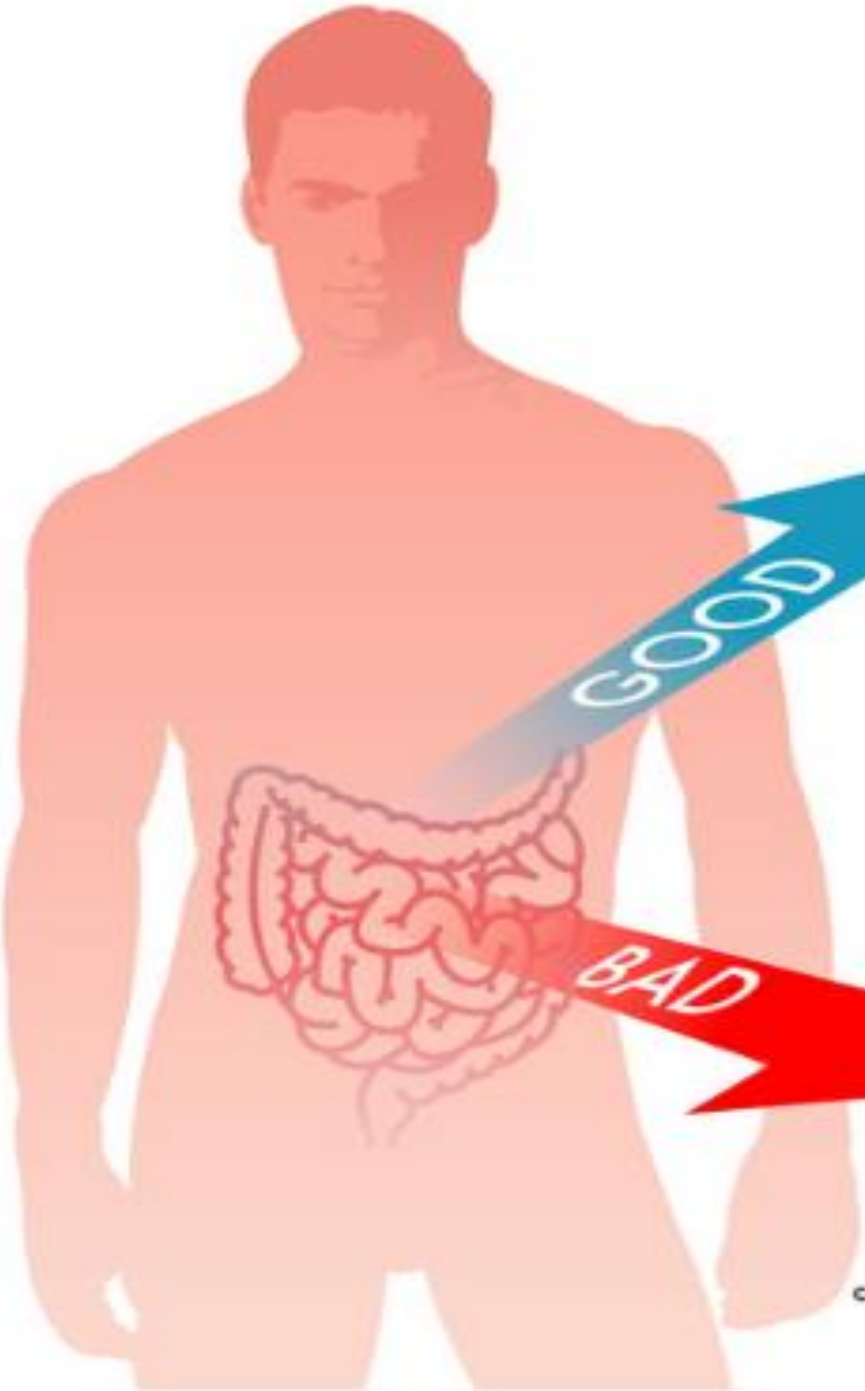
- Enhanced **immune reactivity** against microbial antigens has long been recognized in IBD
- Patients with **CD** have **circulating serum antibodies** against microbial antigens, including **Saccharomyces cerevisiae (baker's yeast), Escherichia coli**, outer membrane protein C, anti-Cbir1 flagellin (the CD-related bacterial sequence I2) and anti-Pseudomonas fluorescens.
- In patients with **CD**, there is an increased abundance in **Bacteroidetes** and **Proteobacteria** and a decrease in abundance of **Firmicutes**, as well as a decreased bacterial **diversity**.
- Evidence of abnormal gut microbiota in patients with **UC** has also been documented, but to a somewhat lesser degree than for CD.

- A product of the **human** **symbiont** **Bacteroides fragilis**, can **suppress** **IL-17** production & improve experimental colitis, & a reduced number of Faecalibacterium prausnitzii, which have anti-inflammatory properties, is found in patients with CD with an increased risk of postoperative recurrence after resection for **ileal disease**.



- In new-onset paediatric patients with CD, an increase in the abundance of **Enterobacteriaceae**, **Pasteurellaceae**, **Vellonellaceae** and **Fusobacteriaceae** & a decrease in the abundance of **Erysipelotrichales**, **Bacteroidales** & **Clostridiales** has been reported, which strongly correlated with **levels of inflammation**.
- **Antibiotic** exposure amplifies this **dysbiosis**, again reinforcing the fundamental importance of environmental factors in shaping gut microbial communities.

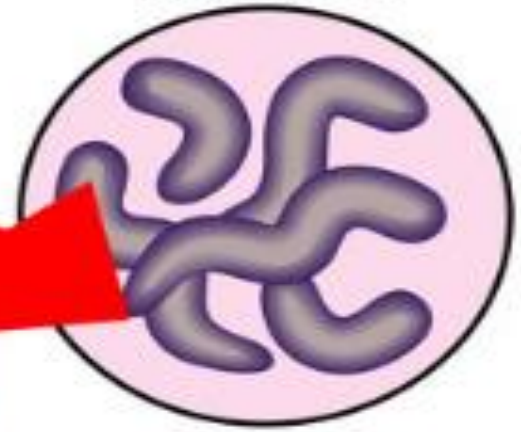
Good and Bad Bacterial Flora



BIFIDOBACTERIA
The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.

ESCHERICHIA COLI
Several types inhabit the human gut. They are involved in the production of vitamin K2 (essential for blood clotting) and help to keep bad bacteria in check.
But some strains can lead to illness.

LACTOBACILLI
Beneficial varieties produce vitamins and nutrients, boost immunity and protect against carcinogens.

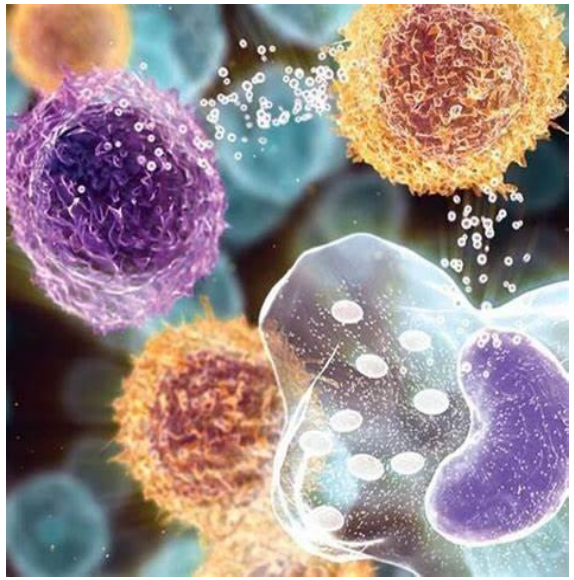


CAMPYLOBACTER
C Jejuni and C coli are the strains most commonly associated with human disease. Infection usually occurs throught the ingestion of contaminated food.

ENTEROCOCCUS FAECALIS
A common cause of post-surgical infections.

CLOSTRIDIUM DIFFICILE
Most harmfull following a course of antibiotics when it is able to proliferate.

Cytokines



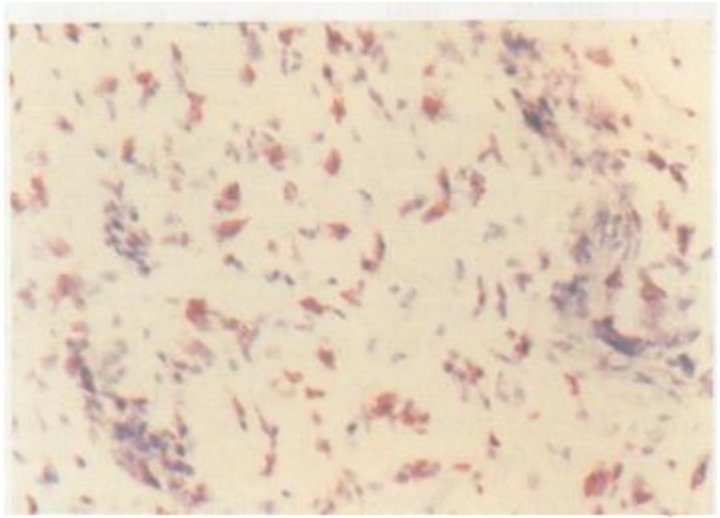
- Several pro-inflammatory cytokines are involved in the **progression** of IBD.
- The **IL-1 family** of cytokines has a **key role** in IBD pathogenesis.
- In **UC, IL-1β** promotes inflammation because IL-1 originates from monocytes, macrophages, & active IL-1β is expressed in the **colonic mucosa**.
- **IL-18** is also an IL-1 family member and is increased in the **mucosa** of CD patients. It has been suggested that **IL-18 increases** the Th1 response. However, in CD patients with active disease, IL-10 released from mucosal T cells was decreased by IL-18.
- **IL-33**, another member of the IL-1 family, **stimulates mucus secretion** to protect the **epithelium** & **upregulates** the expression of **IL-5** and **IL-13** as part of the **Th2** response.
- There is evidence that the expression of IL-33 and its receptor **ST2** are increased in UC patients.
- **IL-6** activates signal **STAT3** & has an important function in the inflammatory response.
- IL-6 & its **soluble IL-6 receptor** were increased in UC and CD patients. IL-6 also has a key role in the pathogenesis of UC and the **carcinogenesis** of **colorectal cancers** related to **UC**.

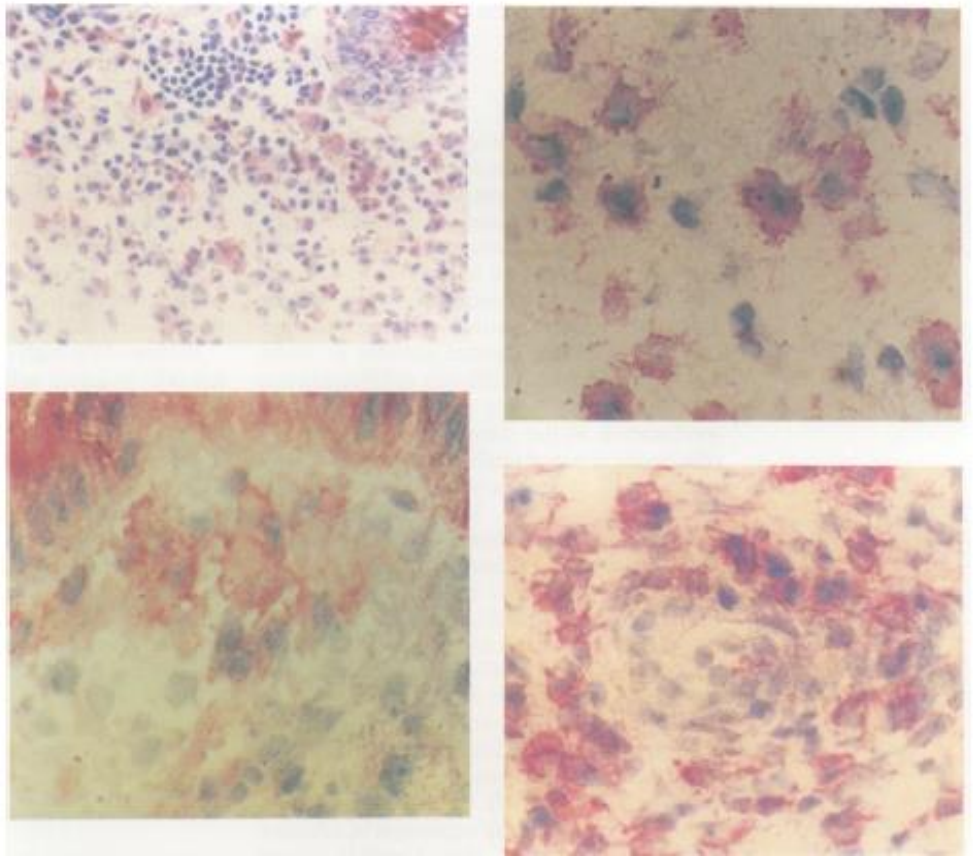
- **TNF-α** has a **significant function** in IBD **pathogenesis** because IL-1β, IL-6, and IL-33 expression can all be increased by TNF-α.
- The clinical severity of UC and CD were correlated with **TNF-α levels** in the **serum** of IBD patients.

Gut 1993; 34: 1705–1709

Location of tumour necrosis factor α by immunohistochemistry in chronic inflammatory bowel disease

S H Murch, C P Braegger, J A Walker-Smith, T T MacDonald

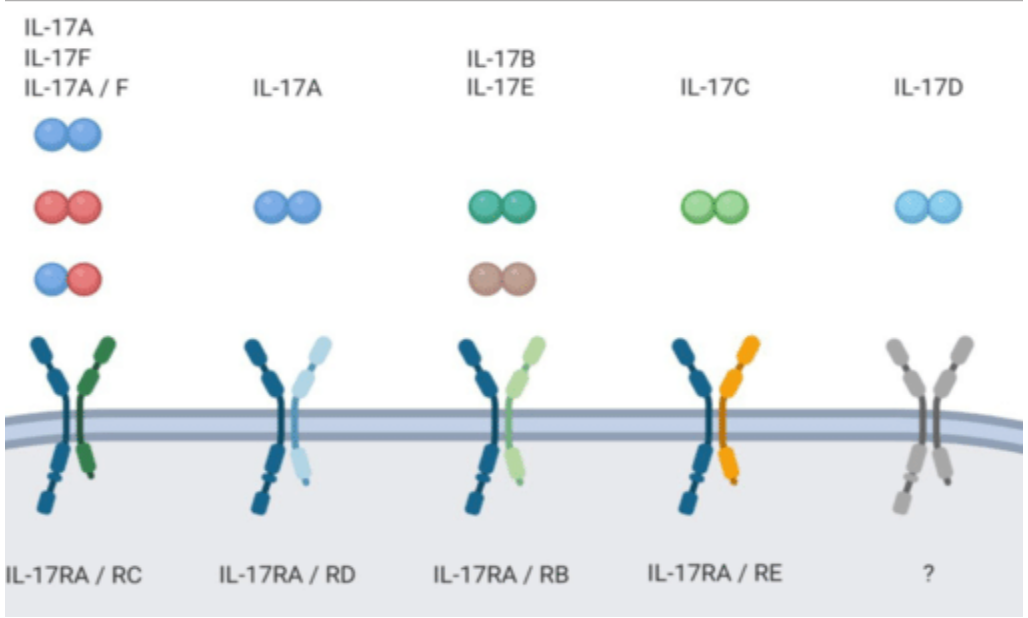




- **IL-10** is a typical **immunosuppressive cytokine** that may have **therapeutic value** for treating chronic IBD. Although IL-10 is an **anti-inflammatory cytokines**, there are **inconsistencies** of **IL-10 concentrations** in IBD.
- A study showed that **gut IL-10 expression levels** were either the **same or higher** in IBD patients than in **normal controls**. It is well documented that **IL-10 gene expression** is higher in the mucosal T cells of UC patients than normal controls.
- Furthermore, IL-10 production is **enhanced in the serum** of CD patients the other hand, other investigation demonstrated that IL-10 levels in serum of patients with UC and CD are similar to healthy subjects. It is also well documented that downregulation of IL-10 promotes disease progression in patients with CD.

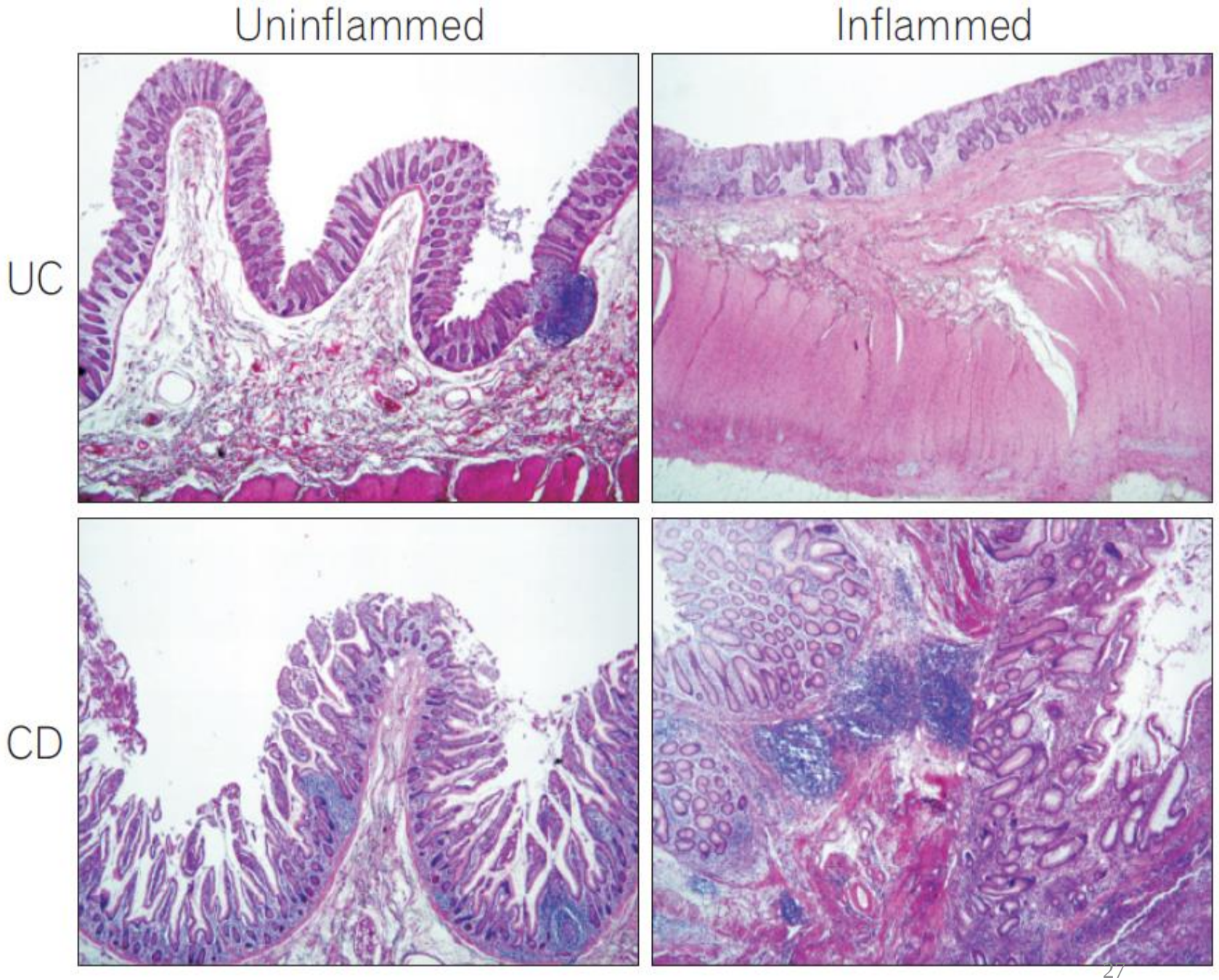
- **TGF-β** has dual activities in the pathogenesis of IBD.
- It stimulates **epithelial compensation** and **fibrosis** and induces tolerance and homeostasis through an impressive immunoregulatory function.
- In the **lamina propria**, TGF-β1 levels in mononuclear cells were enhanced in UC patients but decreased in CD patients.
- TGF-β improved intestinal inflammation by **reducing** the expression of IL-33.

- **IL-17** is a **pro-inflammatory cytokine** that **activates STAT3**, which stimulates a **strong chronic** immune inflammatory response. IL-17 is critical in the pathogenesis of IBD.
- IL-17 mRNA levels were **enhanced** in the inflamed **mucosa** of patients with IBD (both UC & CD).



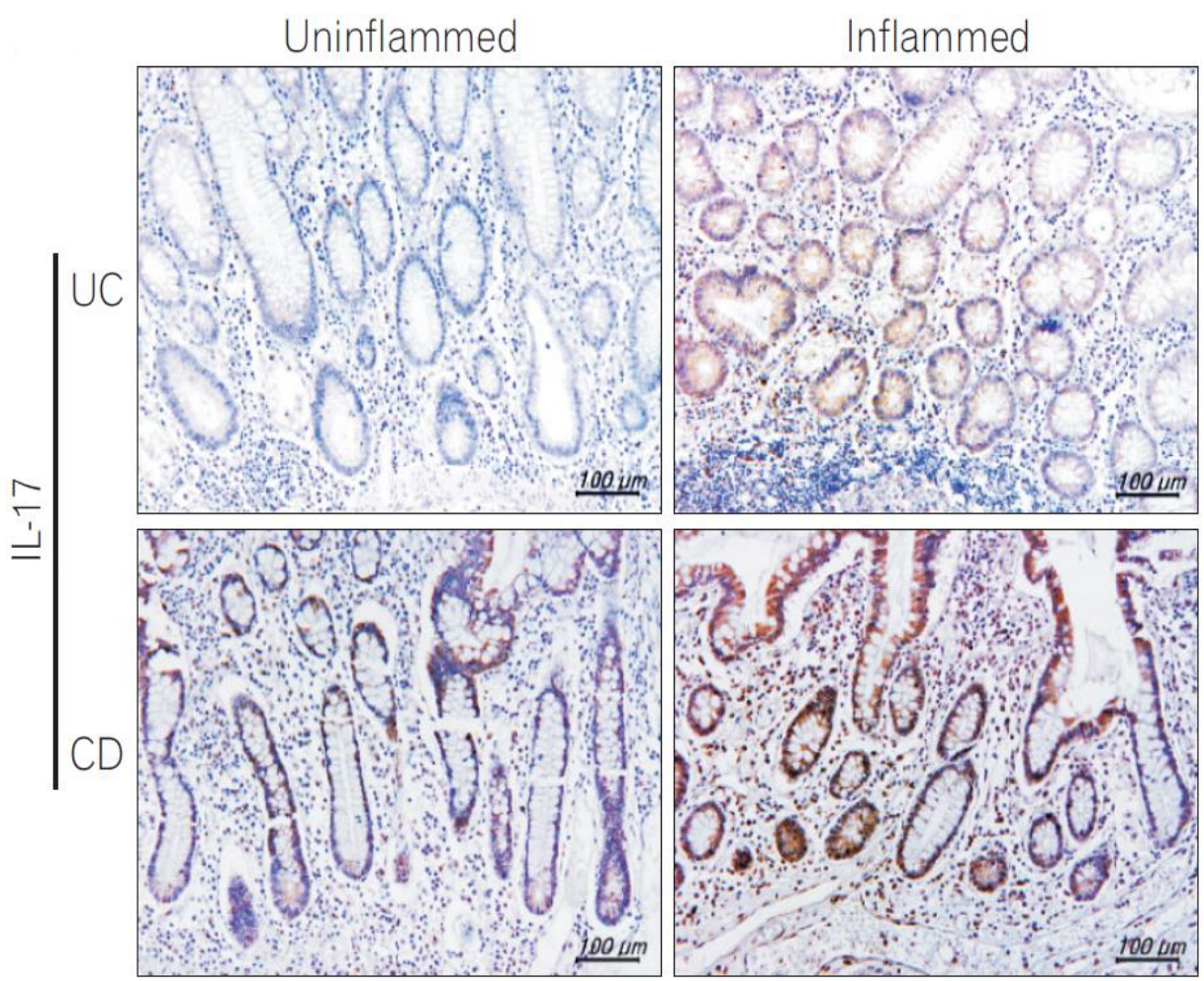
- It has been suggested that **IL-17A inhibition** mediated by phosphorylated STAT3 suppression **decreases inflammation** and the progression **of acute colitis**, whereas **IL-17A** can **improve** experimental colitis.
- Additionally, by reinforcing **tight junction** formation, IL-17 can also protect human intestinal epithelial cells.
- **IL-17** is recognized as a significant inflammatory factor in **CD** pathogenesis. Some studies found higher levels of IL-17 and CD161+ memory cells expressing IL-17 and IFN-γ in CD patients.
- It has been reported that IL-17 can **increase the recruitment** of T cells into the **lamina propria** during the inflammatory response

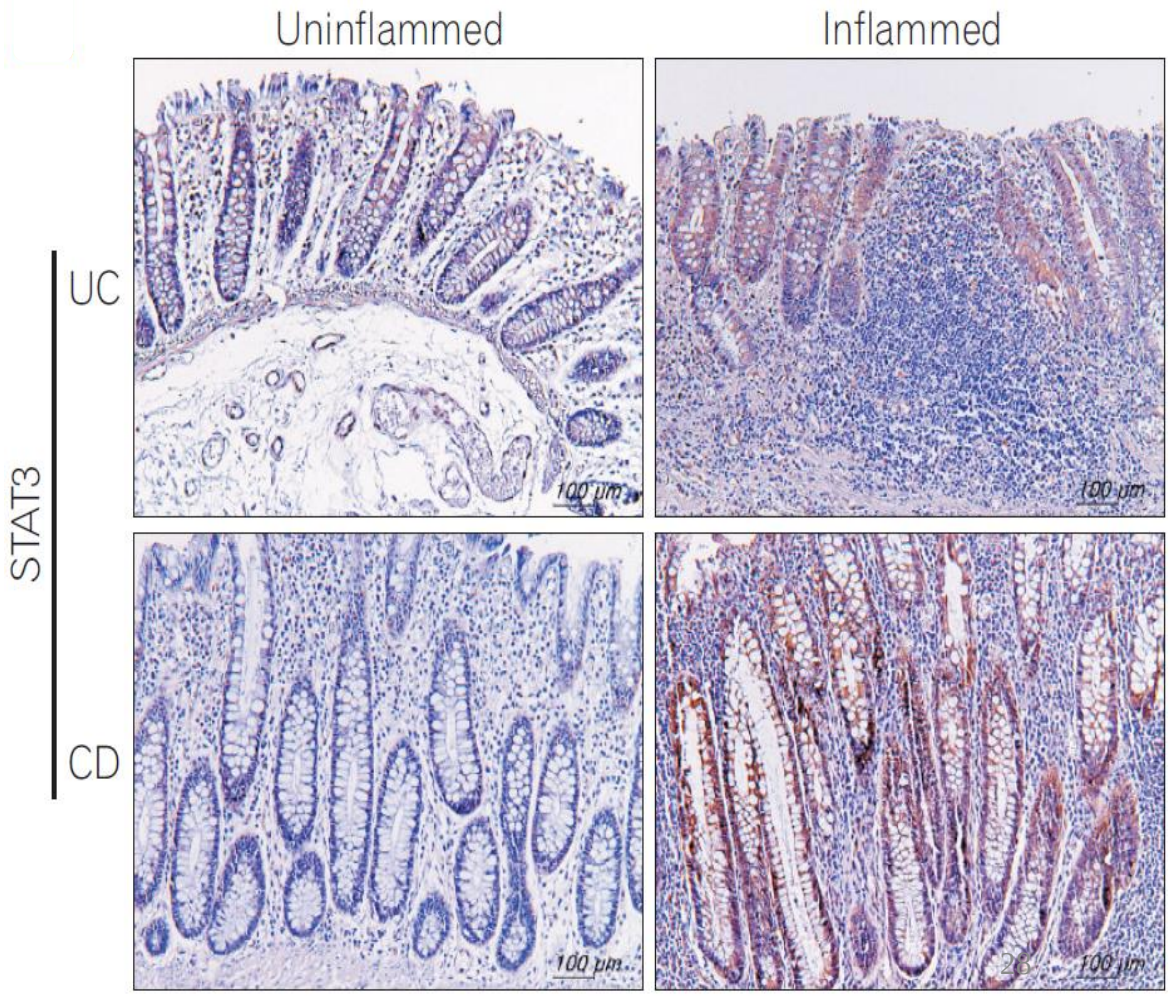
H&E of colon tissue from UC and CD patients (H&E, ×40)



STAT3 and IL-17 expression in colon tissue from UC and CD patients

(Immunohistochemistry, ×200)

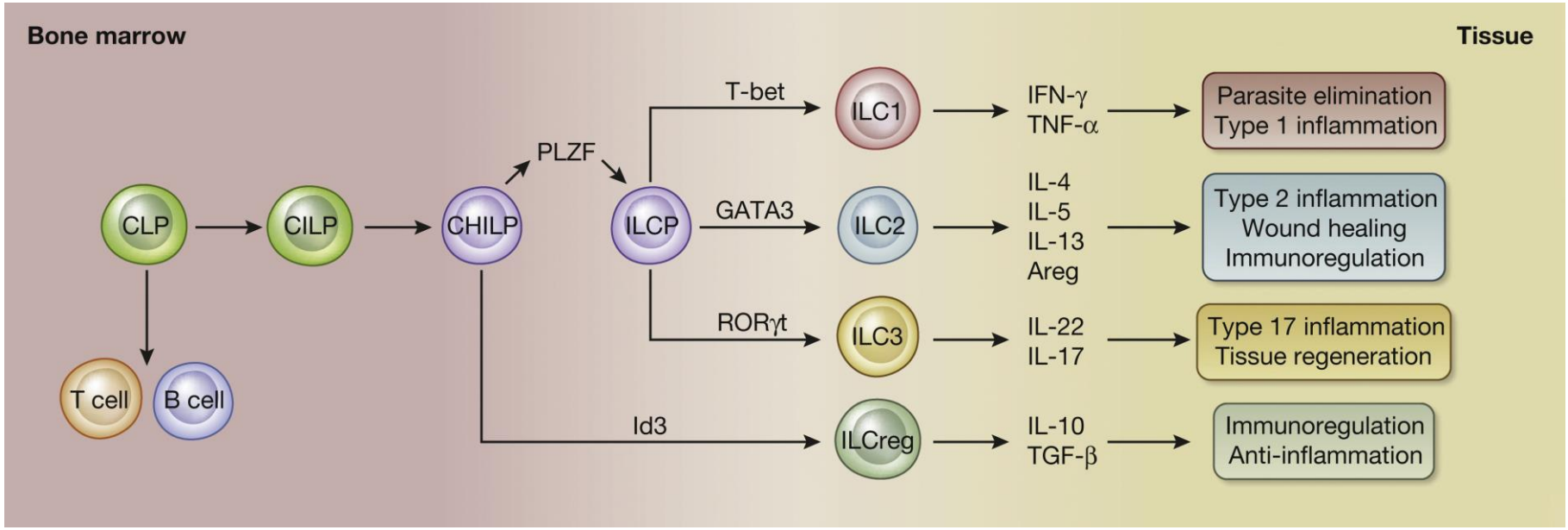




Chemokines (chemotactic cytokines)

- **IL-8** is mainly a **neutrophil chemoattractant** that induces the migration of neutrophils from **peripheral blood** into **inflamed tissue**.
- It is well known that **IL-8 production** is increased in the tissue of UC patients compared with that of normal controls.
- Moreover, other chemokines are elevated in the mucosa of IBD patients.
- Various reports have shown that the expression of chemokines and ligands. For example **CCL2** (also known as monocyte chemoattractant protein [MCP]−1), **CCL3** (also known as macrophage inflammatory proteins [MIP]−1α), **CCL4**, …, and **RANTES** are upregulated in tissues from IBD patients.

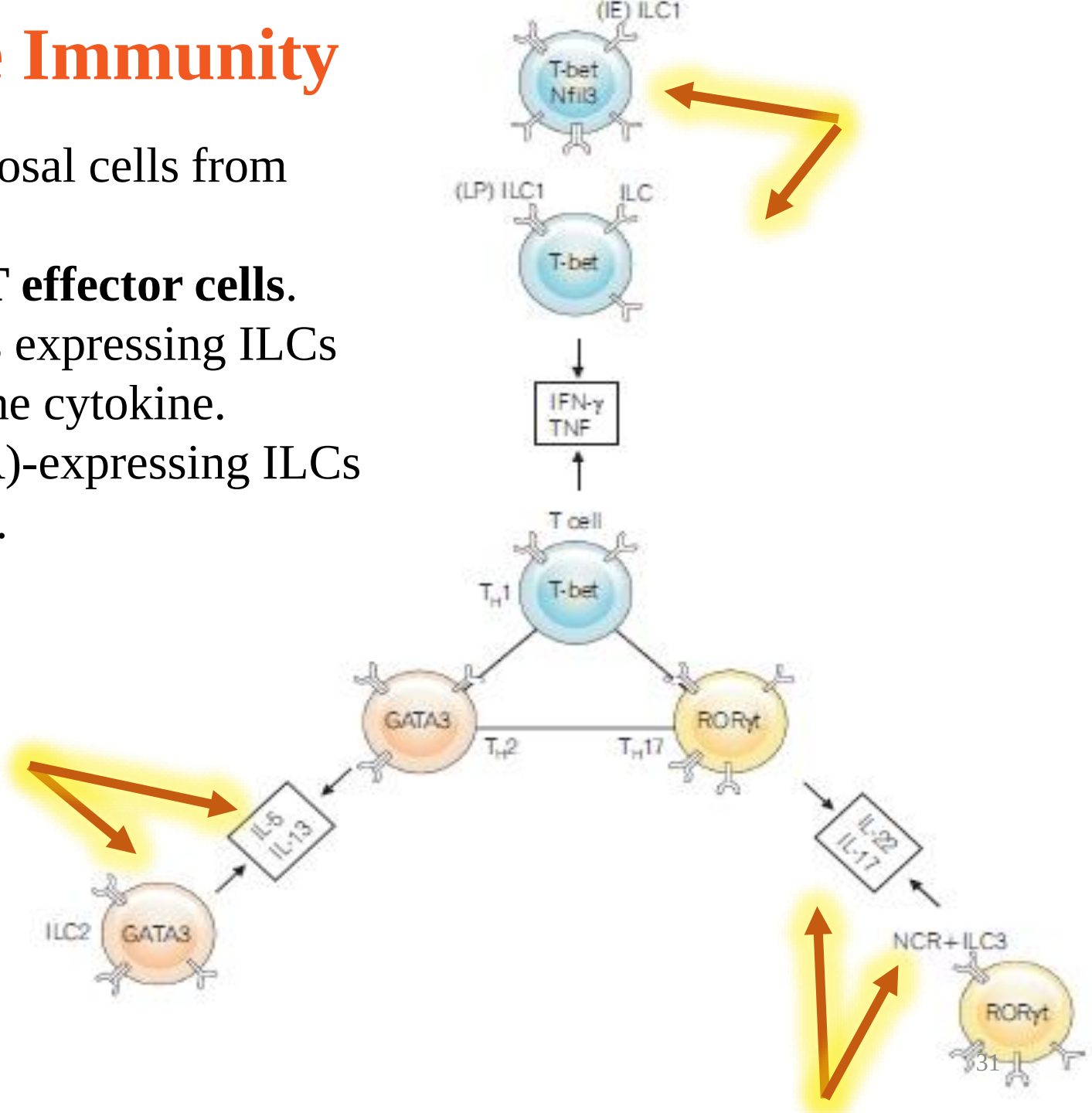
Innate Lymphoid Cells (ILCs) in IBD



- **ILCs** provide host **protective immunity** in the mucosal tissues.
- ILCs are a novel family of effector **lymphocytes** in IBD that produce IBD relevant cytokines.
- LCs are unique in that they **lack Ag-specific receptors** & phenotypic markers associated with immune cells but do have a **lymphoid morphology**.
- The **ILC family** can be subdivided into 3 subsets based on the types of transcription factors they express for lineage differentiation: **ILC1**, **ILC2**, and **ILC3**.
- The lineage **specific transcription factors** expressed in ILC1, ILC2, and ILC3 are **T-bet**, **GATA-3**, and **RORγt**, respectively. Cytokines secreted by ILCs are the same as those of T effector cells

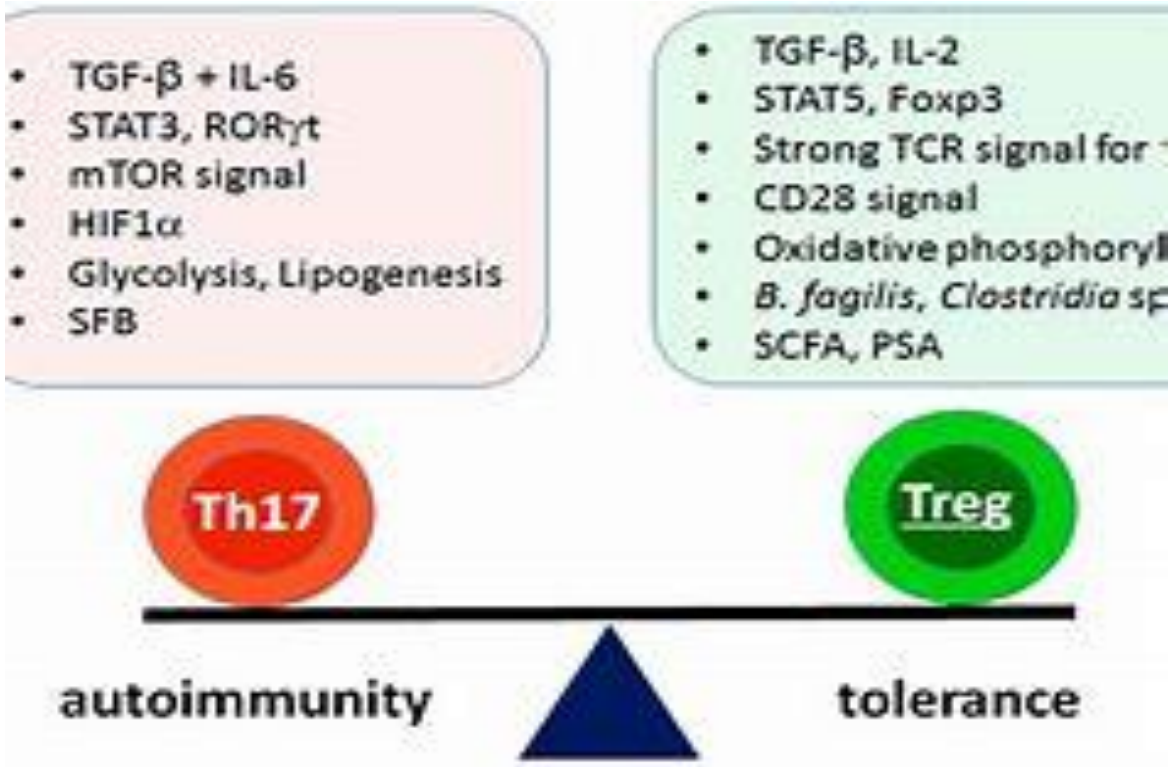
ILCs in Intestinal Innate Immunity

- **Pathogenic ILCs** and **T cells** in mucosal cells from IBD patients.
- ILCs have common properties with **T effector cells**.
- Lineage-specific transcription factors expressing ILCs or a subset of T cells produce the same cytokine.
- **Natural cytotoxicity receptor** (NCR)-expressing ILCs are classified differently from T cells.



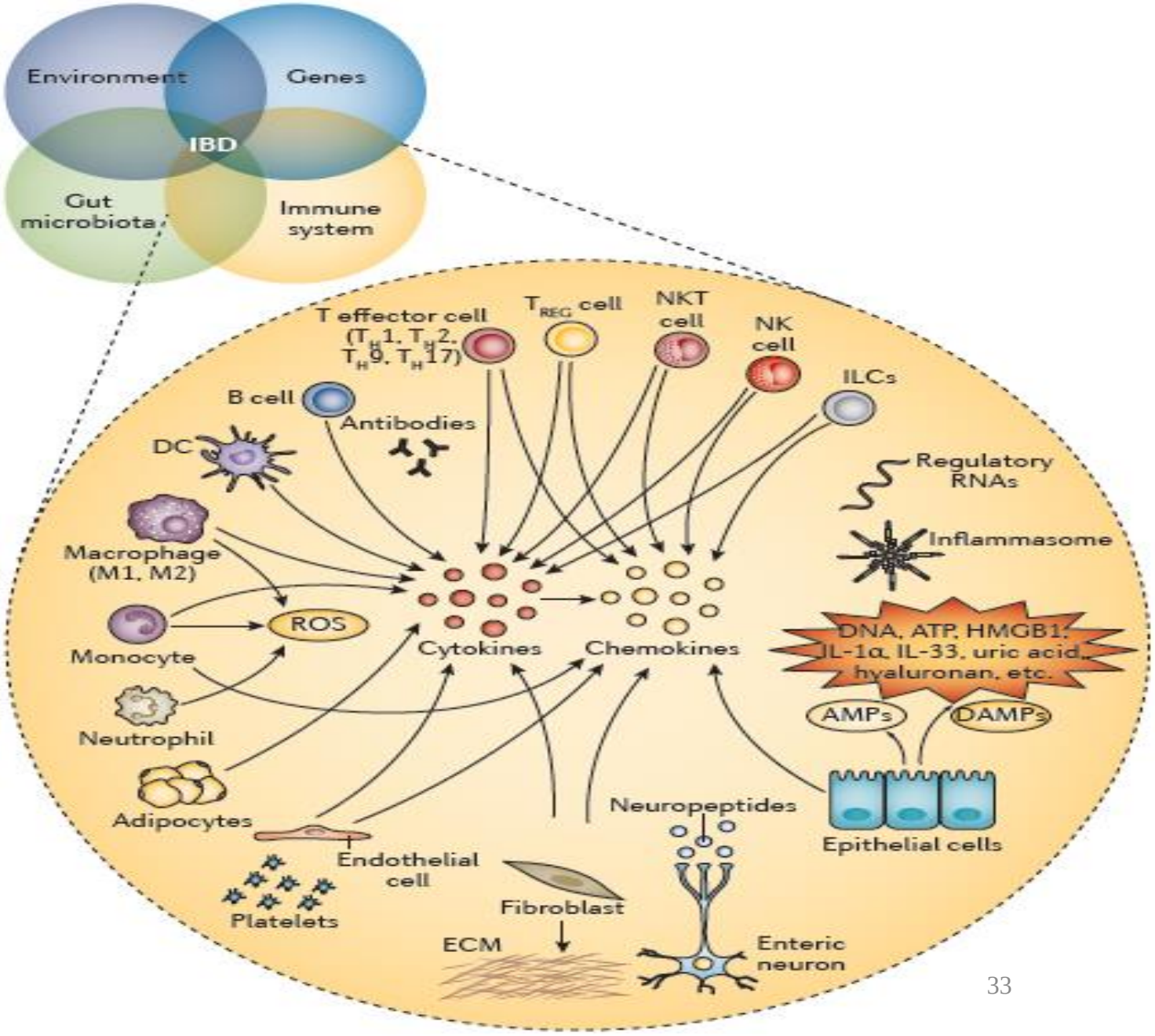
Th17 CELLS ARE KEY FACTORS IN THE PATHOGENESIS OF IBD

- **Th17** Cell Differentiation in the Intestine
- **Th17** Cells and the Microbiota
- **Th17** Cells Function in Intestinal Inflammation
- Maintenance of Intestinal **Th17** and **Treg** Cell Proliferation



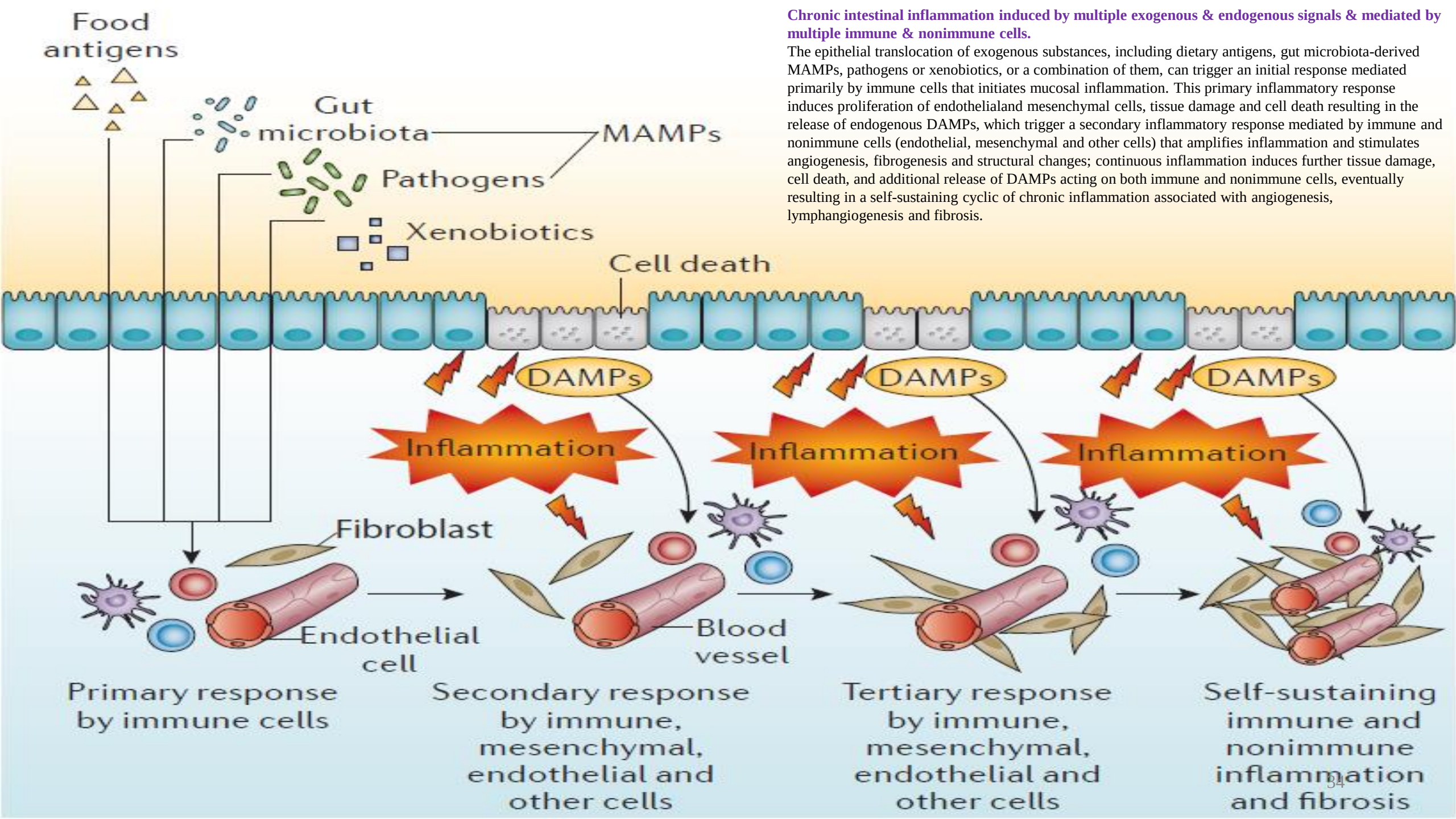
The **intricate universe** of immune & nonimmune components involved in IBD immunopathogenesis

- A **dysregulated immune response** represents the effector arm of the inflammatory response, which includes a number of diverse cell types of immune & nonimmune (myeloid, lymphoid, epithelial, endothelial, mesenchymal, neurogenic) origin as well as their products (cytokines, chemokines, neuropeptides, ROS, AMPs, DAMPs, etc.), in addition to regulatory & mediator elements (regulatory RNAs, inflammasome, etc.).
- A large number of specific and nonspecific stimuli (**diet, microbes, infectious agents, xenobiotics**) can activate the **mucosal immune system**, but at present the temporal sequence of downstream events leading to chronic inflammation is still uncertain, making it impossible to distinguish primary from secondary abnormalities in IBD immunopathogenesis.

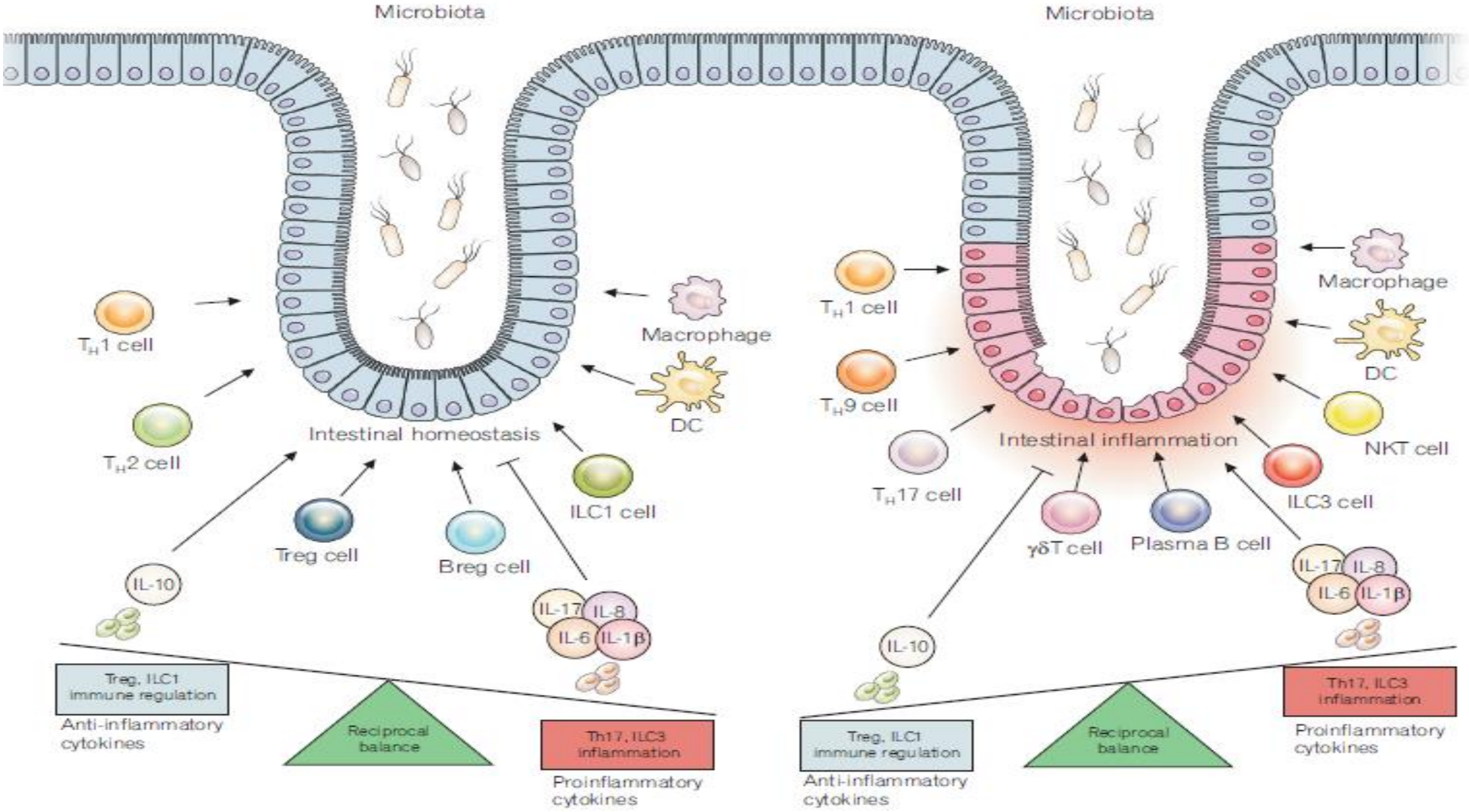


Chronic intestinal inflammation induced by multiple exogenous & endogenous signals & mediated by multiple immune & nonimmune cells.

The epithelial translocation of exogenous substances, including dietary antigens, gut microbiota-derived MAMPs, pathogens or xenobiotics, or a combination of them, can trigger an initial response mediated primarily by immune cells that initiates mucosal inflammation. This primary inflammatory response induces proliferation of endothelialand mesenchymal cells, tissue damage and cell death resulting in the release of endogenous DAMPs, which trigger a secondary inflammatory response mediated by immune and nonimmune cells (endothelial, mesenchymal and other cells) that amplifies inflammation and stimulates angiogenesis, fibrogenesis and structural changes; continuous inflammation induces further tissue damage, cell death, and additional release of DAMPs acting on both immune and nonimmune cells, eventually resulting in a self-sustaining cyclic of chronic inflammation associated with angiogenesis, lymphangiogenesis and fibrosis.

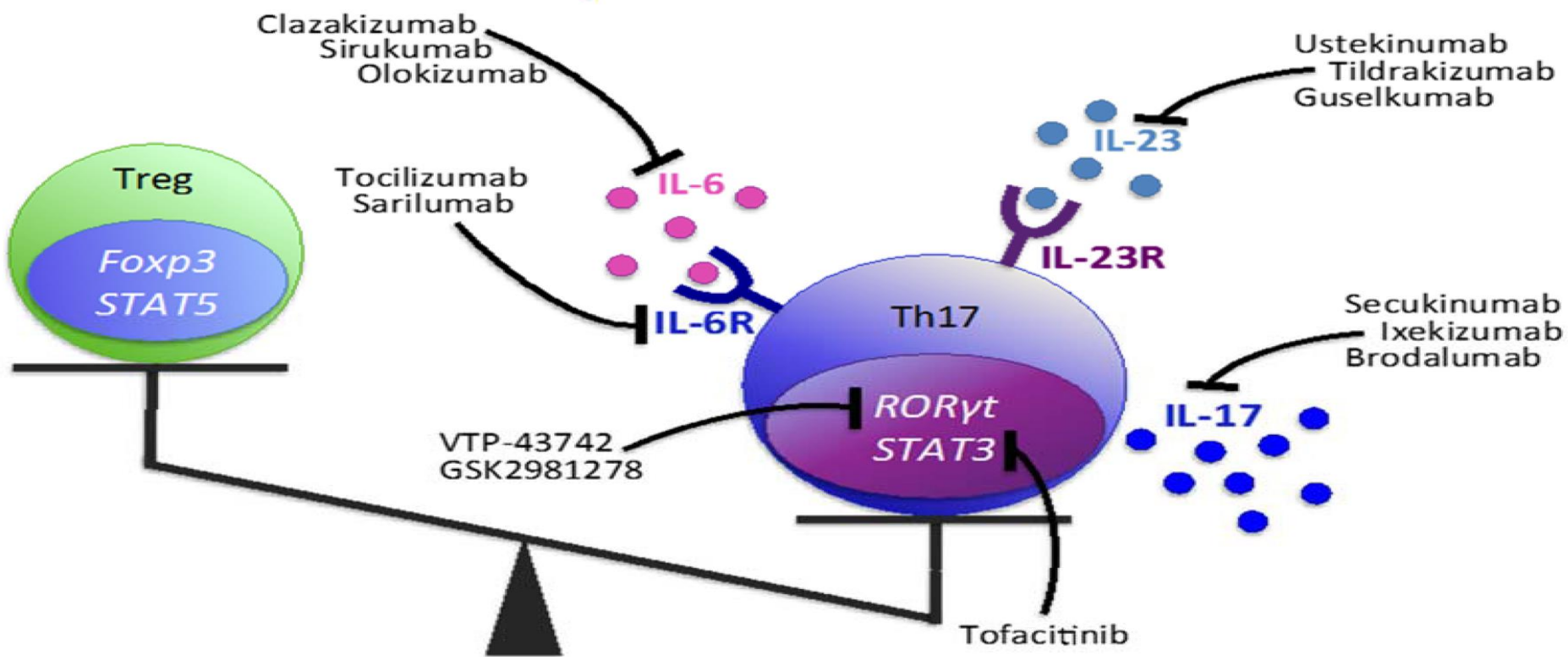


Reciprocal balance for intestinal immune homeostasis and inflammation



IBD THERAPIES THAT TARGET Th17

- **Th17 Cell Blockade**
- **Inhibition of Specific Transcription Factors (STAT3) Associated with Th17 Cells**



➢ IBD therapies byTh17 Cell Blockade

- Potential strategies for IBD treatment include a blockade of **pro-inflammatory cytokines** related to Th17 cells. Suppression of IL-17 expression using the oral **immunosuppressive drug** **vidofludimus** reduced the proliferation of lymphocytes in vitro . Furthermore, the safety and therapeutic efficacy of vidofludimus was demonstrated in a clinical trial involving IBD patients.

- Theoretically, pro-inflammatory cytokines, including IL- 6, can increase Th17 cell differentiation and proliferation. Consistent with this, neutralizing IL-21 antibody treatment downregulated the infiltration of colonic T cells and the expression of pro-inflammatory cytokines such as IL-6 and IL-17A in inflamed intestinal tissue from mice with DSS-induced colitis.

J Pharmacol Exp Ther. 2012 Sep;342(3):850-60. doi: 10.1124/jpet.112.192203. Epub 2012 Jun 12.

Vidofludimus inhibits colonic interleukin-17 and improves hapten-induced colitis in rats by a unique dual mode of action

Leo R Fitzpatrick [1], Jeffrey S Small, Robert Doblhofer, Aldo Ammendola

Affiliations + expand

PMID: 22691298 DOI: 10.1124/jpet.112.192203

Clinical Trial J Crohns Colitis. 2013 Sep;7(8):636-43. doi: 10.1016/j.crohns.2012.09.016. Epub 2012 Oct 16.

Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study

K R Herrlinger [1], M Diculescu, K Fellermann, H Hartmann, S Howaldt, R Nikolov, A Petrov, W Reindl, J M Otte, S Stoynov, U Strauch, A Sturm, R Voiosu, A Ammendola, B Dietrich, B Hentsch, E F Stange

Affiliations + expand

PMID: 23078909 DOI: 10.1016/j.crohns.2012.09.016

J Exp Med. 2011 Oct 24;208(11):2279-90. doi: 10.1084/jem.20111106. Epub 2011 Oct 10.

Involvement of interleukin-21 in the regulation of colitis-associated colon cancer

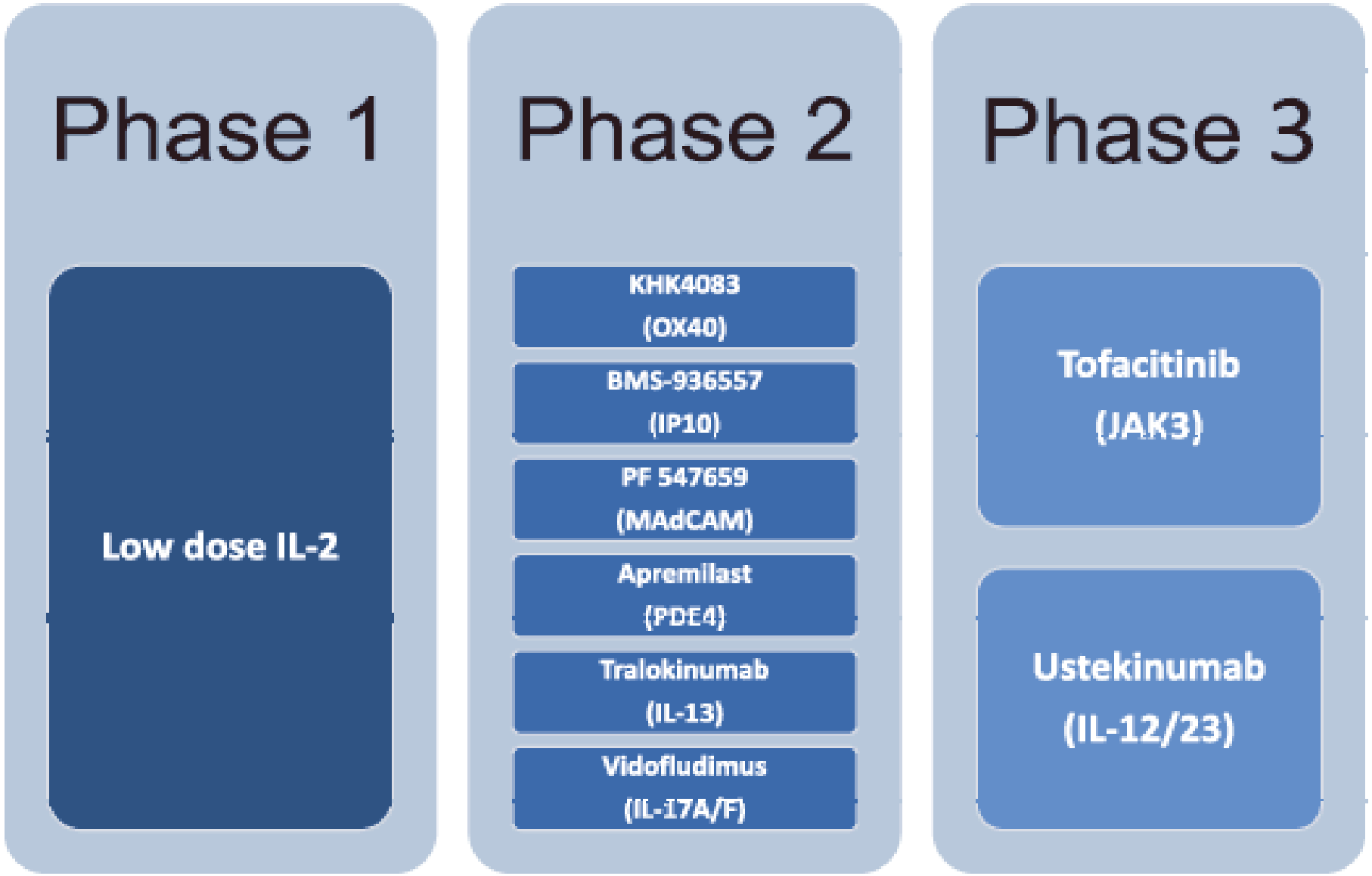
Carmine Stolfi [1], Angelamaria Rizzo, Eleonora Franzè, Angela Rotondi, Massimo Claudio Fantini, Massimiliano Sarra, Roberta Caruso, Ivan Monteleone, Pierpaolo Sileri, Luana Franceschilli, Flavio Caprioli, Stefano Ferrero, Thomas T MacDonald, Francesco Pallone, Giovanni Monteleone

Affiliations + expand

PMID: 21987656 PMCID: PMC3201207 DOI: 10.1084/jem.20111106

Free PMC article

New therapeutic agents for ulcerative colitis. New therapeutic agents for ulcerative colitis with drug targets in parenthesis



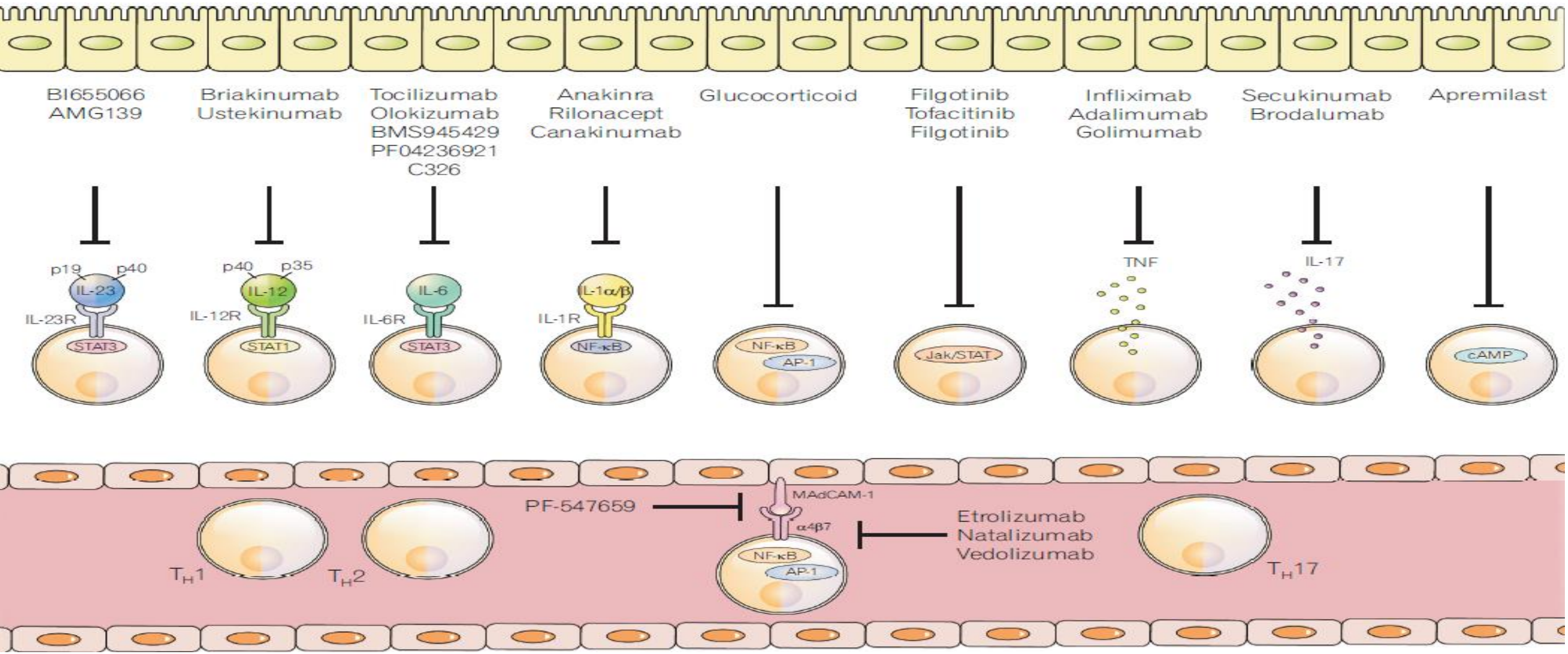
IBD THERAPEUTICS

Classical Drugs for IBD Treatment

There are 2 main categories of therapeutics for treating IBD: (1) anti-inflammatories or immunosuppressive agents
(2) biological agents

- Azathioprine, methotrexate, and cyclosporine-A are classical immunosuppressive drugs used in IBD therapy. Classically, anti-inflammatory drugs, 5-aminosalicylates (5-ASAs), are used to treat UC.
- TNF-α is the main pathogenic factor that is produced by immune and non-immune cells in the gut of IBD patients. Anti-TNF agents, including infliximab, adalimumab, & golimumab, are classic IBD therapies.
- Combination therapy with infliximab and azathioprine is very effective for maintenance of remission in both CD and UC.

- Inhibition of Lymphoid Cell Homing
- Inhibition of IBD-Related Lymphoid Cell Survival
- Targeting Epithelial Cells
- Targeting Cytokines in IBD Therapy



Present IBD therapeutic strategies that involve prevention of T cell and innate ILC production or their inhibition. T cells and ILCs have a common therapeutic target. Compared with classical IBD therapeutic agents, new therapeutic strategies may involve T cells; ILCs such as IL-23 and IL-12-, TNF-α, and integrin-targeting agents; and signal STAT inhibitors.


سپاس از حسن توجه

Irritable bowel syndrome (IBS) is a chronic and debilitating functional gastrointestinal disorder that affects 9%-23% of the population across the world.

- The percentage of patients seeking health care related to IBS approaches 12% in primary care practices and is by far the largest subgroup seen in gastroenterology clinics.
- It has been well documented that these patients exhibit a **poorer quality of life** and utilize the health care system to a greater degree than patients without this diagnosis.
- The pathophysiology of IBS is not clear. Many theories have been put forward, but the exact cause of IBS is still uncertain.
- According to the updated ROME III criteria, IBS is a clinical diagnosis and presents as one of the 3 predominant subtypes: IBS with constipation (IBS-C); IBS with diarrhea (IBS-D); and (3) mixed IBS (IBS-M); former ROME definitions refer to IBS-M as alternating IBS (IBS-A).
- Across the IBS subtypes, the presentation of symptoms may vary among patients and change over time.
- Patients report the most distressing symptoms to be abdominal pain, straining, myalgias, urgency, bloating and feelings of serious illness.
- The complexity and diversity of IBS presentation makes treatment difficult.

Diagnosis

No specific laboratory or imaging tests can diagnose irritable bowel syndrome. Diagnosis should be based on symptoms, the exclusion of worrisome features, and the performance of specific investigations to rule out organic diseases that may present similar symptoms.[3][66]

The recommendations for physicians are to minimize the use of medical investigations.[67] Rome criteria are usually used. They allow the diagnosis to be based only on symptoms, but no criteria based solely on symptoms is sufficiently accurate to diagnose IBS.[68][69] Worrisome features include onset at greater than 50 years of age, weight loss, blood in the stool, iron-deficiency anemia, or a family history of colon cancer, celiac disease, or inflammatory bowel disease.[3] The criteria for selecting tests and investigations also depends on the level of available medical resources.[34]

Name	Family name	Receptor	Coreceptor	Property	Chromosomal location
IL-1α	IL-1F1	IL-1RI	IL-1RacP	Proinflammatory	2q14
IL-1β	IL-1F2	IL-1RI	IL-1RacP	Proinflammatory	2q14
IL-1Ra	IL-1F3	IL-1RI	NA	Antagonist for IL-1α, IL-1β	2q14.2
IL-18	IL-1F4	IL-18Rα	IL-18Rβ	Proinflammatory	11q22.2-q22.3
IL-36Ra	IL-1F5	IL-1Rrp2	NA	Antagonist for IL-36α, IL-36β, IL-36γ	2q14
IL-36α	IL-1F6	IL-1Rrp2	IL-1RAcP	Proinflammatory	2q12 - q14.1
IL-37	IL-1F7	Unknown	Unknown	Anti-inflammatory	2q12 - q14.1
IL-36β	IL-1F8	IL-1Rrp2	IL-1RAcP	Proinflammatory	2q14
IL-36γ	IL1-F9	IL-1Rrp2	IL-1RAcP	Proinflammatory	2q12 - q21
IL-38	IL-1F10	Unknown	Unknown	Unknown	2q13
IL-33	IL-1F11	ST2	IL-1RAcP	Th2 responses, proinflammatory	9p24.1