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Pathophysiology of gastrointestinal system II

18. 2. 2020

GIT physiology - repetition

- The gastrointestinal (GI) system is responsible for the digestion and absorption of ingested food and liquids.
- the major factors affecting GI physiology and function are the intestinal microbiota, chronic stress, inflammation, and aging with a focus on the neural regulation of the GI tract and an emphasis on basic brain-gut interactions that serve to modulate the GI tract.
- GI diseases refer to diseases of the esophagus, stomach, small intestine, colon, and rectum.
- The major symptoms of common GI disorders include recurrent abdominal pain and bloating, heartburn, indigestion/dyspepsia, nausea and vomiting, diarrhea, and constipation.
- GI disorders rank among the most prevalent disorders, with the most common including esophageal and swallowing disorders, gastric and peptic ulcer disease, gastroparesis or delayed gastric emptying, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD).
- Pathophysiology knowledge the most important approach!

GIT physiology - repetition

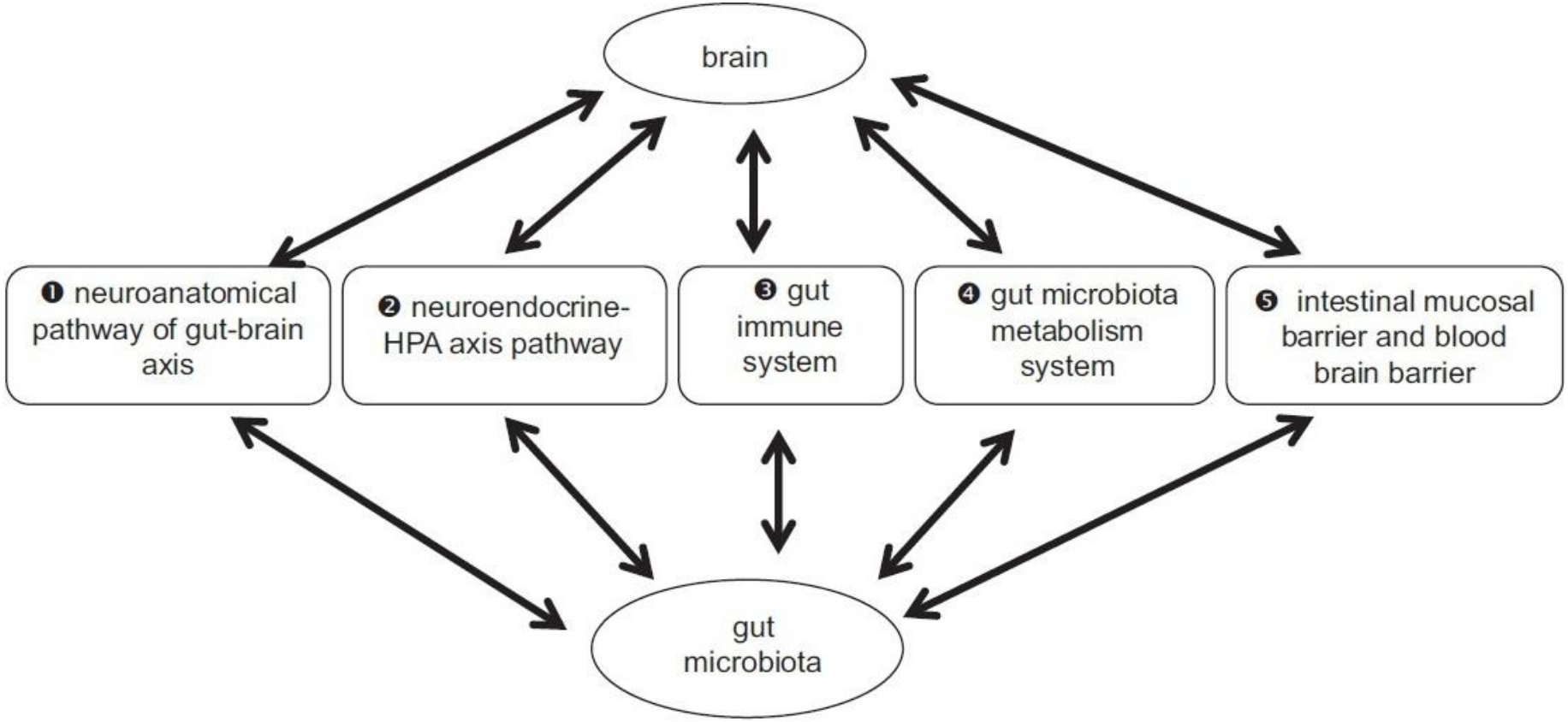
- The overall function of the GI tract is to digest ingested nutrients through complex processes of digestive enzyme secretion and nutrient absorption. Luminal contents move along the GI tract via smooth muscle peristalsis, while smooth muscle segmentation ensures adequate contact time and exposure to the absorptive epithelial mucosal surface.
- The gut is capable of handling about 9 L of fluid per day, which is mainly absorbed by the small intestine. This fluid movement can occur through paracellular or transcellular routes. Paracellular pathway involves water movements coupled to nutrient absorption via alterations in tight junction expression, while the transcellular route involves the passage of water through apical and basolateral membranes of epithelial cells by passive diffusion, cotransport with ions and nutrients, or through aquaporins.
- During intestinal absorption the epithelial barrier is specifically designed to protect against the movement of potentially harmful antigenic, toxic, or infectious material across the GI mucosal surface (Camilleri et al. 2012).

GIT physiology - repetition

- To ensure effective digestion and proper GI tract health requires a complex series of coordinated neural events accomplished by the central nervous system (CNS), the nerve network within the gut itself known as the enteric nervous system (ENS), and a whole host of GI endocrine peptides that target specific cells and tissues that make up the GI tract.
- Specialized endoderm-derived epithelial cells termed enteroendocrine cells (EECs) form the largest endocrine organ in the body and are widely distributed throughout the GI tract. EECs play a key role in the control of GI function including secretion, motility, and regulation of food intake, postprandial glucose levels, and metabolism.

GIT physiology - repetition

- The gut also performs important immune functions and a vast array of inflammatory mediators can influence the recruitment of lymphocytes and other immune cells to the gut wall including mast cells, and at the same time modulate the activity of the gut neural networks. Additionally, the abundance of microbiota residing in the human intestine estimated at 10^{14} microorganisms plays a pivotal role in the development of the enteric nervous sytem (ENS), the overall health not only of the GI tract but also the entire human body via mechanisms that include activation of the immune system, and production of short-chain fatty acids (SCFAs) to promote colon cell health as well as brain-gut interactions.



Gut microbiota-brain axis. Five possible communication routes (–) between gut microbiota and brain: intestinal mucosal barrier and blood-brain barrier is the important base for neuroendocrine-HPA axis pathway , gut immune system , and gut microbiota metabolism system. Substances produced by neuroendocrine-HPA axis pathway , gut immune system , and gut microbiota metabolism system, only into the system circulation and brain through the intestinal mucosal barrier and blood-brain barrier system can play effect of gut microbiota on the brain. HPA: Hypothalamic-pituitary-adrenal.

Wang HX, Wang YP. Gut Microbiota-brain Axis. *Chin Med J (Engl)*. 2016;129(19):2373–2380. doi:10.4103/0366-6999.190667

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Gut microbiota-brain axis

- gut microbiota-brain axis is a “bottom-up” term as opposed to a “top-down” term of “brain-gut-microbiota axis”, no matter what is called, its meaning refers to a bidirectional communication network between gut and brain. Its composition includes gut microbiota and their metabolic products, ENS, sympathetic and parasympathetic branches, neural-immune system, neuroendocrine system, and central nervous system.
- Tthere might have possible five routes of communicating between gut microbiota and brain, including the gut-brain's neural network, neuroendocrine-HPA axis, gut immune system, some neurotransmitters and neural regulators synthesized by gut bacteria, and barriers including intestinal mucosal barrier and blood-brain barrier. In this communicating network, the brain affects gut movement, sensory and secretion function, and viscera signal from the gut also affects brain function. For example, incoming and outgoing branches of VN play an important role in gut message transmission. Vagal activation has anti-inflammatory effect. Positive effects of many gut microbiota and probiotics on brain function are dependent on the vagal activity.

Wang HX, Wang YP. Gut Microbiota-brain Axis. *Chin Med J (Engl)*. 2016;129(19):2373–2380. doi:10.4103/0366-6999.190667

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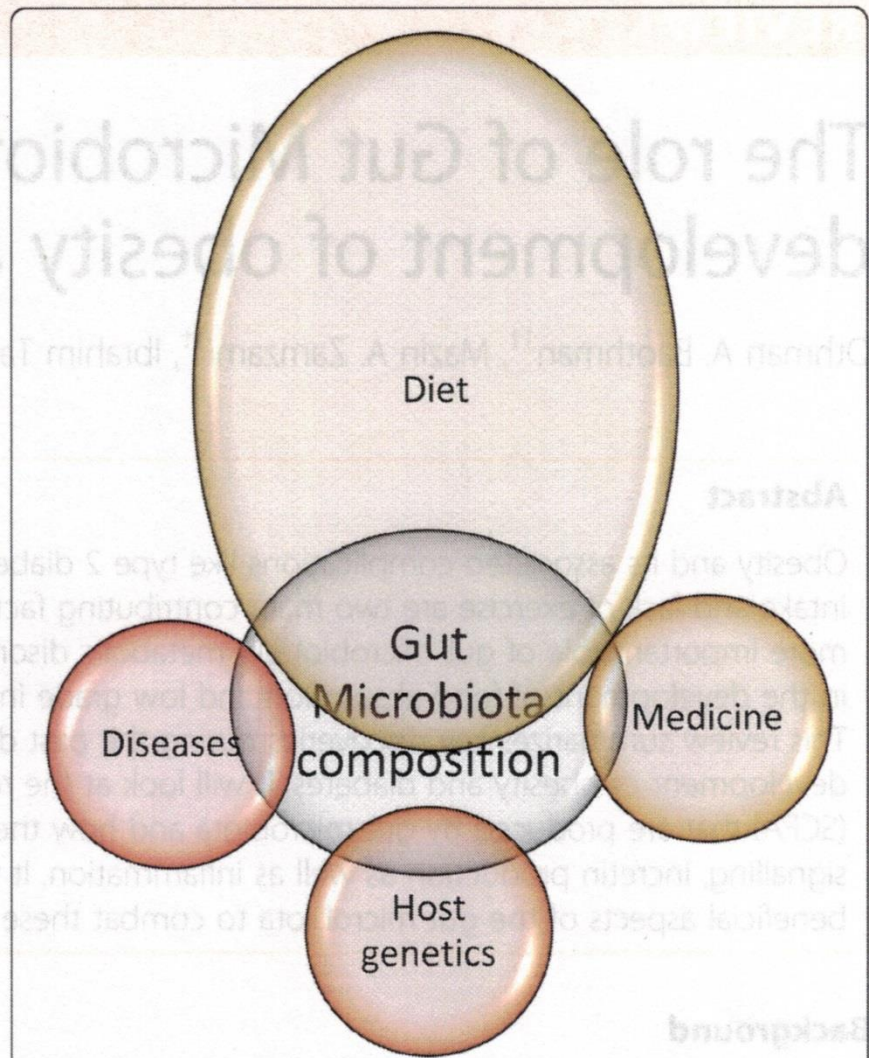
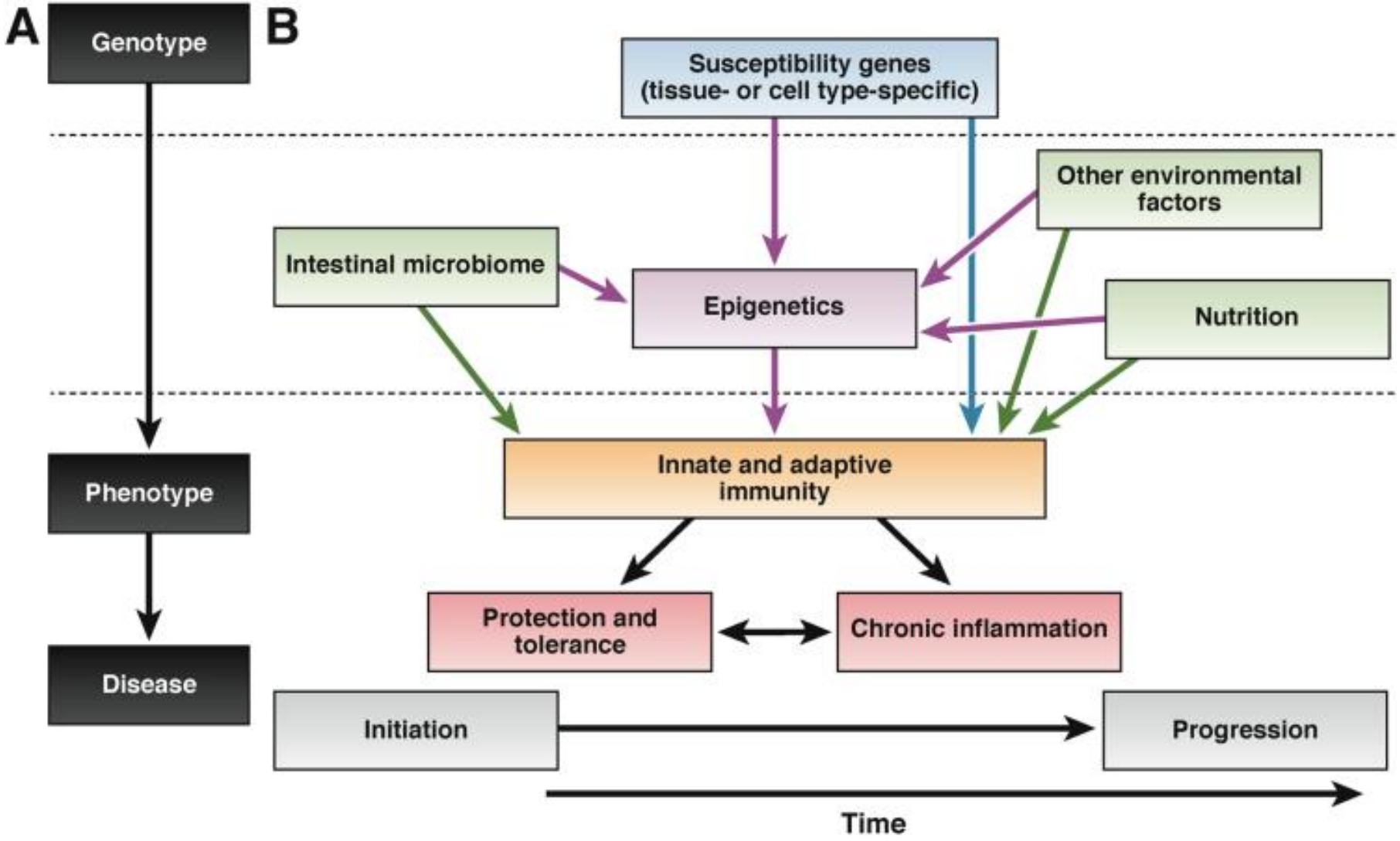
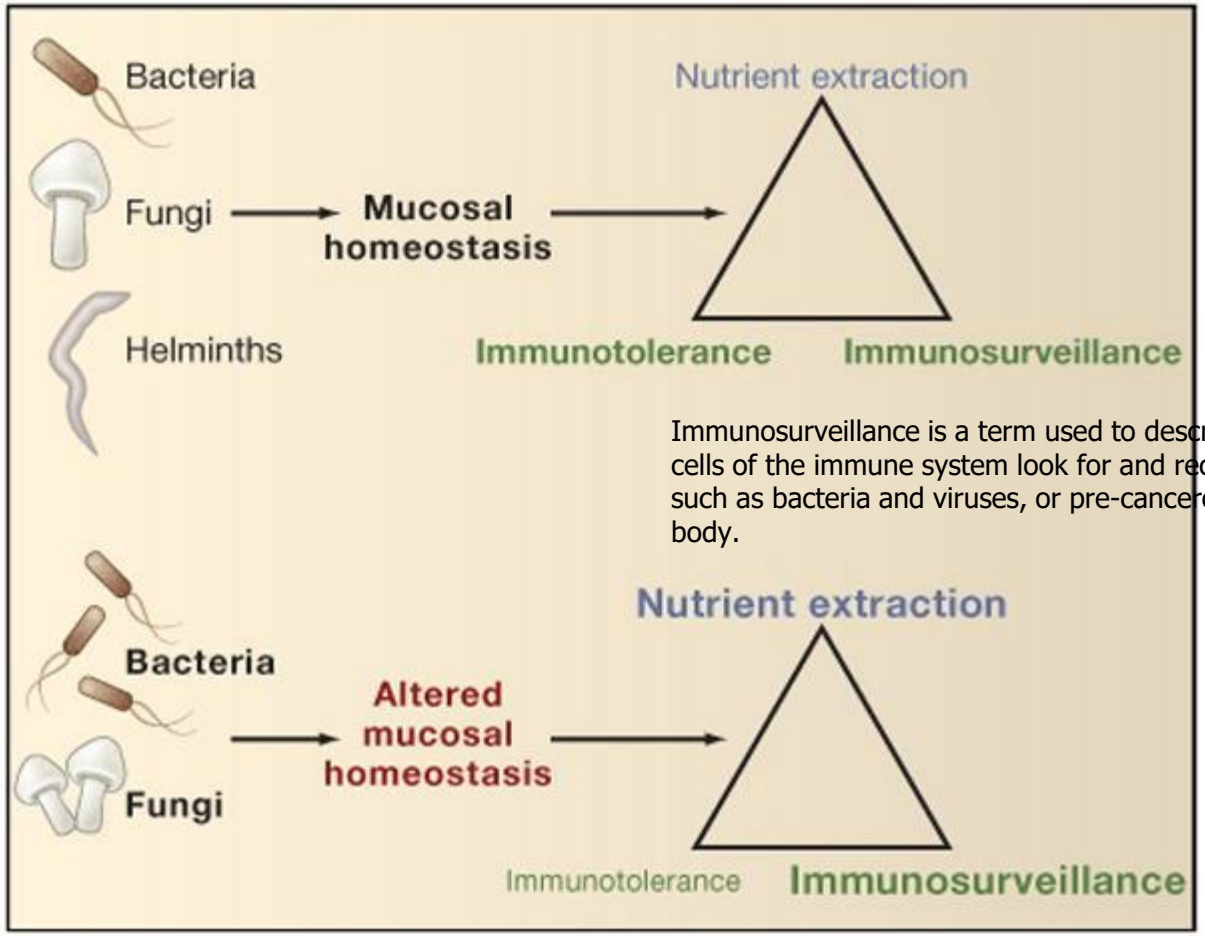


Fig. 1 A diagram showing main factors affecting the gut microbiota composition highlighting the great impact of diet on this composition

Pathogenesis of diseases

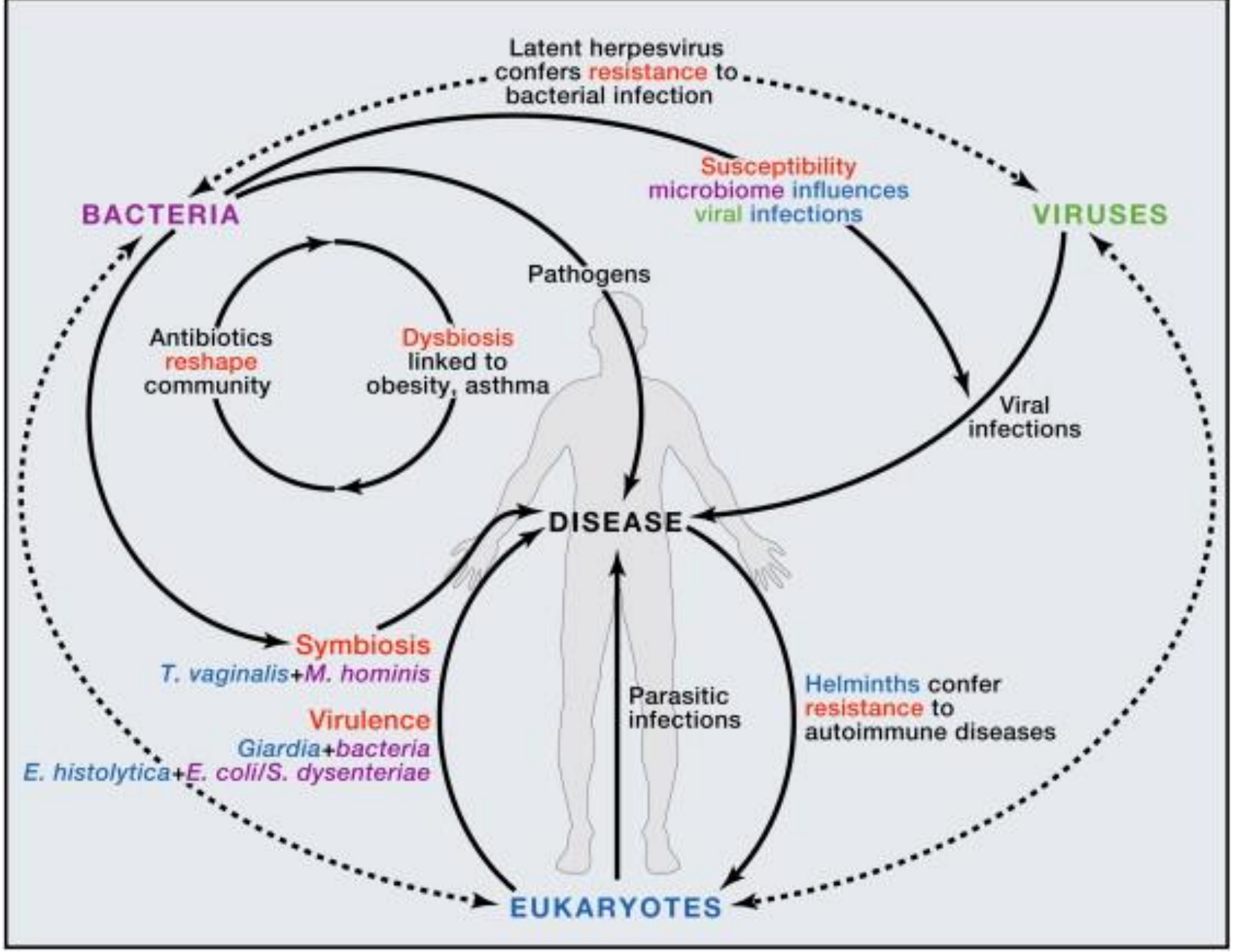


Beyond Gene Discovery in Inflammatory Bowel Disease: The Emerging Role of Epigenetics
Gastroenterology. 2013 August;145(2):293-308.



Immunosurveillance is a term used to describe the processes by which cells of the immune system look for and recognise foreign pathogens, such as bacteria and viruses, or pre-cancerous and cancerous cells in the body.

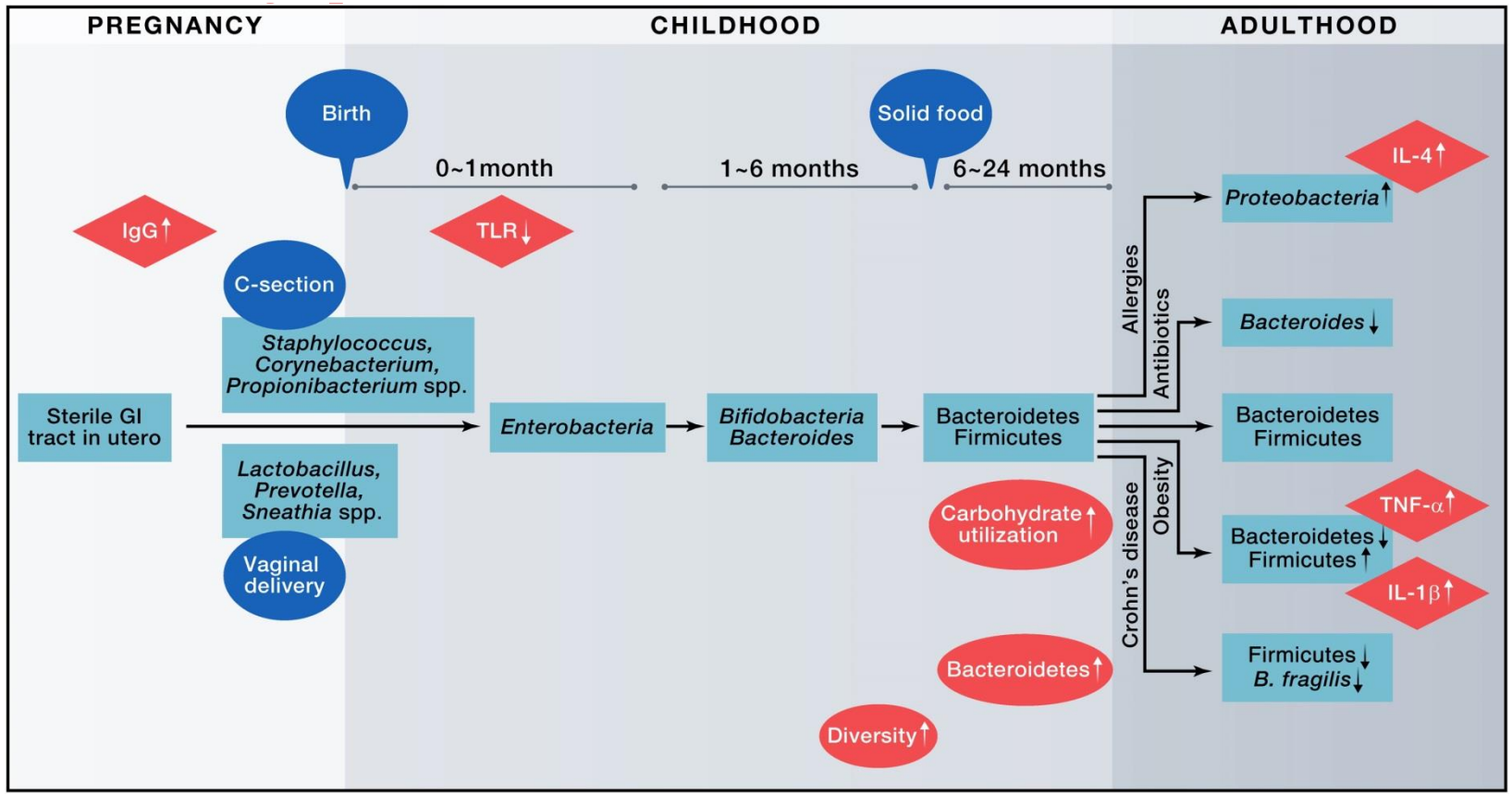
The loss of universal helminth infection as occurred in earlier human evolution may alter the numbers or types of bacterial and fungal commensals and thus affect normal mucosal tissue homeostasis. In susceptible or highly exposed individuals, such alterations might alter the balance between immunotolerance, immunosurveillance and nutrient extraction. This imbalance may contribute to the appearance of inflammatory systemic dysregulation at mucosal surfaces, resulting in increases in asthma and allergic diseases, particularly in the setting of environmental changes that have increased exposure to indoor allergens and pollutants, and even to increases in obesity, which can be a risk factor for severe asthma.



Cell 2012; 148: 1258–1270

Cell 2012; 148: 1258–1270

Development of gut microbiota



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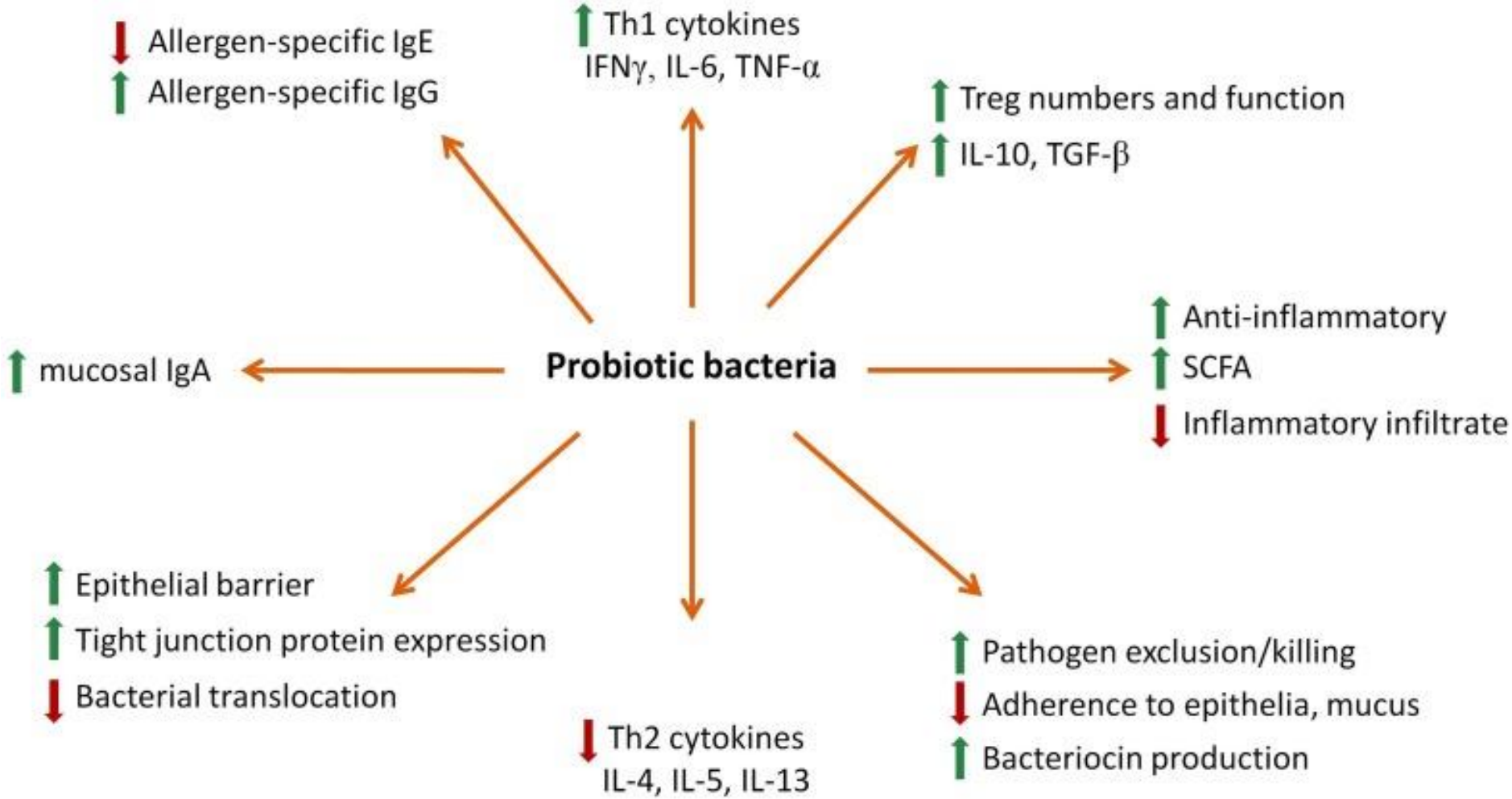
↓ Allergen-specific IgE
↑ Allergen-specific IgG
↑ Th1 cytokines
IFNγ, IL-6, TNF-α
↑ Treg numbers and function
↑ IL-10, TGF-β
↑ mucosal IgA
Probiotic bacteria
↑ Anti-inflammatory
↑ SCFA
↓ Inflammatory infiltrate
↑ Epithelial barrier
↑ Tight junction protein expression
↓ Bacterial translocation
↓ Th2 cytokines
IL-4, IL-5, IL-13
↑ Pathogen exclusion/killing
↓ Adherence to epithelia, mucus
↑ Bacteriocin production

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Table 2 The effect of various diets on the composition of gut microbiota diversity

Diet Type	Effect on bacteria
High Fat Diet	Decrease of genera within the class Clostridia in the ileum. Increase Bacteroidales in large intestine [130]
	Increase Lactobacillus spp., Bifidobacterium spp., Bacteroides spp., and Enterococcus spp. Decrease Clostridium leptum and Enterobacter spp. [131]
	Increase Firmicutes to Bacteriodetes ratio. And increased Enterobecteriaceae [132]
	increase Bacteroidales, Clostridiales and Enterobacteriales [133]
Vegetarian Diet	Decrease Acteroides spp., Bifidobacterium spp., Escherichia coli and Enterobacteriaceae spp. [134]
	Decrease Enterobacteriaceae and increase Bacteroides [135]
	Increase Bacteroidetes, and decrease Firmicutes and Enterobacteriaceae [136]
Calorie restricted	Decrease Firmicutes to Bacteroidetes ratio [137]

ENS

- The relationship between the gut microbiota and ENS neurons is relatively complex.
- First, the microbiota can influence the development of the ENS, and this has consequences on ENS activity and neurochemistry (such as neuronal subpopulations).
- Second, gut bacteria can use different modes of communication to talk with ENS neurons, including a direct “sensing” with intrinsic primary afferent neurons or the release of numerous bacterial messengers (e.g., neurotransmitters, bioactive lipids, gaseous factors). Along those lines, it is worth noting that the immune cells infiltrating the gut epithelium may also communicate with the microbiota.

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Glucagon-like peptide-1 (GLP-1) is

- Glucagon-like peptide-1 (GLP-1) is a key endocrine factor that could participate in the control of the gut-brain axis by gut microbiota because of its location (i.e., released by intestinal L cells).
- GLP-1 could act on ENS neurons to modify the gut-brain axis to control food intake and glucose metabolism.

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Endocannabinoid system (ECS)

- In the context of energy homeostasis, the endocannabinoid system (ECS) plays a major role.
- Endocannabinoids (eCBs) are bioactive lipids that are synthesized in and exert their action on several organs involved in metabolism and appetite regulation.
- Depending on the action exerted by eCBs on the intestinal mucosa, they can be clustered as a “gate opener” (anandamide) and “gate keeper” (palmitoylethanolamine, 2-oleoylglycerol).
- Gut microbiota can modulate intestinal eCB tone. An “obesity microbiota” is associated with an increased intestinal level of anandamide, thus increasing gut permeability.

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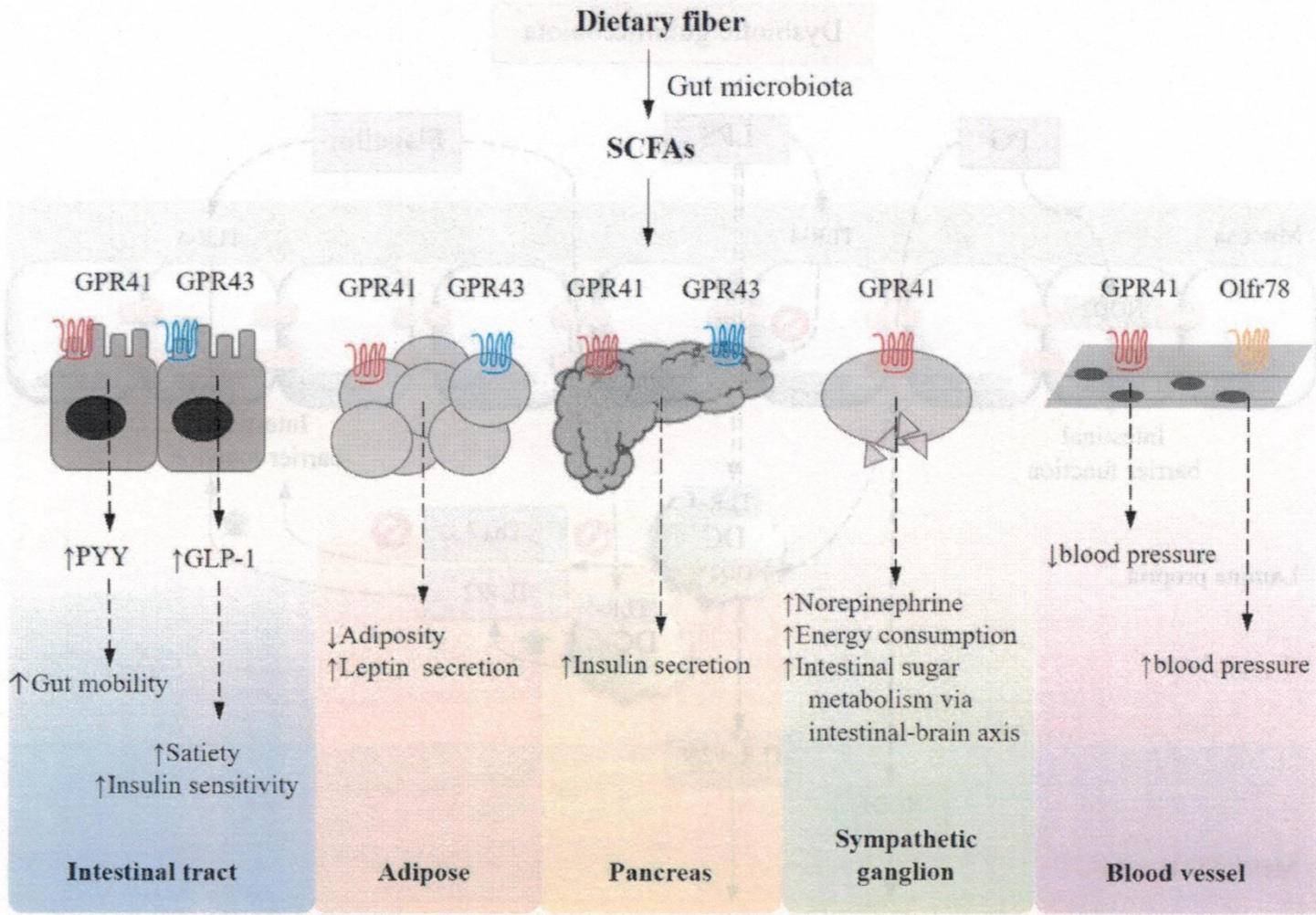

FIGURE 2 | Short-chain fatty acid (SCFA)-receptor-mediated pathways and their effects on host energy metabolism in peripheral tissues. Gut microbes can ferment dietary fiber into SCFAs, which induce an array of G-protein coupled receptor-mediated signaling pathways that are essentially implicated in host energy homeostasis in multiple tissues.

GIT pathophysiology

- A generally accepted hypothesis is that dysfunction of the bidirectional communication between the brain and the gut in response to chronic stress activates the hypothalamic pituitary (HPA) axis and autonomic nervous system and plays a role in the symptomatology of functional GI disorders such as IBS. Inflammation of the gut mucosal surface has substantial effects on enteric and extrinsic afferent neuronal function though complex changes in neuroimmune interaction.
- Although the effects of an intestinal inflammation on the CNS are not fully understood, patients with IBD exhibit centrally mediated comorbidities including anxiety, depression, and fatigue, which strongly suggests altered brain function in response to peripheral inflammation perhaps through alterations in central immune-mediated mechanisms.
- Recent evidence points to changes in the gut microbiota playing a key role in GI disorders. Specifically, disorders directly affecting the GI tract have been shown to exhibit microbial dysbiosis. Gut inflammation causes marked alterations in the gut microbiota populations and may play a role in gut-brain miscommunication. Another important factor altering the physiology of the GI tract is age. The normal functioning of the gut is compromised as we age, with the elderly often complaining of constipation, hemorrhoids, heartburn, decreased energy, and food allergies.

Malabsorption

Malabsorption indicates impaired uptake of nutrients, ions or water along the gastrointestinal tract which can occur with and without morphological changes of the small intestinal mucosa. Thereby, disturbed digestion (maldigestion) and absorption (malabsorption) can work alone or together (malassimilation).
Malabsorption occurs when a primary transport disorder (without morphological changes) or a secondary transport defect due to morphological changes arises, when the absorptive area is reduced or the transport of absorbed ingesta from the intestine is affected.
Depending on localization and extent of the disturbance the functional impairment is either global, partial or compensated.

Disease		
Whipple's disease	Lamina propria macrophages with PAS-positive material	Biopsy, PCR, EM
Intestinal lymphoma	Lymphoma cells in the lamina propria and submucosa	Biopsy, T-cell receptor clonality
Intestinal lymphangiectasia	Dilated lymphatic ducts with partial villus atrophy	Biopsy
Eosinophilic gastroenteritis	Eosinophilic infiltrates	Biopsy
Amyloidosis	Amyloidal deposits	Biopsy
Crohn's disease	Skip lesions with detection of granuloma	Biopsy
Infectious diseases	Detection of microorganisms	Stool microbiology, serum titre and PCR
Mastocytosis	Mast cell infiltrates	Biopsy, IgE
Coeliac disease	Villus reduction, crypt hyperplasia, increased intraepithelial lymphocytes	Biopsy, tissue transglutaminase antibodies, HLA-DQ2
Giardia lamblia infection	Partial villus atrophy	Stool ELISA, indirect immunofluorescence
Blind loop syndrome	Partial villus atrophy and increased intraepithelial lymphocyte count	H_2-test (glucose), quantitative culture from small intestinal mucus
Vitamin-B12 deficiency	Macrocytotic anaemia, ileal inflammation, gastric resection or atrophic gastritis	Serum vitamin B_{12}, parietal cell antibodies, Schilling test, gastric pH
Radiation enteritis	Inflammation of the intestine	Endoscopy
Zollinger–Ellison syndrome	Ulcers and erosions of gastric mucosa and small intestinal partial villus atrophy	Serum gastrin, endoscopic ultrasound, CT
Starvation, malnutrition or parenteral nutrition	Mucosal hypotrophy (villus and crypt reduction)	Biopsy

Malabsorption syndromes: partial, global, compensated

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Coeliac disease

- Coeliac disease is a common cause of malabsorption in Caucasians, especially those of European descent. Coeliac disease has variable manifestations, almost all of which are secondary to nutrient malabsorption, and a varied natural history, with the onset of symptoms occurring at all ages.
- There is no functional test to diagnose coeliac disease. An early duodenal biopsy in combination with specific antibodies (anti-gliadin, anti-endomysial, anti-tissue transglutaminase) is the diagnostic test of choice. Furthermore, almost all patients with coeliac sprue express a distinct HLA-DQ2 allele (DQA1*0501+DQB1*0201). Therefore, absence of this DQ2 allele virtually excludes the diagnosis.
- The gold standard of coeliac disease diagnosis is the presence of an abnormal small intestinal biopsy and the clinical and histopathological response to the elimination of gluten from the diet.
- Since the diarrhoea in coeliac disease has several pathogenetic mechanisms, tests for (secondary) lactase deficiency, fructose intolerance and rarely bile acid malabsorption are encouraged to guide the patient and counsel him regarding the diet of choice or medical therapy. Some patients may obtain temporary improvement with dietary lactose, fructose or fat restriction, while awaiting the full effects of total gluten restriction. In some patients a therapeutic trial with cholestyramine with/without prior SeHCAT test and/or stool fat test can be helpful when ileal involvement with bile acid diarrhoea is suspected.

Giardia lamblia infection

- In the Western world chronic infection with *Giardia lamblia* is probably the most important infectious agent causing malabsorption in the immunocompetent as well as in immunocompromised people (mainly humoral defect of the immune system).
- Diarrhoea is thought to result mainly from malabsorption due to a partial villous atrophy and reduced disaccharidase activity, although there is also a leak-flux and secretory component to this type of diarrhoea.

Whipple’s disease

– Whipple's disease is characterized by diarrhoea, steatorrhea, weight loss, arthropathy and fever. It is caused by the ubiquitous bacterium *Tropheryma whipplei*. New experimental approaches point to defects in T-cell and macrophage immunity in these patients. The steatorrhea is generally considered to be secondary to small intestinal mucosal injury and lymphatic obstruction due to the massive infiltration of PAS-positive macrophages in the lamina propria.

Short bowel syndrome

- The short bowel syndrome (SBS) can appear clinically as a partial or global malabsorption syndrome. The incidence of symptoms is variable.
- The exact definition of resection extent and the length of the remaining small intestinal segment with or without colon are essential for the understanding of the symptoms and therapy planning.

Bacterial overgrowth

- Small bowel bacterial overgrowth (SBO) syndrome is characterized by diarrhoea, weight loss, bloating and macrocytic anaemia and is caused by an increased number of colonic-type bacteria in the small intestine.
- Physiologically, the number of bacteria in the small intestine is reduced by several mechanisms. Most importantly, antegrade peristalsis prevents attachment of ingested microorganisms and an intact ileocoecal valve inhibits retrograde ascension of bacteria into the small bowel from the colon with its high bacterial content. Furthermore, gastric acid, bile and proteolytic enzymes destroy many microorganisms or prevent them from entering the small intestine from the stomach. In addition, the mucosal barrier with its mucus layer and anti-bacterial factors including the innate (e.g. defensins) and acquired immune system (e.g. immunoglobulins) inhibit bacteria from overgrowth.
- The pathopysiological basis for this syndrome can be any disturbance in the factors mentioned above. In most cases, an intestinal stasis caused either by impaired peristalsis (functional stasis, e.g. scleroderma, amyloidosis, diabetes) or by changes in intestinal anatomy (anatomic stasis, e.g. stricture, blind loop, diverticula) predispose to bacterial overgrowth syndrome.

Bacterial overgrowth

- The increased number of bacteria in the small intestine can cause several changes in small intestinal function. First, bacteria deconjugate bile acids in the proximal small intestine which are then not re-absorbed anymore leading to a decrease in the bile acid pool and a lack of intraluminal bile acids. This leads to fat malabsorption with consequent steatorrhoe. Furthermore, a variable degree of non-specific inflammation or epithelial defects are sometimes noted due to bacterial proteases, exotoxins or invasive strains.
- As most bacteria require cobalamin for growth, increased concentrations of bacteria can lead to cobalamin deficiency with megaloblastic anaemia and potentially neurologic changes. That is why a typical laboratory feature is the combination of a low serum cobalamin level with an elevated serum folate level, since bacteria frequently produce folate compounds that are then absorbed.

Carbohydrate malabsorption

- Carbohydrates represent the main source of energy in the diet and are present mainly in the form of starch, disaccharides (saccharose and lactose) and glucose. Carbohydrates are absorbed in the small intestine as monosaccharides. Therefore, carbohydrates must be digested by salivary and pancreatic amylase, gastric acid and by the intestinal brush border disaccharidases (maltase, isomaltase, lactase, saccharase) to monosaccharides (glucose, fructose and galactose).
- Absorption of glucose and galactose occurs via the transport protein SGLT1. The intestinal Na^+-glucose cotransporter SGLT1 uses sodium and electrical gradients across the apical enterocyte membrane to drive sugar and water against their concentration gradients. Glucose and galactose are both handled by SGLT1, whereas fructose is transported across the brush border by its own carrier, the facilitated fructose transporter GLUT5. All three monosaccharides share a common exit on the basolateral membrane of the enterocyte through another facilitated sugar transporter (GLUT2) into the portal blood. Furthermore, GLUT2 can also be inserted apically and then represent a very dynamic high capacity low affinity pathway for monosaccharides.
- Malabsorbed monosaccharides generate an osmotic load that draws water and electrolytes into the lumen leading to osmotic diarrhoea. In addition, non-absorbed sugars are a substrate for the intestinal microflora which produce fatty acids and gases (methane, hydrogen, carbon dioxide) leading to bloating and flatulence. The increase in luminal fatty acids leads to a lowered faecal pH which can be measured in infants in whom carbohydrate malabsorption is suspected.

Lactose intolerance

- Lactose is broken down by the brush border lactase into glucose and galactose. The enzyme lactase is invariably present in humans (as well as in other mammalians) in the postnatal period but then physiologically disappears in many populations, except for most of the Caucasians where lactase activity persists by about 80% throughout life.
- Clinically three different types of lactase intolerance syndromes can be distinguished, namely congenital, primary and secondary lactase deficiency.
- The congenital lactase deficiency is an extremely rare autosomal-dominant inherited disease with a complete absence of lactase activity immediately after birth.
- Primary lactase deficiency is a genetically determined relative or absolute absence of lactase which progressively develops in childhood at various ages in different ethnic groups and is the most common type of lactose intolerance.
- Secondary lactase deficiency occurs in association with small-intestinal mucosal disease (e.g. infectious diarrhoea, coeliac disease, Crohn's disease) with structural and consequently functional changes of the small intestinal mucosa.
- Individuals with symptomatic lactose malabsorption develop one or more of the following symptoms after ingestion of lactose-containing food: abdominal pain, diarrhoea, nausea, bloating, and/or flatulence. Development of symptoms of lactose intolerance is related to the amount of lactose appearing in the small intestine and the activity of mucosal lactase. Besides the amount of ingested lactose several other factors, e.g. rate of gastric emptying, intestinal transit time and composition of microflora can influence the onset and severity of symptoms.

Lactose intolerance

- A precise clinical history remains the most important approach to a patient with suspected lactase deficiency and often reveals a correlation between lactose ingestion and onset of symptoms. If lactose malabsorption is suspected, a 2-week trial of lactose-free diet is reasonable, under which the symptoms should ameliorate or disappear. Then, the re-introduction of lactose into the diet with recurrence of symptoms is considered diagnostic. Alternatively or in more subtle cases the hydrogen breath test is the least invasive and best diagnostic tool for the diagnosis of lactose malabsorption.

Glucose–galactose malabsorption

- Glucose–galactose malabsorption (GGM) is a very rare disease and is due to a mutation in the SGLT1.
- The disease is characterized by severe diarrhoea in newborns when individuals ingest carbohydrates that contain actively transported monosaccharides (e.g. glucose or galactose) but not monosaccharides that are not actively transported (e.g. fructose). The most reliable diagnostic test for GGM is the hydrogen breath test. The H_2 breath test for glucose or galactose results in a great elevation in patients with GGM, while no such increase is noted in controls or patients who eat fructose. Children with GGM normalize on fructose-containing diets, but symptoms promptly return even in adulthood after glucose provocation and the H_2 breath test remains positive

What is a Hydrogen Breath Test?

– A hydrogen breath test is used to measure how well certain sugars such as lactose and fructose, are digested and absorbed as well as diagnosing certain gastrointestinal conditions including Intestinal Bacterial Overgrowth Syndrome (SIBO). Hydrogen is produced when the bacteria in the colon is exposed to certain unabsorbed sugars and carbohydrates.

Hydrogen breath testing is used for the following conditions:

- Lactose Intolerance
- Fructose Intolerance
- Small Intestinal Bacterial Overgrowth Syndrome (SIBO)

What is the preparation for the tests?

- All 3 tests require the same prep:
- Discontinue all Proton Pump Inhibitors (PPI) which include Omeprazole, Lansoprazole, Dexlansoprazole, Esomeprazole, Pantoprazole and Rabeprazole seven (7) days prior to the test.
- Discontinue H2 Blockers (Pepcid, Zantac, Tagamet, Axid, Rantidine, Famotidine) five (5) days prior to the breath test.
- The day before your test, please limit your diet to the following foods ONLY:
  - Baked or broiled chicken, fish or turkey with only salt and pepper seasoning if needed
  - White bread only
  - Plain steamed white rice
  - Eggs
  - Clear chicken or beef broth (no vegetable broth)
  - Plain tofu with only salt and pepper seasoning if needed
  - Coffee and Tea with no cream or sugar
- Avoid all other foods and drinks except water
- You should begin a complete fast (no food or drinks other than water) 12 hours prior to your breath test.
- On the day of your test, there is no smoking (including second hand smoke) at least 1 hour before or at any time during the test.
- No sleeping or vigorous exercise for at least 1 hour before or at any time during the test.
- Nothing by mouth one (1) hour before you start your breath test. This means no water, gum, mints, smoking, etc.

How is the breath test administered?

Each test is 3 hours in length and begins with a base line breath sample. Then, depending on the test, you will drink a specialized solution. Lactose and Fructose tests require 1 breath sample each hour of the test. SIBO tests require a breath sample every 20 minutes. You will remain in the office throughout the entire 3 hours.

Fructose intolerance (?)

- Fructose is taken up by the brush border transport protein GLUT 5 and as shown recently also by GLUT2. Since fructose is rapidly cleared from the circulation, luminal uptake of fructose is guaranteed. A true fructose malabsorption, as in lactase deficiency or in SGLT1 mutation, has not yet been reported. Fructose intolerance is rather defined as “any situation in which free fructose is available to fermentative metabolism by luminal bacteria before it can be absorbed across the small intestinal mucosa”.
- Fructose intolerance is not widely accepted as a disease and it rather represent intolerance to a wide range of badly- or non-absorbed fermentable monosaccharides. Due to the increasing load of fructose-containing solutions in the Western diet the capacity of the fructose absorption system may be overloaded leading to symptoms of carbohydrate malabsorption. On the other hand in chronic intestinal disease like irritable bowel disease, inflammatory bowel disease or coeliac disease fructose malabsorption may play a role in maintaining gastrointestinal symptoms despite adequate therapy. In this situation breath testing might be applicable. Therapy should then be aimed at reducing the fructose content in the diet.

Malabsorption of specific nutrients, e.g. iron, bile acids

Oral iron absorption test

- When iron deficiency with or without anaemia occurs a detailed work up following guidelines should be performed including urine and faecal blood analysis, screening for coeliac disease and in most cases endoscopy of the upper and lower GI tract.

Bile acid absorption test

- Bile acids are secreted with bile in the duodenum and are almost exclusively re-absorbed in conjugated form in the distal ileum. Malabsorption of bile acids can be due to resection or mucosal disease (e.g. ileitis terminalis) of this part of the small bowel. Bile acids entering the colon can lead to the so called bile acid diarrhoea due to a direct action on colonocytes.

Protein-losing enteropathy

Protein-losing enteropathy is not a specific disease but rather a syndrome that is characterized by hypoproteinaemia and peripheral oedema in the absence of proteinuria, defects in protein synthesis or protein malnutrition. It can occur in numerous gastrointestinal and non-gastrointestinal diseases. These diseases causing protein-losing enteropathy can be classified into three groups according to the mucosal alterations:

(1)

mucosal ulceration, such that the protein loss primarily represents exudation across ulcerations, e.g. ulcerative colitis, Crohn's disease, gastrointestinal carcinomas or peptic ulcer.

(2)

non-ulcerated mucosa, but with evidence of mucosal changes so that the protein loss represents loss across epithelia with altered permeability, e.g. coeliac disease, Ménétrier's disease, collagenous colitis and Whipple's disease.

(3)

lymphatic dysfunction, representing either primary lymphatic disease or secondary to partial lymphatic obstruction

Protein-losing enteropathy

The diagnosis of protein-losing enteropathy is suggested by the presence of peripheral oedema and low serum albumin levels in the absence of protein malnutrition and renal or hepatic disease.

Schulzke JD, Tröger H, Amasheh M. Disorders of intestinal secretion and absorption. *Best Pract Res Clin Gastroenterol*. 2009;23(3):395–406. doi:10.1016/j.bpg.2009.04.005

Inflammatory bowel diseases

- Inflammatory bowel diseases (IBD), mainly consisting of Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBDU), are chronic relapsing and remitting diseases resulting in uncontrolled inflammation of the gastrointestinal (GI) tract.
- The distribution of the diseases varies geographically, but the majority of patients are diagnosed with UC (approximately 55%), followed by CD and IBDU.
- The treatment aims to relieve and prevent GI tract inflammation and has until the 1990s consisted of anti-inflammatory and immunosuppressive drugs or surgical procedures (e.g., removal of the colon, limited resections). The introduction and development of biological treatment options during the last two decades likely have improved the natural disease course of IBD and possibly decreased surgery rates. However, the majority of the patients will, despite treatment, alternate between periods of remission and periods of active disease. Because of the unpredictable disease course and onset in patients of young age, IBD represents a major physical and psychological burden on patients.

Weimers P, Munkholm P. The Natural History of IBD: Lessons Learned. *Curr Treat Options Gastroenterol*. 2018;16(1):101–111. doi:10.1007/s11938-018-0173-3

Inflammatory bowel diseases - etiology

- The etiology of these diseases is unknown, but that genetic, environmental, and intestinal microbial factors play an important role in the development of IBD has been scientifically verified.
- The prevalence of IBD has increased during the last decades and it is estimated to be five million patients affected by the disease globally. With an increasing prevalence and the need for expensive medical treatments, IBD represents a significant strain on the health care system.

Weimers P, Munkholm P. The Natural History of IBD: Lessons Learned. *Curr Treat Options Gastroenterol*. 2018;16(1):101–111. doi:10.1007/s11938-018-0173-3

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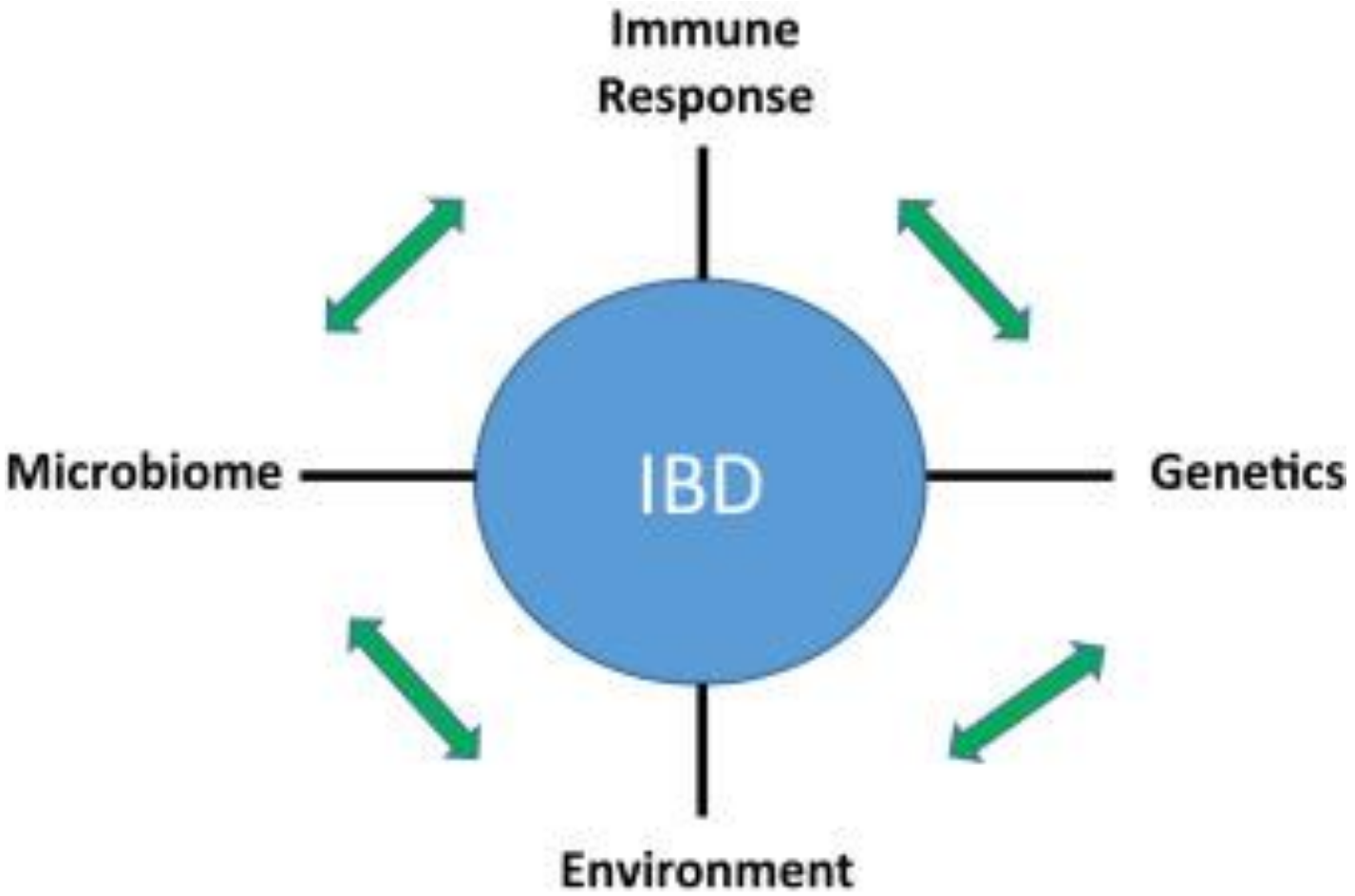

Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. *J Allergy Clin Immunol*. 2020;145(1):16–27. doi:10.1016/j.jaci.2019.11.003

IBD

- Inflammatory bowel disease (IBD) is a chronic immune-mediated disease affecting the gastrointestinal tract. IBD consists of 2 subtypes: ulcerative colitis and Crohn disease. IBD is thought to develop as a result of interactions between environmental, microbial, and immune-mediated factors in a genetically susceptible host. Of late, the potential role of the microbiome in the development, progression, and treatment of IBD has been a subject of considerable interest and enquiry. Indeed, studies in human subjects have shown that the gut microbiome is different in patients with IBD compared with that in healthy control subjects.

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IBD

- Other evidence in support of a fundamental role for the microbiome in patients with IBD includes identification of mutations in genes involved in microbiome-immune interactions among patients with IBD and epidemiologic observations implicating such microbiota-modulating risk factors as antibiotic use, cigarette smoking, levels of sanitation, and diet in the pathogenesis of IBD. Consequently, there has been much interest in the possible benefits of microbiome-modulating interventions, such as probiotics, prebiotics, antibiotics, fecal microbiota transplantation, and gene manipulation in the treatment of IBD.

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Disease course

- The clinical course of UC and CD is unpredictable and is characterized by times of remission and times of active disease with characteristic symptoms of abdominal pain, diarrhea, and weight loss.
- Despite many similarities between the two diseases, disease phenotype and progression differ significantly. Thus, while CD can affect the whole GI tract causing transmural inflammation, UC are confined to the mucosal and occasionally the submucosal layer of the colon.

Ulcerative colitis

- Aproximately one third of the patients are diagnosed with proctitis, one third with left sided colitis, and one third with pancolitis. However, the proportions may vary with geography and population; thus, proctitis is described more frequently in some Asian cohorts and left-sided colitis in some European cohorts Since UC is a dynamic and sometimes unpredictable disease, the disease course may progress over time and the proportion of patients with extensive colitis might increase to 46% after a few years.

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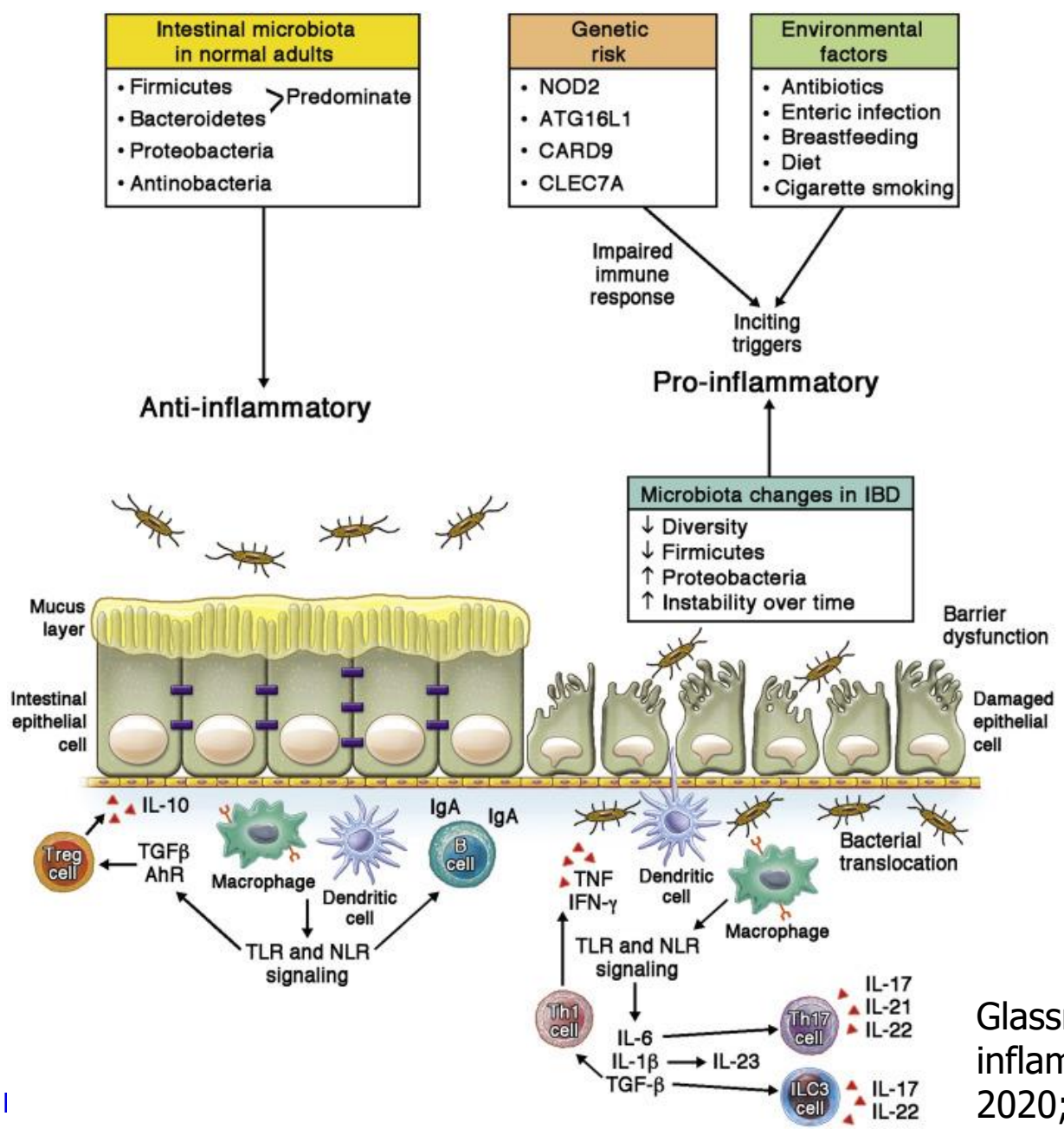
Crohn’s disease

- Since inflammation and lesions caused by CD can affect any segment of the GI tract, the location of the disease as well as treatment options differs from UC. At the time of diagnosis, roughly one third of the patients have ileocolonic disease, one third have isolated ileal disease, one third have isolated colonic disease, and a minority have isolated upper GI inflammation.
- The course of CD is considered to be more stable regarding disease extension compared to UC, with only 20% with isolated disease (ileal or colonic) developing ileocolonic disease after a few years.
- Approximately 25–41% of the patients presents a stricturing or penetrating disease phenotype at diagnosis. The behavior (inflammatory, stricturing, penetrating) of CD is dynamic, and the cumulative risk of developing stricturing or penetrating phenotype is approximately 50% after 10–20 years of disease duration.
- An important aspect of the penetrating phenotype is the development of fistulas.

Pathophysiology of IBD

- Gut microbiota composition is known to be important in maintaining health and mediating disease
- Dysbiosis, a change in the normal microbial ecology, occurs in the intestine in the context of IBD
- Gut inflammation in IBD is characterized by a reduced diversity of microbiota, which could render the host more susceptible to colonization with pathogens or pathobionts
- Environmental factors probably have a major role in IBD; antibiotic use, childbirth mode, breastfeeding, air pollution, NSAID use, hypoxia or high altitude, diet and urban environments have been studied



Genetic, environmental, and immune-mediated microbiome interactions in the pathogenesis of IBD. Genetic mutations and environmental factors act as inciting triggers and lead to an impaired immune response to gut microbiota, resulting in a proinflammatory state.
Toll-like receptors *(TLR)* and NOD-like receptors *(NLRs)* on dendritic cells, macrophages, and epithelial cells interact with the microbiota and lead to differentiation of T_H17 cells, type 3 innate lymphoid cells *(ILC3s)*, and T_H1 cells, which secrete proinflammatory cytokines. This in turn causes inflammation, epithelial barrier dysfunction, and bacterial translocation. Microbiota changes, including decreased diversity and increased instability of the gut microbiota composition over time, decreases in *Firmicutes* species, and increases in *Proteobacteria* species, are seen in association with IBD. In healthy subjects bacteria sensed by TLRs and NLRs lead to production of IgA-secreting B cells and differentiation of regulatory T *(Treg)* cells under the influence of TGF-β and AhR signaling. IgA produced from B cells neutralizes pathogenic bacteria, and IL-10, an anti-inflammatory cytokine produced by regulatory T cells, acts to maintain gut homeostasis.

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– 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)*. *NOD2* encodes an intracellular pattern recognition receptor that interacts with the peptidoglycan found in both gram-positive and gram-negative bacteria.

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NOD2

- NOD2 is expressed in intestinal epithelial cells, functions as a defensive factor against intracellular bacteria, and contributes to the immune response to commensal microbes. In human subjects mutations in *NOD2* are associated with a decrease in levels of IL-10, an anti-inflammatory cytokine, and increased numbers of mucosa-associated bacteria. Patients with *NOD2* mutations have microbiota that are characterized by decreased abundance of *Faecalibacterium* species and increased abundance of *Escherichia* species. In patients with CD, *NOD2* is associated with ileal disease, an increased risk of postoperative recurrence after ileocecal resection, and a more aggressive fistulizing and fibrostenotic disease phenotype.

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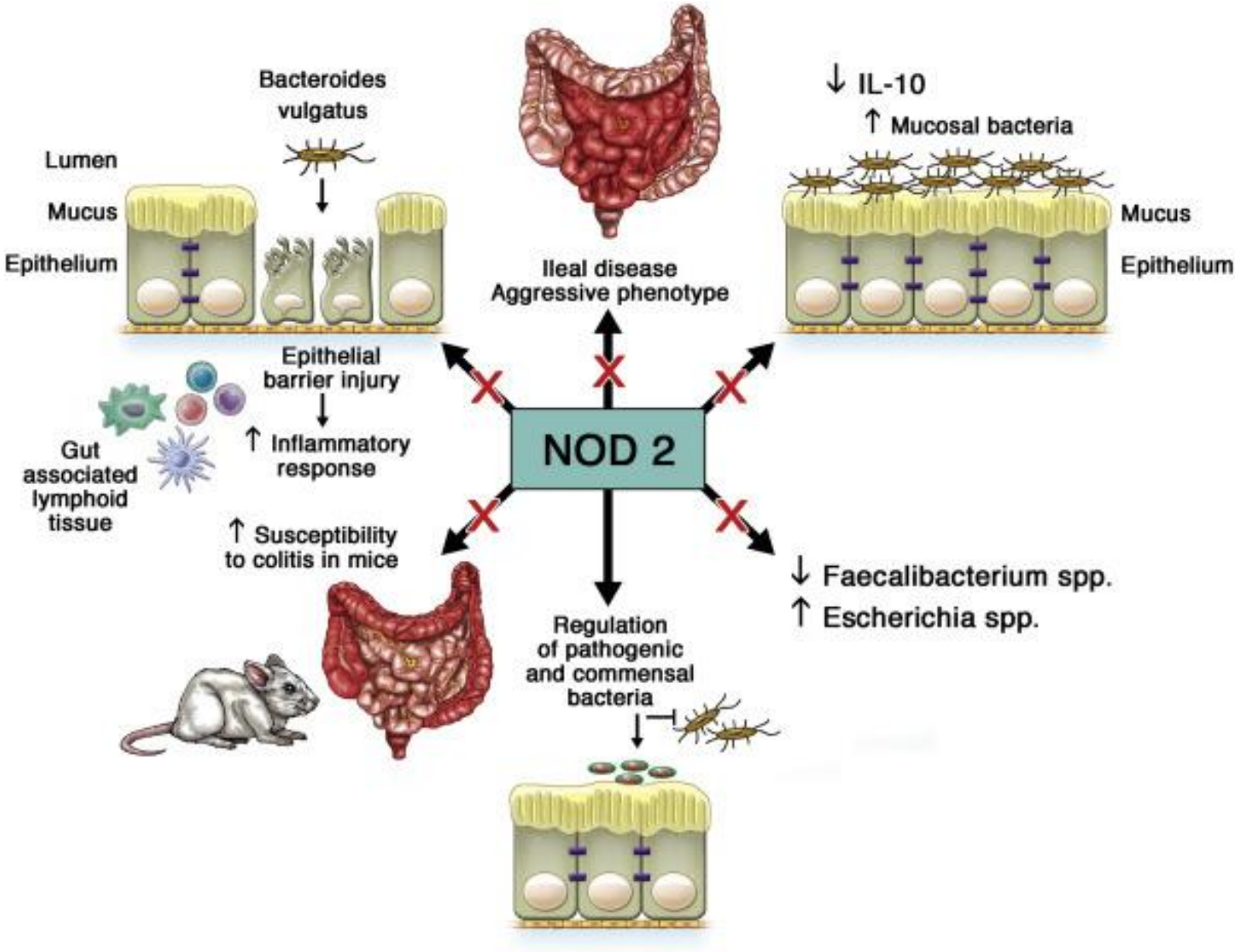

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To the previous picture

- Role of *NOD2* in bacteria-host interactions in patients with IBD. *NOD2* encodes an intracellular pattern recognition receptor that interacts with peptidoglycan of gram-positive and gram-negative bacteria. *NOD2* is involved with regulation of both pathogenic and commensal bacteria. Mutations in *NOD2* lead to decreased levels of anti-inflammatory cytokines, such as IL-10, and an increase in mucosal bacteria. In human subjects with *NOD2* mutations, there is an enrichment of *Escherichia* species and a depletion of *Faecalibacterium* species. In patients with CD, *NOD2* is associated with ileal disease and an aggressive disease phenotype with stricturing and fistulizing disease activity.

IBD and environmental factors

- number of environmental factors have been associated with the development of IBD. Alteration of the gut microbiota, or dysbiosis, is closely linked to initiation or progression of IBD, but whether dysbiosis is a primary or secondary event is unclear. Nevertheless, early-life events such as birth, breastfeeding and exposure to antibiotics, as well as later childhood events, are considered potential risk factors for IBD. Air pollution, a consequence of the progressive contamination of the environment by countless compounds, is another factor associated with IBD, as particulate matter or other components can alter the host's mucosal defences and trigger immune responses.

Breast-feeding is protective against the development of IBD.

- The oligosaccharides in breast milk have prebiotic effects that contribute to the establishment of the infant gut microbiota. In addition, human milk oligosaccharides have been found to inhibit the adhesion of enteropathogenic *E coli*, *Vibrio cholerae*, and *Salmonella fyris* to epithelial cells.
- Infants who are breast-fed have a lower incidence of gastrointestinal tract infections. Breast-feeding has been shown to lead to an increased abundance of Firmicutes and Actinobacteria compared with formula-fed infants.

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Breast-feeding is protective against the development of IBD.

- human breast milk is microbially diverse and has both probiotic and prebiotic effects. Breast milk contains *Lactobacillus rhamnosus*, *Lactobacillus gasseri*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, and Bifidobacteria. Microbiota in breast milk promote immune tolerance, prevent infection, and play a role in the maintenance of the epithelial barrier through an immune-mediated influence on intestinal microbiota composition.

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Dietary changes

- Dietary changes, if sufficiently drastic, can alter the intestinal microbiome in as little as 24 hours. Animal-based diets lead to increased abundance of bile-tolerant bacteria, including *Alistipes*, *Bilophila*, and *Bacteroides* species, and a decreased abundance of Firmicutes. In contrast, plant-based diets lead to increased abundance of Firmicutes. Certain diets have been associated with an increased risk for IBD.

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Dietary changes

- Patients with IBD were found less likely to have consumed unpasteurized milk or eaten pork.
- Diets high in total fats, omega-6 fatty acids, and meat were associated with an increased risk of IBD, whereas higher fiber and fruit intakes were associated with a decreased risk for CD, and a high intake of vegetables was associated with a decreased risk for UC.
- These findings can be explained by diet-induced shifts in the microbiome, such as the decreased abundance of Firmicutes with animal-based diets. Decreased abundance of *Faecalibacterium prausnitzii*, a member of the Firmicutes phylum with anti-inflammatory effects, has been associated with CD.

Cigarette smoking

- Cigarette smoking has a complex interaction, with IBD being apparently protective against UC but negatively affecting the natural history of CD.

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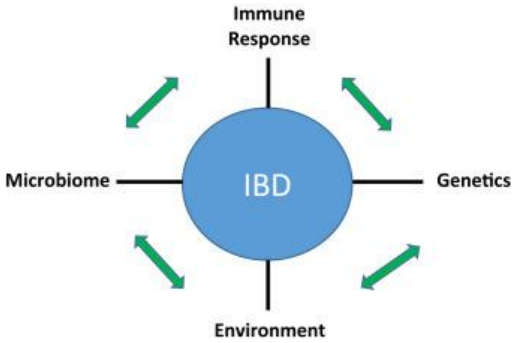
Cigarette smoking

- there is evidence that the gut microbiota of current and former smokers differs from that of nonsmokers, with a relative increase in the numbers of Bacteroidetes and decrease in Firmicutes and Proteobacteria in one of these studies. In a study evaluating the microbiota of cigarette smokers before and after smoking cessation, cigarette smokers had a lower abundance of *Bifidobacterium* species compared with nonsmoking control subjects, and increases in *Bifidobacterium* species were seen after smoking cessation. There was also a decrease in *Bacteroides* species after smoking cessation. Some of the differences seen in the gut microbiota of cigarette smokers mirror those seen in patients with CD and those with UC, suggesting a potential link between smoking, microbiota changes, and development of IBD.

Summary



- there is some evidence to suggest that environmental factors, such as early antibiotic use, enteric infections, breast-feeding, diet, and cigarette smoking, affect the gut microbiota and drive immune activation in subjects genetically susceptible to the development of IBD.

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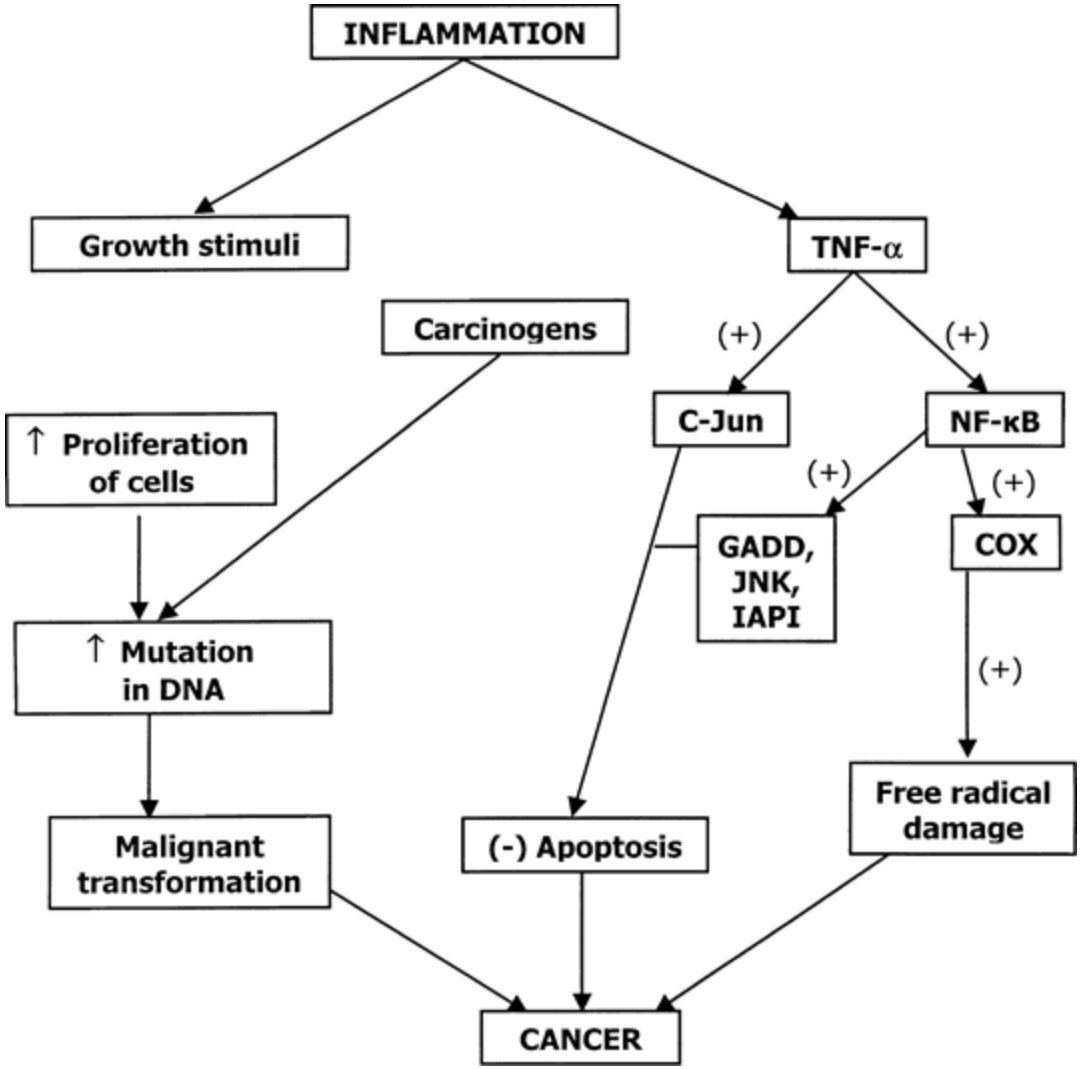
Relations between inflammation and cancer



Cancer

- IBD patients are at a greater risk of developing colorectal cancer, small bowel cancer, and some extra-intestinal cancers compared to the general population. The cause is considered to be multifactorial, and potential drivers of the carcinogenesis are assumed to be inflammation and immunosuppression:
- **Colorectal cancer**
- **Small bowel cancer**
- **Extraintestinal cancer (**the risk of developing cancer in the upper GI tract, bladder, skin (squamous cell), and lungs was significantly increased in CD. UC patients on the contrary had increased risk for developing hepatic and biliary cancer, as well as leukemia but a decreased risk of lung cancer compared to the general population). Weimers P, Munkholm P. The Natural History of IBD: Lessons Learned. *Curr Treat Options Gastroenterol*. 2018;16(1):101–111. doi:10.1007/s11938-018-0173-3

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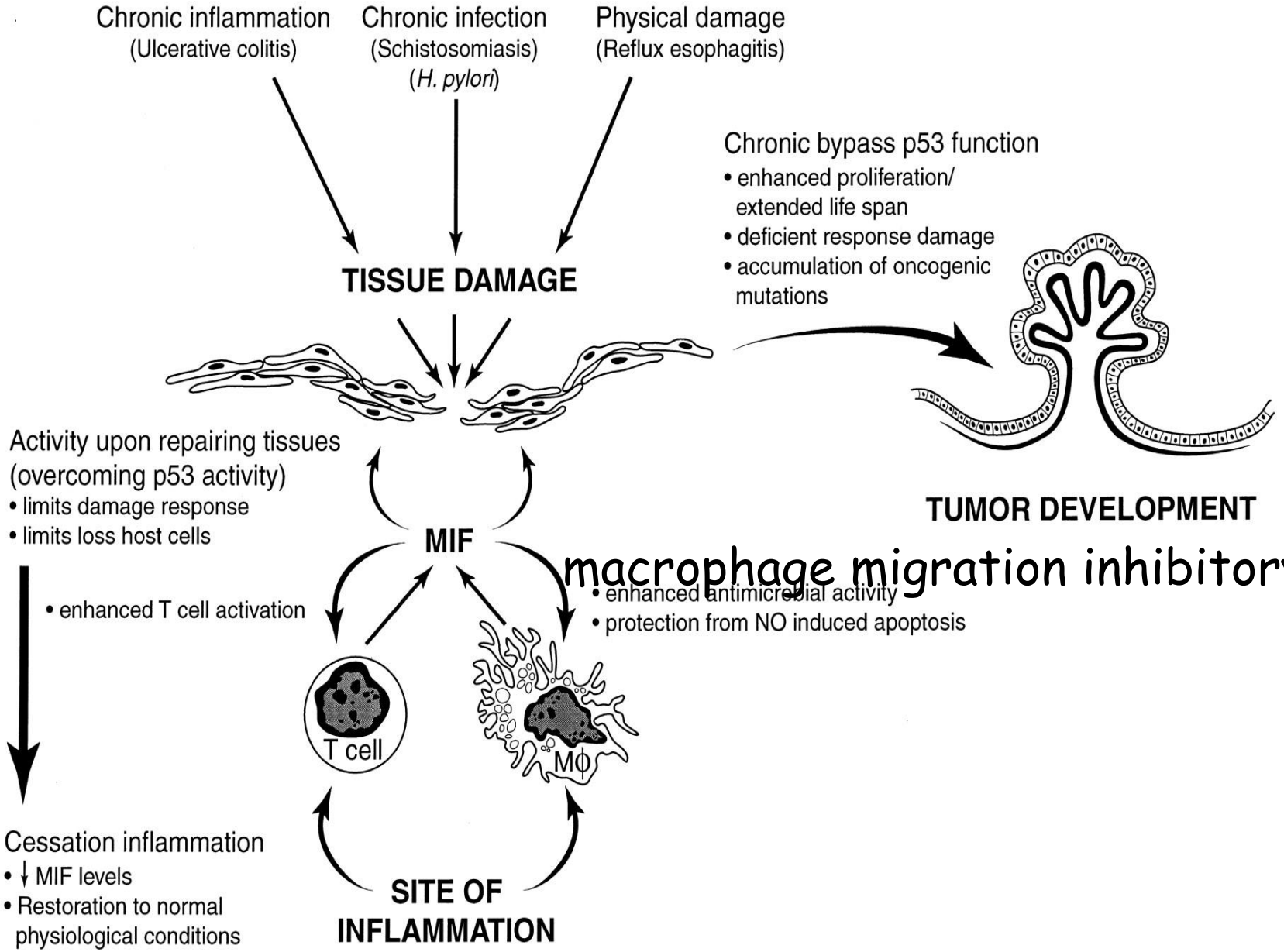
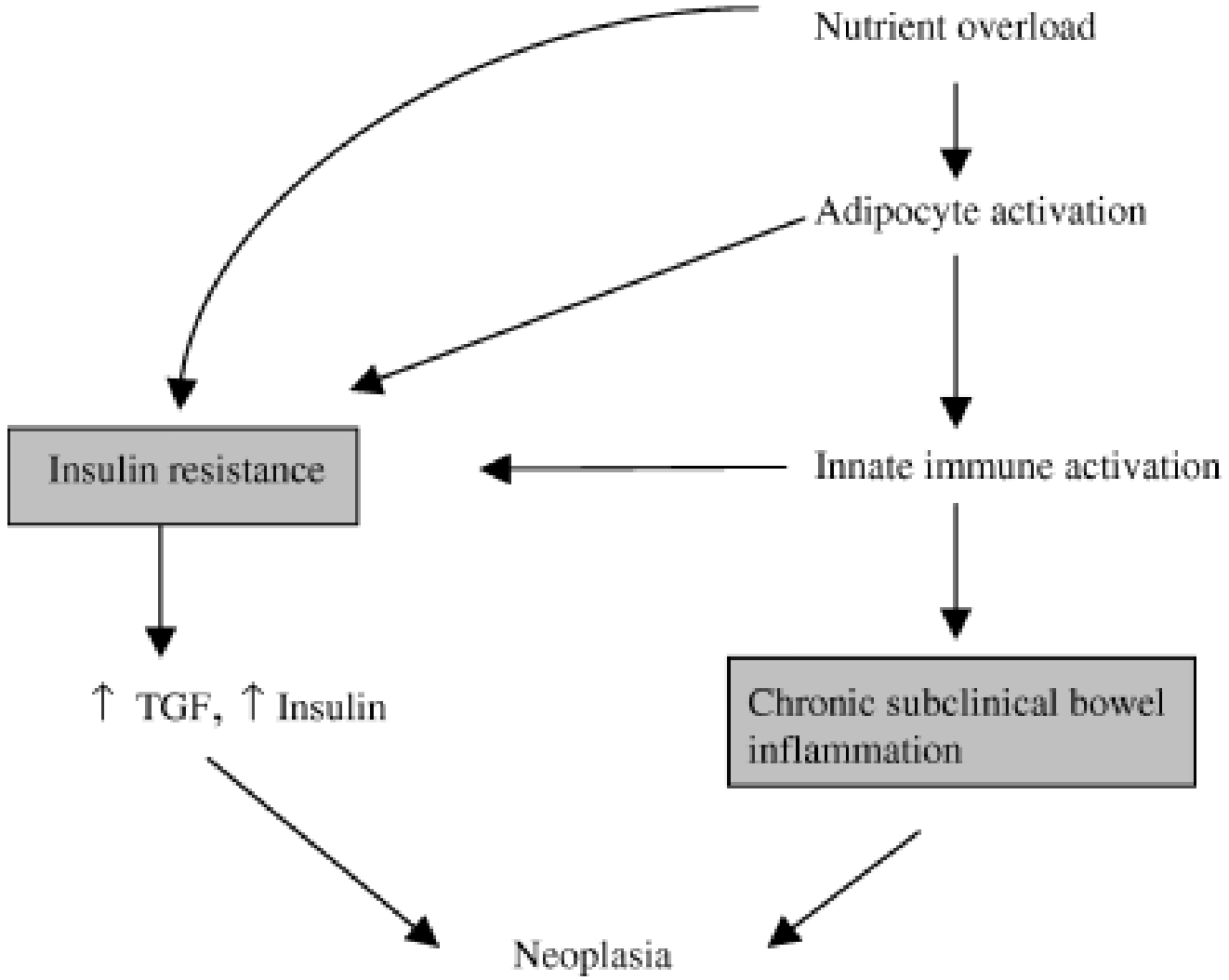


macrophage migration inhibitory factor



John BJ, 2006

Pathophysiological mechanisms connecting obesity and gastrointestinal tract

Thank you for your attention

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