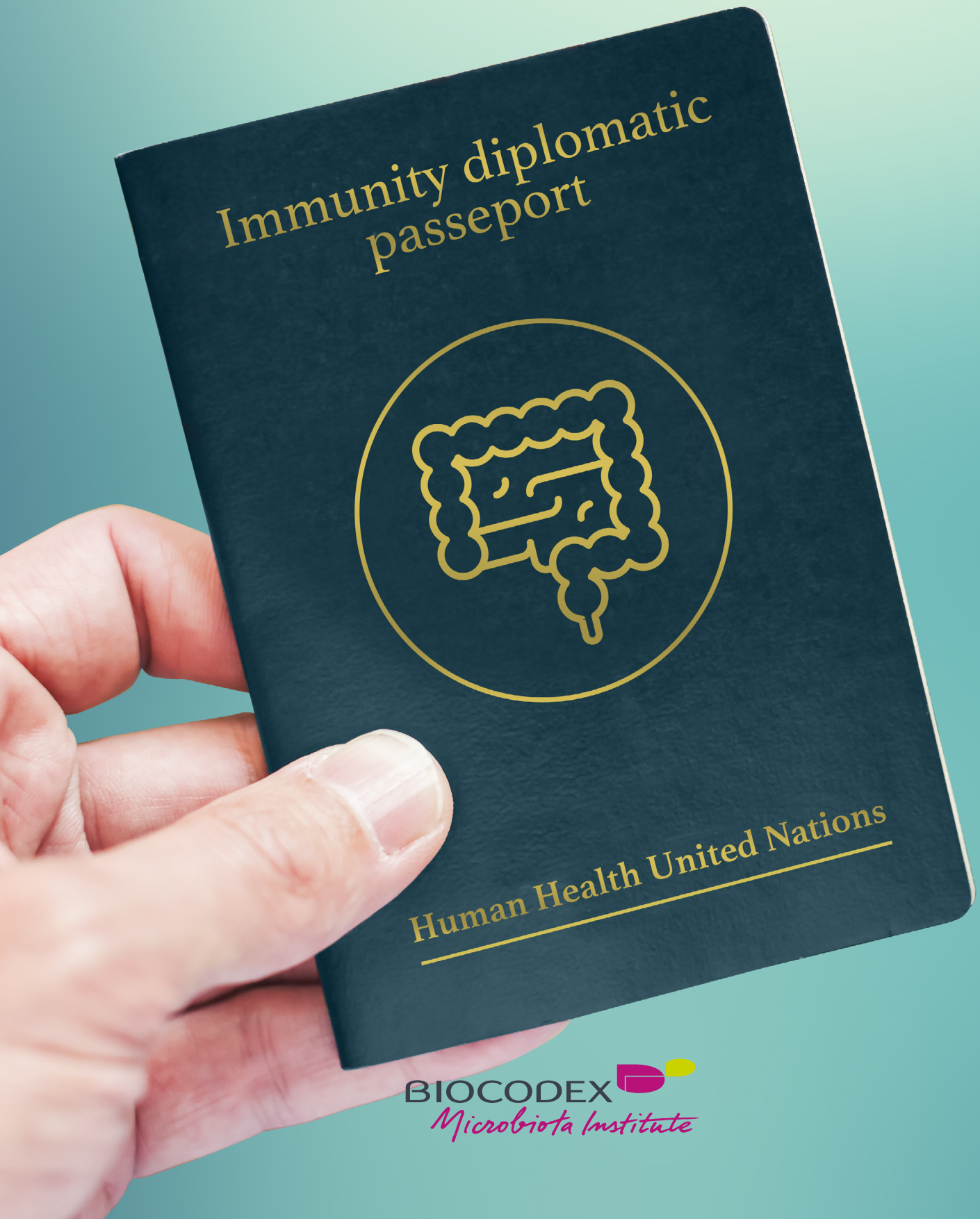
MICROBIOTA,
a diplomatic immunity?



BIOCODEX
Microbiota Institute

SUMMARY

CONTRIBUTIONS

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UNDERSTANDING THE COMPLEX INTERPLAY between the microbiota and immunity is only just beginning

(By Dr. Bruce Vallance)

Your body is home to trillions of bacteria that together with viruses, fungi and other organisms, collectively make up the human microbiota. These microbes play an important role in promoting our health, as well as controlling our susceptibility to disease, by influencing different aspects of our daily lives. For example, the metabolic activity of our gut microbiota determines whether certain medications like acetaminophen are toxic to our livers.[1] Specific members of the microbiota can also change and evolve in response to new dietary sources of carbohydrates, allowing us to digest foods like sushi[2] or produce important and protective chemicals such as short chain fatty acids (SCFA).[3] Other microbes selectively shape our immune systems to become reactive, or tolerant to invading organisms, thereby controlling our risk of severe gastrointestinal (GI) infections.[4] **During the 1000 first days of life, the critical window of early childhood growth and development (period from conception to 2 years of age), any interference with microbiota establishment in the neonatal gut may potentially lead to negative health outcomes.**[5] Although scientists have established the importance of the microbiota in maintaining human health, our understanding of the complex interplay between the microbiota and immunity is only just beginning.

1. Clayton TA, Baker D, Lindon JC, *et al.* Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. *Proc Natl Acad Sci U S A.* 2009 Aug 25;106(34):14728-33. **2.** Hehemann JH, Kelly AG, Pudlo NA, *et al.* Bacteria of the human gut microbiome catabolize red seaweed glycans with carbohydrate-active enzyme updates from extrinsic microbes. *Proc Natl Acad Sci U S A.* 2012 Nov 27;109(48):19786-91. **3.** Yang W, Yu T, Huang X, *et al.* Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat Commun.* 2020 Sep 8;11(1):4457. **4.** Atarashi K, Tanoue T, Shima T, *et al.* Induction of colonic regulatory T cells by indigenous Clostridium species. *Science.* 2011 Jan 21;331(6015):337-41. **5.** Aires J. First 1000 Days of Life: Consequences of Antibiotics on Gut Microbiota. *Front Microbiol.* 2021 May 19;12:681427.

THE INFANT'S GUT at the heart of immunity

By Dr. Travis J. De Wolfe

DEVELOPMENT OF INNATE IMMUNE BARRIERS

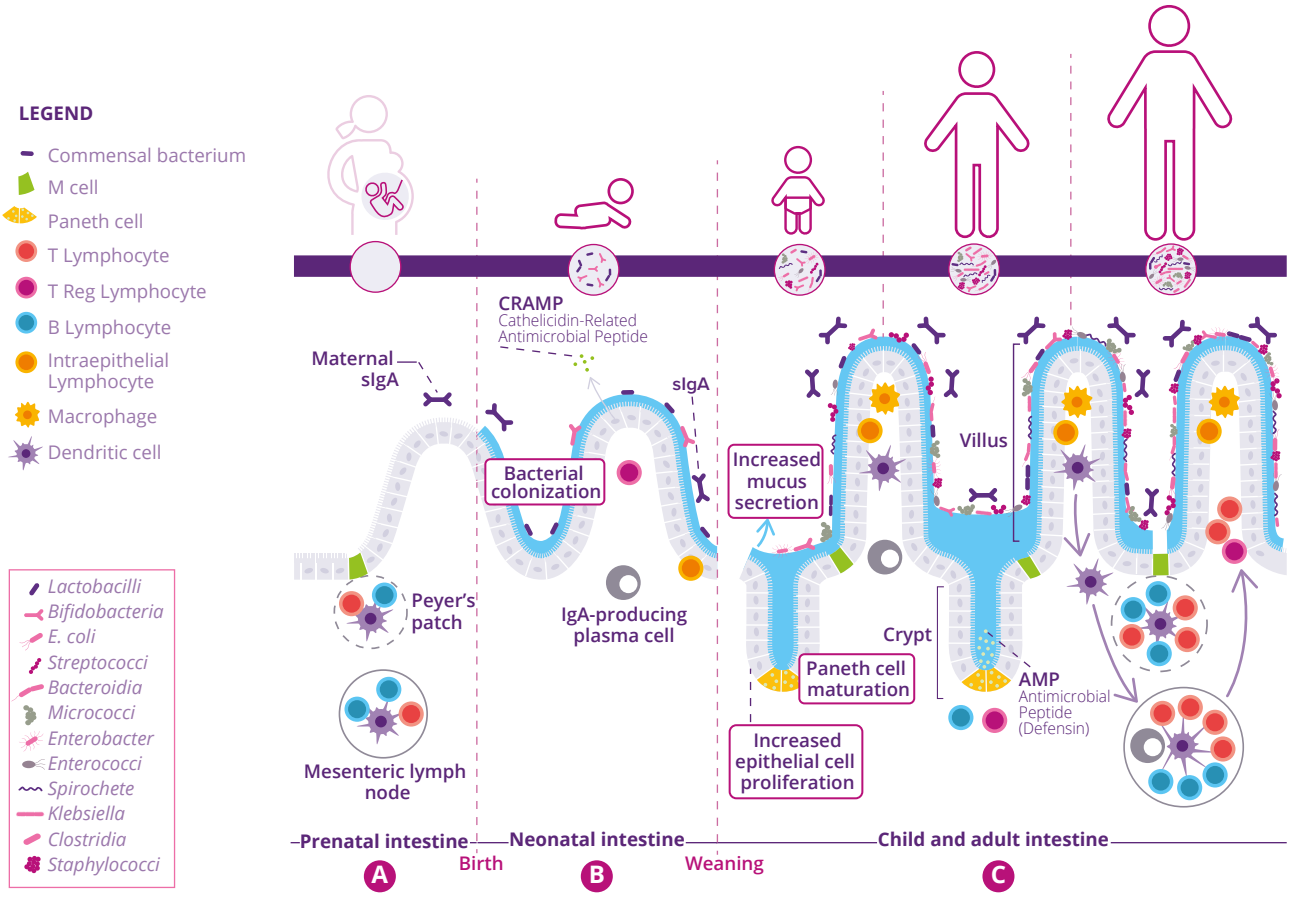
Development of the intestinal immune system begins before birth and continues throughout neonatal weaning. *In utero*, immature lymphoid structures including Peyer's patches and mesenteric lymph nodes are generated **(Fig 1A)**. Since these structures are not fully functional until later in development, to compensate, antimicrobial peptides (AMP) are produced by the gut epithelium and function as a defense barrier in response to the first bacterial colonizers **(Fig 1B)**.[1] Mucus is another important barrier structure which is produced by goblet cells and secreted at the apical surface of the GI tract. Together, these **innate immune barriers play a key role in limiting direct contact of the gut microbiota with host epithelial cells**, especially as the microbiota establishes itself within the infant intestine.

NEONATAL ADAPTIVE IMMUNE SYSTEM IS ALSO CRITICAL DURING DEVELOPMENT

Immunoglobulin A (IgA) are produced with varying affinity toward members of the microbiota as well as specific food antigens ingested by the neonate. Secreted IgA act to cross-link these targets in the intestinal lumen and limit their ability to adhere to and/or penetrate the gut epithelium **(Fig 1B)**.[2] Correspondingly, **during weaning, the neonatal gut microbiota becomes increasingly diverse and concentrated** in response to a changing diet and development of crypt-villous architecture. This requires further protection of the

> *« At least 80% of the body Ig-producing cells are located in the gut.[3] »*

FIGURE 1: Development of gut microbiota and intestinal immune system before birth (A), before (B) and after weaning (C). Adapted from Brandtzaeg P, 2017[3] and Ximenez C *et al*, 2017[6]



1. Kai-Larsen Y, Bergsson G, Gudmundsson GH, *et al.* Antimicrobial components of the neonatal gut affected upon colonization. *Pediatr Res.* 2007 May;61(5 Pt 1):530-6. 2. Corthésy B. Multi-faceted functions of secretory IgA at mucosal surfaces. *Front Immunol.* 2013 Jul 12;4:185. 3. Brandtzaeg P. (2017) Role of the Intestinal Immune System in Health. In: Baumgart D. (eds) Crohn's Disease and Ulcerative Colitis. Springer, Cham. 4. Commins SP. Mechanisms of Oral Tolerance. *Pediatr Clin North Am.* 2015 Dec;62(6):1523-9. 5. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell.* 2014 Mar 27;157(1):121-41. 6. Ximenez C, Torres J. Development of Microbiota in Infants and its Role in Maturation of Gut Mucosa and Immune System. *Arch Med Res.* 2017 Nov;48(8):666-680. 7. Schroeder BO. Fight them or feed them: how the intestinal mucus layer manages the gut microbiota. *Gastroenterol Rep (Oxf).* 2019 Feb;7(1):3-12.

epithelial barrier through maturation of local lymphoid structures. Activated Paneth cells begin to produce host defense proteins (defensins) at the base of small intestinal crypts, allowing other epithelial cells to transition away from producing AMP at baseline. Lastly, proliferation of epithelial cells increases alongside the increased secretion of mucus **(Fig 1C)**.

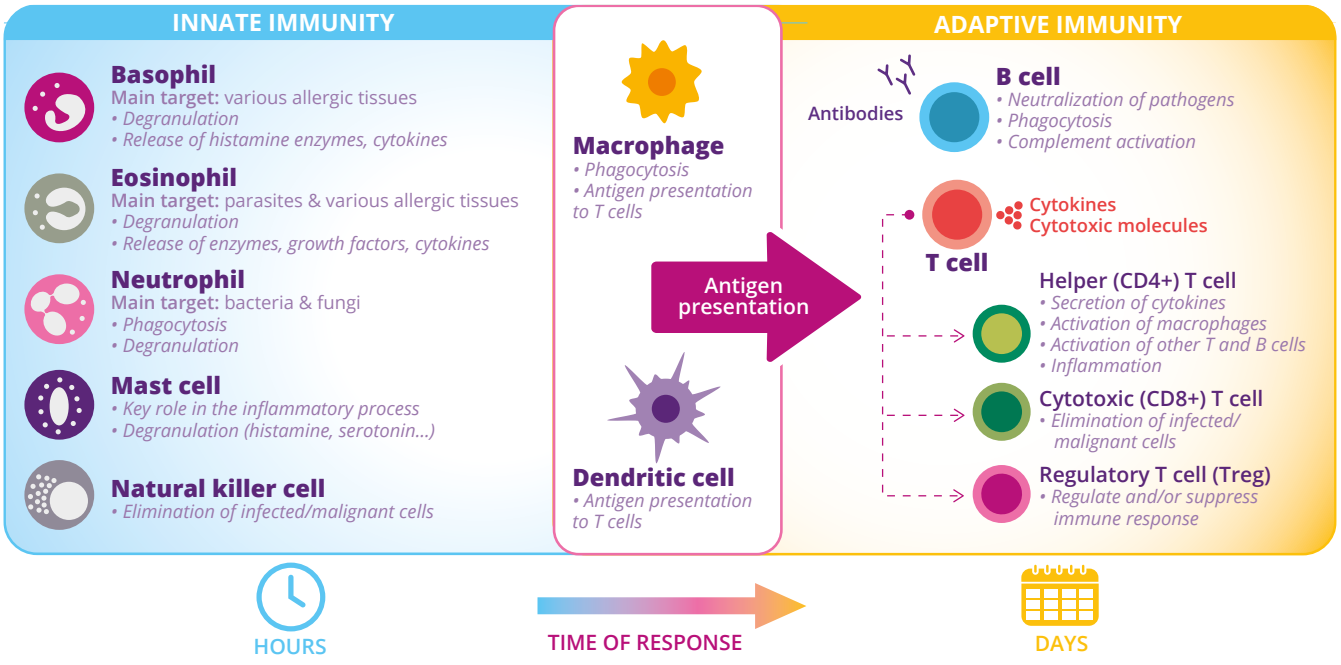
IMPORTANCE OF INTESTINAL HOMEOSTASIS

At least 80% of the body's Ig-producing cells are located in the gut:[3] this is the largest effector organ of humoral immunity. Specialized antigen-sampling epithelial cells (M cells) have a gatekeeping function by facilitating the transport of antigens - arising from commensal bacteria, diet or pathogens - from the gut lumen to the underlying lymphoid cells. These antigens will then be digested by dendritic cells (DC) and presented to the adaptive immune system. Together, the different components of intestinal immunity promote homeostasis through two anti-inflammatory strategies **(Fig 1C)**:
1) Immune exclusion of foreign antigens limits/prevents the gut microbiota from colonizing or penetrating the intestinal mucosa. This is performed by sIgA.[3]
2) Oral tolerance acts to limit local and peripheral immune responses to innocuous antigens that come in contact with the epithelial barrier.[4] This depends on Treg cells with regulatory functions **(Fig 2)**.[3]
When these strategies are operating properly, immune system regulation along with the actions of commensal microbiota in the development and training of this system will lead to the establishment of a **durable and homeostatic host-commensal relationship** that has long-term implications for human health.[5]

BEYOND IMMUNE CELLS: the importance of intestinal mucus barrier *(by Dr. Larissa Celiberto)*

The gut is lined by a single layer of cells, called the intestinal epithelium, over top of which lies a dense mucus layer **(Fig 1)**. Together these barriers confine microbes within the gut lumen, as well as protect the underlying immune system from unnecessary activation by the microbiota.[3] Intestinal mucus generate and release the mucin 2 (MUC2), a sugar-coated glycoprotein that provides structure to the mucus. Recent studies have shown **that the maturation and function of the mucus layer are strongly influenced by the gut microbiota,** while the types of sugars found on MUC2 can also influence which bacteria are able to bind to it or use it, and its sugar chains as a nutrient source.[7] Notably, a mucus barrier that is disrupted or dysfunctional can lead to **increased penetration or passage of potentially harmful bacteria out of the lumen (e.g. leaky gut)**, resulting in systemic infection and inflammation.[8] Moreover, a defective mucus layer, and a corresponding gut microbiota dysbiosis,[9] has been observed in several diseases (such as inflammatory bowel disease (IBD),[10,11] diabetes...[12]) thus highlighting the importance of this protective barrier to human health.

FIGURE 2: Innate and adaptive immune cells and functions.



8. Miner-Williams WM, Moughan PJ. Intestinal barrier dysfunction: implications for chronic inflammatory conditions of the bowel. *Nutr Res Rev.* 2016 Jun;29(1):40-59. 9. Levy M, Kolodziejczyk AA, Thaiss CA, *et al.* Dysbiosis and the immune system. *Nat Rev Immunol*. 2017;17(4):219-232. 10. Swidsinski A, Loening-Baucke V, Theissig F, et al. Comparative study of the intestinal mucus barrier in normal and inflamed colon. *Gut.* 2007 Mar;56(3):343-50. 11. Johansson ME, Gustafsson JK, Holmén-Larsson J, *et al.* Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut.* 2014 Feb;63(2):281-91. 12. Chassaing B, Raja SM, Lewis JD, *et al.* Colonic Microbiota Encroachment Correlates With Dysglycemia in Humans. *Cell Mol Gastroenterol Hepatol.* 2017 Apr 13;4(2):205-221.

FACTORS INFLUENCING MICROBIOTA DEVELOPMENT and maturation of the immune system early in life

Birth represents the biggest substantial environmental change in life as the newborn is exposed for the first time to a countless variety of microbes which colonize all body surfaces, leading to the establishment of the commensal microbiota in parallel with the immune system. Many factors shape the composition of the gut microbiota and the maturation of the newborn immune system (Fig 3). Discrepancies in the microbiota and immunity crosstalk during each developmental stage can have long-term effects on disease susceptibility.[13]

Birth impacts gut microbiota composition...

by Dr. Travis J. De Wolfe

The mode of delivery impacts what type of bacteria from the mother are transmitted to the neonatal intestine.[14] Babies delivered via the birth canal often carry many gut bacteria that synthesize lipopolysaccharide (LPS), a major membrane component of Gram-negative bacteria that can properly train the human immune system to properly respond to microbial threats.[15] In contrast, children delivered by caesarean section are predisposed to being colonized by opportunistic pathogens that circulate in hospitals.[14]

...AS WELL AS MATURATION OF IMMUNE STRUCTURE

These differences in initial microbial colonization can affect the subsequent maturation of the local innate lymphoid structures and alter the population of protective regulatory T cells (Treg), resulting in long-term effects on human intestinal physiology. Maturation of T cells and induction of immune factors can protect against, or in some cases, contribute to autoimmune-mediated diseases (diabetes, multiple sclerosis...) that develop later in life.[15,16]

Antibiotics impact on immune responses

EXPERT OPINION ***(By Dr. Pascal Lavoie)***

Antibiotics are essential to treat serious bacterial infections, however unnecessary antibiotic exposure can have serious adverse health consequences and should be avoided (ie. when the infection is due to a virus). In older adults, prolonged antibiotic use can lead to the overgrowth of a gut bacterial pathogen called Clostridioides difficile, with potentially life-threatening health consequences, particularly in the elderly.[17] Overusing antibiotics can also promote antimicrobial resistance, which can limit treatment options for future infections.[18] In animal models, antibiotic based perturbation of the gut microbiome alters immune functions and immune response thresholds.[19] Data in humans suggest that unnecessary antibiotic use may increase the risk of developing chronic health problems, like type I diabetes, asthma, allergies or even obesity.[20] Prolonged antibiotic use (> 1 week) is known to reduce the diversity of the gut microbiome, with babies born prematurely being the most vulnerable to perturbations in their gut microbiome. Prolonged, broad spectrum antibiotic use in the mother or premature infant reduces gut bacterial diversity, increasing the risk of sepsis and necrotizing enterocolitis.[21] Overall, the data in humans support the concept that the gut microbiome plays a major role helping babies develop into healthy adults. While the risks of excessive antibiotic exposure in adults are less severe, they may still impact the development of their immune responses, therefore antibiotic usage at any age should be restricted to those cases where they are necessary.

13. Kalbermatter C, Fernandez Trigo N, Christensen S, *et al.* Maternal Microbiota, Early Life Colonization and Breast Milk Drive Immune Development in the Newborn. *Front Immunol.* 2021 May 13;12:683022. 14. Shao Y, Forster SC, Tsaliki E, *et al.* Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature.* 2019 Oct;574(7776):117-121. 15. Wampach L, Heintz-Buschart A, Fritz JV, *et al.* Birth mode is associated with earliest strain-conferred gut microbiome functions and immunostimulatory potential. *Nat Commun.* 2018 Nov 30;9(1):5091. 16. Vatanen T, Kostic AD, d'Hennezel E, *et al.* Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. *Cell.* 2016 May 5;165(4):842-53. 17. Guh AY, Kutty PK. Clostridioides difficile Infection. *Ann Intern Med.* 2018 Oct 2;169(7):ITC49-ITC64. 18. Costelloe C, Metcalfe C, Lovering A, *et al.* Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ.* 2010 May 18;340:c2096.

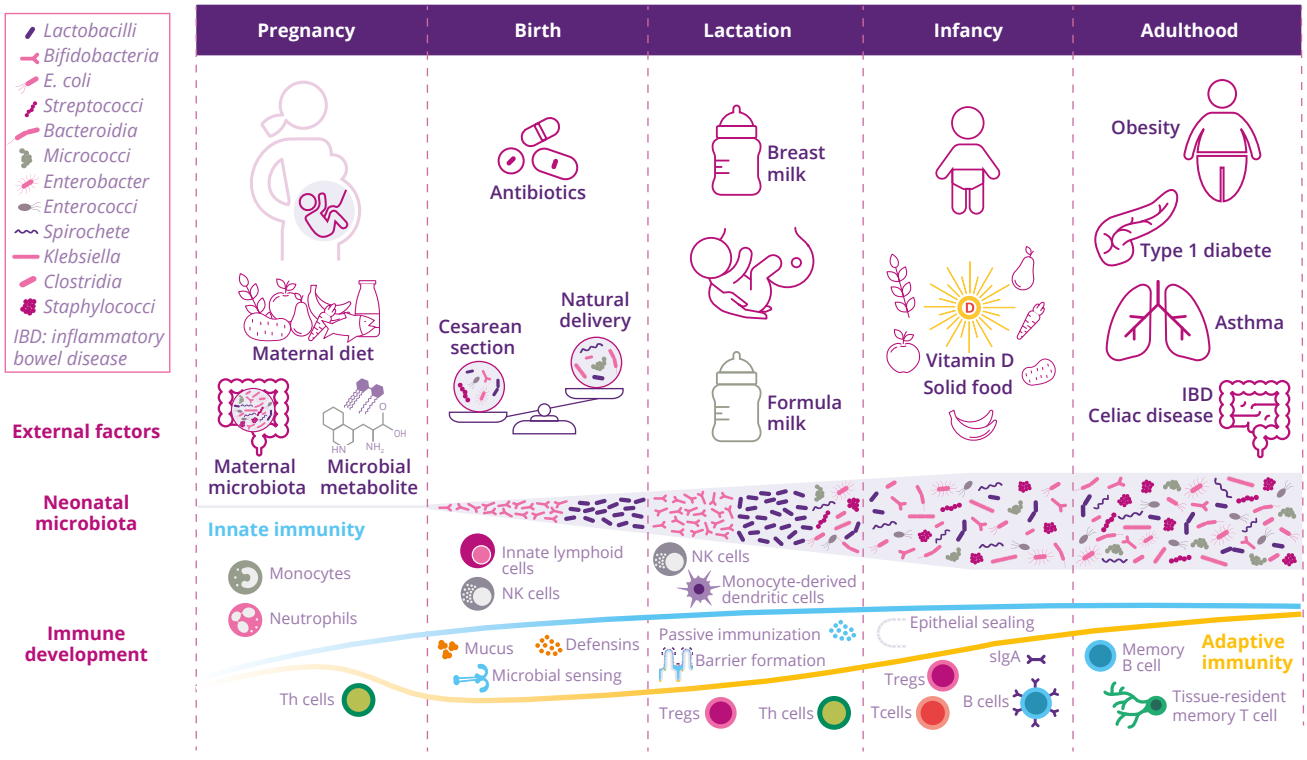
« Dysbiosis is not universal and is defined for each individual, according to their state of health. A common definition describes it as a compositional and functional alteration in the microbiota that is driven by a set of environmental and host-related factors that perturb the microbial ecosystem.[9] »

PROOF OF CONCEPT: gut microbiota colonization is essential for immune system development

(by Dr. Travis J. De Wolfe)

Studies with germ-free mice have demonstrated the important role that **the microbiota plays in preventing a faulty immune system.**[22] Germfree mice are impaired in the production of CD4-positive T helper immune cells, whereas selectively colonizing these mice with *Clostridia*, a commensal bacterial group, can induce the production of these cells that subsequently promote antimicrobial defenses in the gut and protect against pathogen infection.[23] IgA antibodies are another critical component of the immune system, that are deficient in germ-free mice. These antibodies bind to commensal bacteria and prevent them from escaping the GI tract. Selective colonization of germ-free mice with an *Escherichia coli* strain, or distinct *Bacteroides* strains trigger a rapid restoration/normalization of IgA.[24,25]

FIGURE 3: Environmental factors influencing the development of the newborn microbiota and mucosal immune system. Adapted from Kalbermatter C *et al*, 2021[13]



Throughout pregnancy, microbial metabolites (originating from the maternal microbiota and diet) influence fetal immune development. At birth, microbiota colonization starts in parallel with development of the immune system. At this stage, the newborn is still dependent on maternal protection, which is ensured through breastfeeding: maternal milk contains mother-derived bacterial antigens that stimulate the maturation of the innate mucosal immune system. Regarding gut microbiota colonization, *Enterococcacae, Clostridiaceae, Lactobacillaceae, Bifidobacteriaceae, Streptococcaceae* dominate in the first weeks of life. The introduction of solid food in an infant's diet leads to an increase in gut microbiota diversity, evolving to a more adult-like microbiota: the abundance of *Bifidobacteriaceae* decreases, while *Bacteroides, Ruminococcus*, and *Clostridium* become more prevalent. Birth mode, breast milk, solid food, and the intake of antibiotics are factors that shape the early life microbiota and the neonatal immune system.

19. Konstantinidis T, Tsigalou C, Karvelas A, *et al.* Effects of Antibiotics upon the Gut Microbiome: A Review of the Literature. *Biomedicines.* 2020 Nov 16;8(11):502. **20.** Sarkar A, Yoo JY, Valeria Ozorio Dutra S, *et al.* The Association between Early-Life Gut Microbiota and Long-Term Health and Diseases. *J Clin Med.* 2021 Jan 25;10(3):459. **21.** Walker WA. The importance of appropriate initial bacterial colonization of the intestine in newborn, child, and adult health. *Pediatr Res.* 2017 Sep;82(3):387-395. **22.** Sommer F, Bäckhed F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol.* 2013 Apr;11(4):227-38. **23.** Ivanov II, Atarashi K, Manel N, *et al.* Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell.* 2009 Oct 30;139(3):485-98. **24.** Hapfelmeier S, Lawson MA, Slack E, *et al.* Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. *Science.* 2010 Jun 25;328(5986):1705-9. **25.** Yang C, Mogno I, Contijoch EJ, *et al.* Fecal IgA Levels Are Determined by Strain-Level Differences in Bacteroides ovatus and Are Modifiable by Gut Microbiota Manipulation. *Cell Host Microbe.* 2020 Mar 11;27(3):467-475.e6.

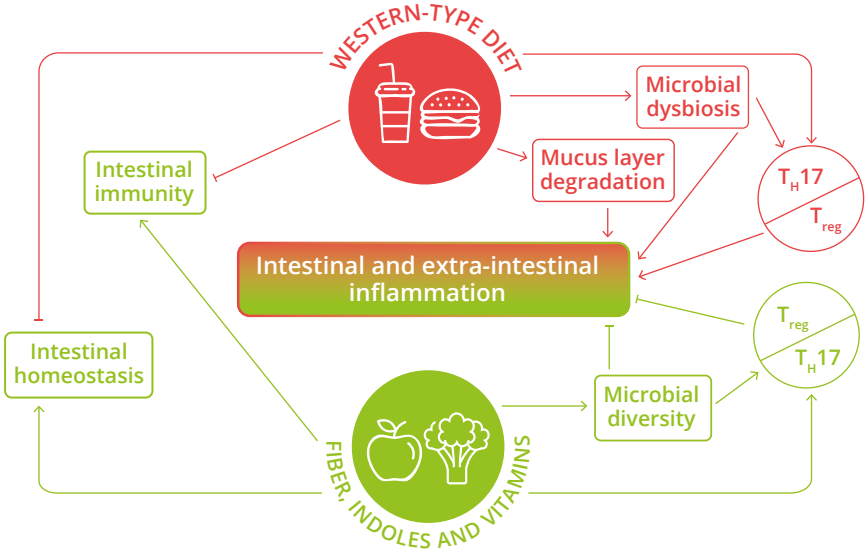
The impact of western diet on the mucus layer

by Dr. Larissa Celiberto

Fiber ingestion helps ensure regular bowel movements. Moreover, since fiber is not digestible by human enzymes, it can also serve as a key nutrient for the gut microbiota as these microbes produce distinct enzymes that are able to ferment and degrade these fibers into important metabolites such as SCFAs.[28]

> *« Microbial dysbiosis, mucus layer degradation and alteration of the balance of pro- and anti-inflammatory T cells in the intestine are observed in individuals consuming Western-type diets, leading to intestinal and extra-intestinal inflammation.[26] »*

FIGURE 4: Impact of Western diet versus diets rich in fiber and vitamins on local and systemic homeostasis and immunity.
Adapted from Siracusa F *et al*, 2019.[26]



The intestinal mucus layer can also serve as an alternative energy source for certain gut microbes (80% of its mass being composed of sugars) when the diet is lacking in fiber.[29] This increase in mucus foraging by gut bacteria can prove detrimental as animal studies have shown that mice fed a diet with no fiber are more susceptible to intestinal infections and inflammation. This susceptibility was due to **the resident microbiota eroding the mucus layer, such that it could no longer protect the underlying epithelium from invading pathogens.**[29] Western diets shift the microbiota composition away from fiber degrading bacteria in favor of bacterial species that thrive on mucus **(Fig 4)**.[30] Thus, our Western diets may be leading to the loss of protective microbes and the **expansion of microbes that weaken key defenses and barriers in the intestine, thereby helping trigger chronic intestinal inflammation.**

WHAT IS WESTERN DIET?

Western style diets largely consist of specific dietary fats, sugars and processed foods, environmental pesticides and are lacking in fiber. Consumption of the Western style diet has been linked to obesity as well as inflammatory and metabolic conditions such as type 2 diabetes, insulin resistance and IBD.[26] Aside from low quality food with high calories, it is also largely devoid of fiber due its lack of fruits, vegetables, legumes and whole grains, which makes achieving the recommended daily fiber intake of 28–35g[27] for adults extremely difficult.

26. Siracusa F, Schaltenberg N, Villablanca EJ, *et al.* Dietary Habits and Intestinal Immunity: From Food Intake to CD4+ T H Cells. *Front Immunol.* 2019 Jan 15;9:3177. **27.** Jones JM. CODEX-aligned dietary fiber definitions help to bridge the 'fiber gap'. *Nutr J.* 2014 Apr 12;13:34. **28.** Koh A, De Vadder F, Kovatcheva-Datchary P, *et al.* From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell.* 2016 Jun 2;165(6):1332-1345. **29.** Desai MS, Seekatz AM, Koropatkin NM, *et al.* A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. *Cell.* 2016 Nov 17;167(5):1339-1353.e21. **30.** Sonnenburg ED, Sonnenburg JL. The ancestral and industrialized gut microbiota and implications for human health. *Nat Rev Microbiol.* 2019 Jun;17(6):383-390. **31.** Vieira AT, Teixeira MM, Martins FS. The role of probiotics and prebiotics in inducing gut immunity. *Front Immunol.* 2013 Dec 12;4:445. **32.** Grimble,RF. Basics in clinical nutrition: Immunonutrition – Nutrients which influence immunity: Effect and mechanism of action. *e-SPEN.* 2009; 4(1):e10-e13 **33.** Cantorna MT, McDaniel K, Bora S, *et al.* Vitamin D, immune regulation, the microbiota, and inflammatory bowel disease. *Exp Biol Med* (Maywood). 2014 Nov;239(11):1524-30.

DAMPENING GASTROINTESTINAL inflammation through nutrition

by Dr. Genelle Healey

There are many ways to influence gut microbiota composition and modulate the immune response (prebiotics, probiotics...).[31] One of the options is **dietary interventions that have the potential to alter the activity of the local immune system,** thereby dampening the increased inflammatory tone observed with these conditions - this is termed immunonutrition.[32] The most widely studied immunonutrients include omega-3 polyunsaturated fatty acids (n-3 PUFA), vitamin D, arginine, nucleotides and glutamine.[32]

EXPERT OPINION ***(By Dr. Deanna Gibson)***

Myth	Reality
Eating a low-fat diet is healthy for the gut microbiome	*Different fats exert different effects on the microbiome and not all fats should be avoided*
Avoid saturated fats	*Including some saturated fat in the diet can improve healing responses after inflammation and is associated with beneficial changes to the gut microbiome*
Eating n-3 PUFA and promoting "anti-inflammatory" microbes is always good	*Inflammation is needed to survive and defend against infections especially during infant development. A well balanced and diverse diet improves the chances of consuming all necessary nutrients for good health*
The Western diet is rich in saturated fats	*The Western diet is rich in sugars, processed foods, n-6 PUFA and devoid of fiber, and this dietary pattern promotes an unbalanced gut microbiome*

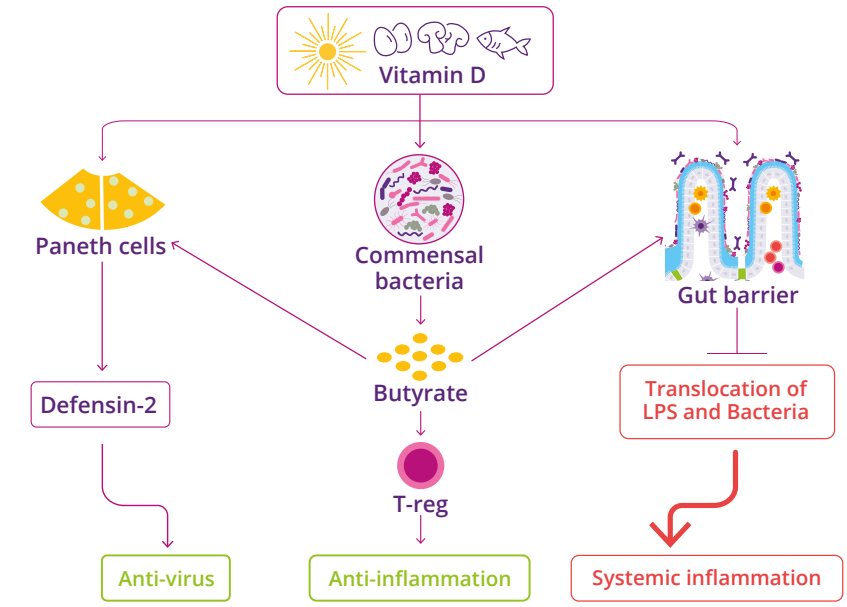
VITAMIN D AND ITS EFFECTS ON INTESTINAL IMMUNE RESPONSES

While the best characterized function of vitamin D is its role in controlling calcium levels and thereby maintain bone health, it is also known to have a significant effect on GI immune responses. Vitamin D regulates several genes that regulate gut barrier function as well as genes that encode antimicrobial peptides, thus helping **to maintain intestinal balance (Fig 5)**.[33] It exerts an **immunomodulatory effect**, including immune cell differentiation, migration and anti-inflammatory functions,[34] and can act directly on Paneth cells to promote defensin-2 secretion.[35] Vitamin D also **promotes the compositional diversity of the gut microbiota, leading to increased production of butyrate**. Butyrate can exert anti-inflammatory effects, increase gut barrier function, and promote Paneth cells to secrete defensins **(Fig 5)**. Interestingly, some probiotic bacteria (*e.g. Lactobacillus* strains) have been shown to increase vitamin D levels in the blood.[36]

VITAMIN D SOURCES:[38]

- **oily fish, cod liver oil**
- **eggs, mushrooms**
- **fortified foods: dairy products, cereal, and milk alternatives (i.e. soy milk)**
- **produced in the skin in response to sunlight exposure[39]**

FIGURE 5: Effects of vitamin D on intestinal cells, gut microbiota and gut barrier. Adapted from Chen J *et al*, 2021.[37]



LPS: lipopolysaccharide

34. Celiberto LS, Graef FA, Healey GR, *et al.* Inflammatory bowel disease and immunonutrition: novel therapeutic approaches through modulation of diet and the gut microbiome. *Immunology.* 2018 Sep;155(1):36-52. 35. Battistini C, Ballan R, Herkenhoff ME, *et al.* Vitamin D Modulates Intestinal Microbiota in Inflammatory Bowel Diseases. *Int J Mol Sci.* 2020 Dec 31;22(1):362. 36. Jones ML, Martoni CJ, Prakash S. Oral supplementation with probiotic L. reuteri NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: a post hoc analysis of a randomized controlled trial. *J Clin Endocrinol Metab.* 2013 Jul;98(7):2944-51. 37. Chen J, Vitetta L. Modulation of Gut Microbiota for the Prevention and Treatment of COVID-19. *J Clin Med.* 2021 Jun 29;10(13):2903. 38. Roseland JM, Phillips KM, Patterson KY, *et al.* Vitamin D in foods: An evolution of knowledge. Pages 41-78 in Feldman D, Pike JW, *et al,* eds. Vitamin D, Vol 2: Health, Disease and Therapeutics, 4th Ed. *Elsevier,* 2018. 39. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: *National Academy Press*, 2010.

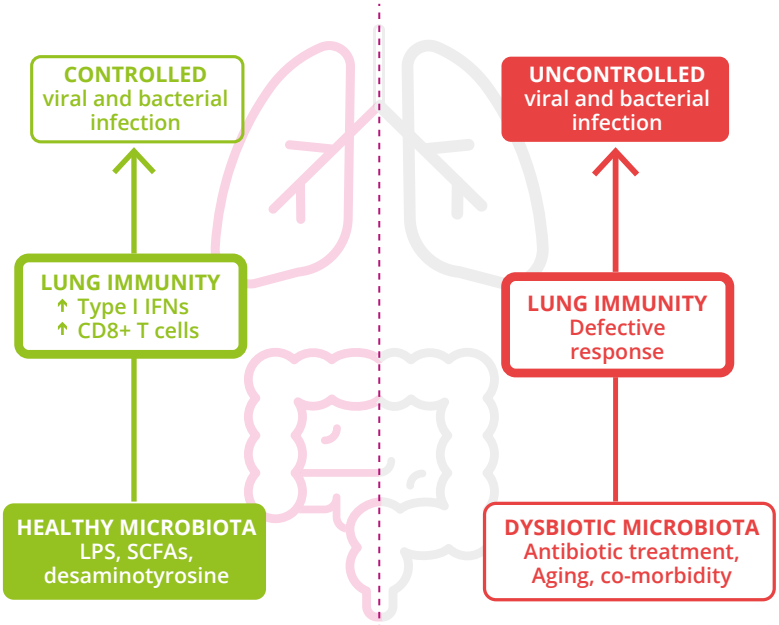
Gut microbiota influences RESPIRATORY IMMUNITY

The microbiota plays a key role in the development, education and function of the immune system, both locally and systemically. While the airway microbiota locally regulates immune function, the gut microbiota can also influence respiratory immunity, via the gut-lung axis.[1] Alteration of the lung and gut microbiota has been observed in many respiratory diseases, however whether the dysbiosis at these sites is a cause or a consequence of disease remains to be determined.[2] Alteration of gut microbiota composition, through either diet, antibiotic use, aging, or disease, is associated with altered immune responses and homeostasis in the airways,[3] highlighting that the gut microbiota can influence disease development throughout the body, including the risk of respiratory infections (Fig 6).[4]

The gut microbiota is involved in the lung's defense against viral respiratory infections

In comparison to the gut microbiota, studies on the lung microbiota are still in their infancy.[5] The lung was originally thought to be sterile but recently, researchers have discovered that the lung harbours its own microbiota, with a composition distinct from the gut microbiota.[6] Studies have shown that **gut microbiota may be involved in providing protection against viral respiratory infections** (such as influenza and respiratory syncytial virus),[2] *via* numerous mechanisms. For example, gut microbial metabolites such as SCFAs (obtained from dietary fiber fermentation by commensal bacteria) and desaminotyrosine (a degradation product of plant flavonoids produced by human gut bacteria[7]) influence the lung production of Type I interferon (IFNs) which elicit anti-viral protection.[8,9] Along with microbial metabolites, microbial components (such as LPS) help arm the lungs against viral respiratory infections **(Fig 6)**. The gut microbiota also plays a role in viral (influenza) clearance by stimulating CD8+ T-cell effector function.[10] **Any factors inducing gut microbiota dysbiosis (aging, antibiotics, diseases such as obesity, diabetes...) can also alter the normally beneficial gut-lung cross-talk, increasing susceptibility to respiratory** infections.[10]

FIGURE 6: The role of the gut microbiota in viral respiratory infections. Adapted from Sencio V *et al*, 2020[10]



LPS: lipopolysaccharide SCFAs: short chain fatty acids

« Any factors inducing microbiota dysbiosis can alter the beneficial gut-lung cross-talk, increasing susceptibility to respiratory infections.[10] »

1. Taylor SL, Wesselingh S, Rogers GB. Host-microbiome interactions in acute and chronic respiratory infections. *Cell Microbiol.* 2016 May;18(5):652-62. 2. Dumas A, Bernard L, Poquet Y, *et al.* The role of the lung microbiota and the gut-lung axis in respiratory infectious diseases. *Cell Microbiol.* 2018 Dec;20(12):e12966. 3. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol.* 2019 Jul;12(4):843-850. 4. Thibeault C, Suttorp N, Opitz B. The microbiota in pneumonia: From protection to predisposition. *Sci Transl Med.* 2021 Jan 13;13(576):eaba0501. 5. Huffnagle GB, Dickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. *Mucosal Immunol.* 2017 Mar;10(2):299-306. 6. Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol.* 2017 May;15(5):259-270. 7. Schoefer L, Mohan R, Schwiertz A, *et al.* Anaerobic degradation of flavonoids by Clostridium orbiscindens. *Appl Environ Microbiol.* 2003 Oct;69(10):5849-54.

Gut-lung axis in viral respiratory infections

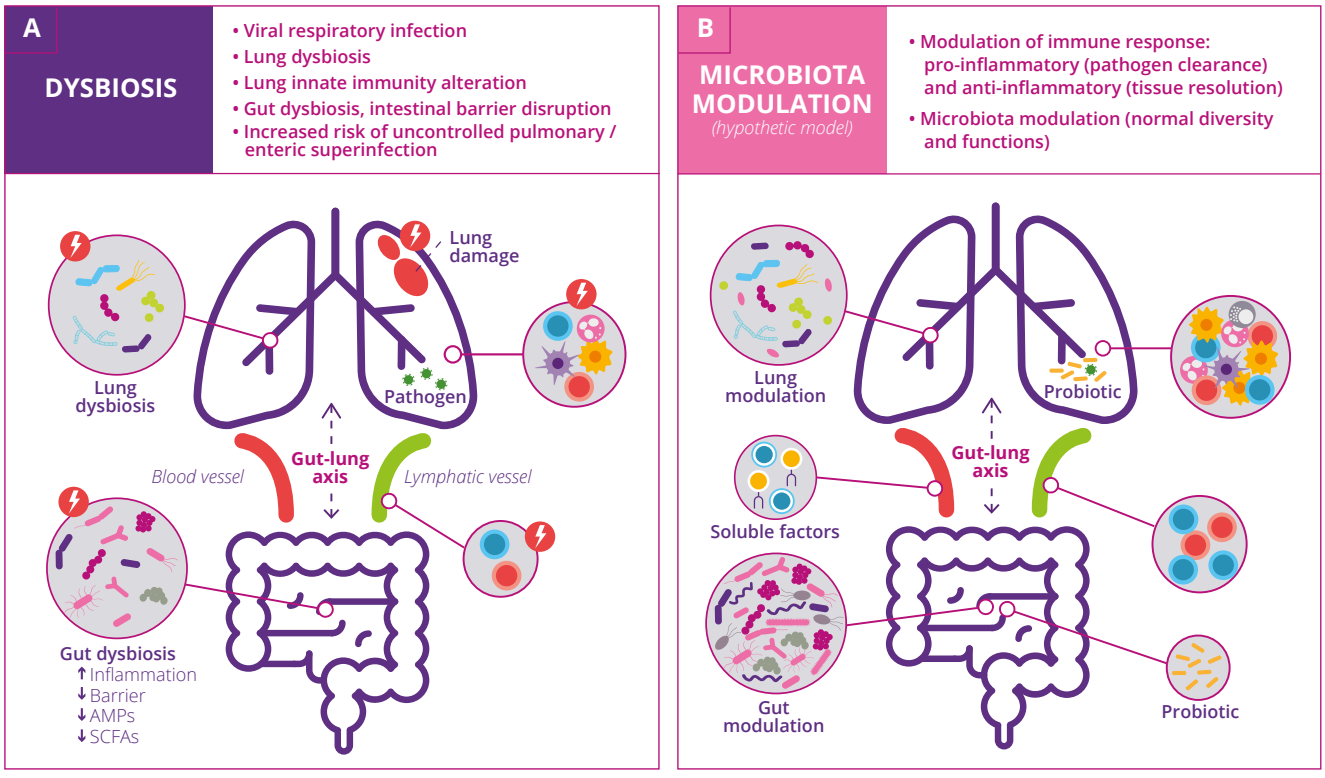
By Dr. Genelle Healey

Interestingly, microbiota at both tissue sites appear to be perturbed during respiratory infections, reinforcing the theory that **all mucosal sites are interconnected and that the gut-lung axis is bidirectional.**[1] Gut bacteria, their fragments, as well as SCFAs may translocate across the intestinal barrier and travel along the mesenteric lymphatic system to reach the systemic circulation and modulate immune cells in the lung.[11] During Influenza respiratory infections, lung microbiota and immune functions are altered, and a gut microbiota dysbiosis is also observed which may explain the commonly associated gastroenteritis-like symptoms **(Fig 7A)**.[10] There are likely several causes of this gut dysbiosis including loss of appetite (leading to reduced food and calorie intake), as well as inflammatory cytokine release. This may have local consequences: intestinal inflammation, disruption of gut barrier, decreased production of antimicrobial peptides (AMPs), a drop in SCFAs, potentially leading to secondary

GUT-LUNG AXIS KEY POINTS:

- **The lung is not sterile as previously thought**
- **Lung and gut dysbiosis are observed during viral respiratory infections**
- **Gut microbiota influences lung immune responses**
- **Alteration of gut microbiota composition (diet, diseases, antibiotics...) is associated with altered immune responses and homeostasis in the airways**
- **Gut microbiota targeted therapies such as probiotics may help reduce susceptibility to respiratory infections via the gut-lung axis**

FIGURE 7: Gut-lung axis during viral respiratory infection (A) and model of microbiota modulation using probiotics (B). Adapted from Dumas A *et al,* 2018[2]



Probiotics may be helpful to recover a healthy status (microbiota homeostasis, infection control, modulation of immune responses) via gut microbiota metabolites (SCFAs...) or host-derived products.

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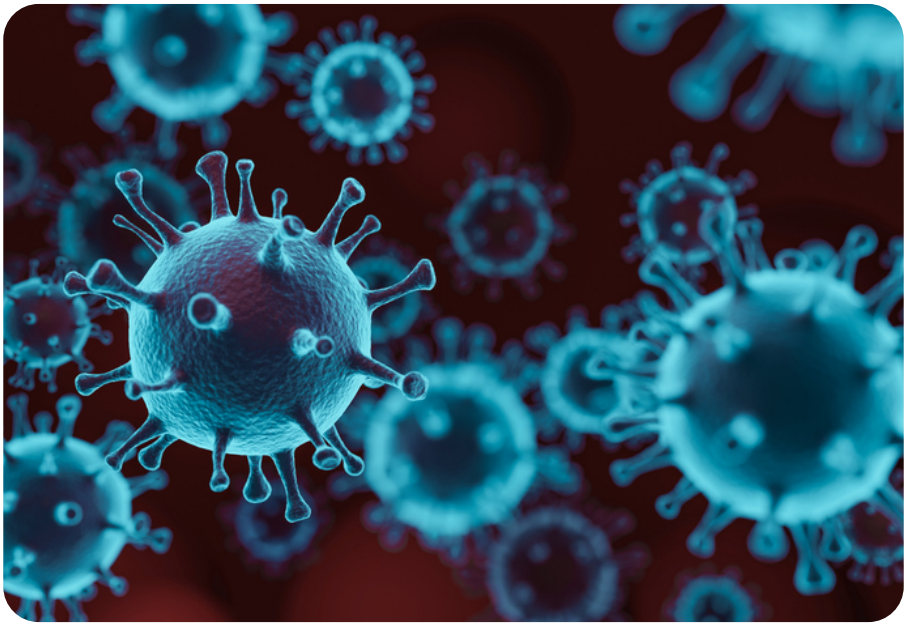
enteric infections.[10] Gut barrier alteration promotes bacterial translocation as well as endotoxin release into the blood, leading to systemic inflammation, lung damage aggravation and increased risk of secondary bacterial infections.[10] The reduced SCFA production by the gut microbiota also contributes to the reduced antibacterial immunity seen in the lungs.[10] This highlights the vital role that the gut microbiota plays in the lung's defenses against respiratory infections. Modulation of the gut microbiota using strategies such as probiotics may help reduce susceptibility to respiratory infections via the gut-lung axis, or they may be helpful in recovering from infection and reaching a healthy status **(Fig 7B)**. Several studies in mice have shown that specific probiotics administered prior to influenza infection led to the reduced accumulation of immune cells in the infected lungs. These probiotics also enhanced viral clearance, improved overall health and reduced alterations in the gut microbiota.[12,13]

The hygiene hypothesis and the COVID-19 pandemic

by Dr. Genelle Healey



«Vaccine-induced immune responses are highly variable between individuals and many factors have been suggested that may alter vaccine immunogenicity and efficacy. One factor known to control vaccine efficacy can be the gut microbiota.[20]»

COVID-19, a highly contagious respiratory disease caused by the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) primarily affects the respiratory tract but gastrointestinal symptoms (i.e. diarrhea, constipation, nausea) have also been reported in some patients.[14] Preliminary studies have found that the gut microbiota is altered in patients with COVID-19 and that its composition correlates with infection severity, suggesting crosstalk between the gut microbiota and lung in response to SARS-CoV-2 infection.[15] It should be noted **that the changes in lifestyle adopted to curb the COVID-19 pandemic could also have a negative impact on the gut microbiome of uninfected individuals.**[16] Over the last few decades, a significant reduction in microbial diversity and the overt extinction of ancestral microbes has occurred due to improvements in hygiene (e.g. hand washing and sanitizer), modern medications (e.g. antibiotics) and urban living.[17] These changes in hygiene, and a corresponding increased incidence of several autoimmune and allergic diseases,[18,19] have given rise to the hypothesis that they are causally linked (hygiene hypothesis). Notably, practices implemented to prevent the spread of COVID-19, such as physical distancing, frequent hand washing and sanitizer use, reduced travel and face mask wearing, will likely lead to further loss of key gut microbes.[16] Taken together, **the preventative health practices that have been implemented due to COVID-19 may exert collateral damage on the gut microbiome as well as long term health outcomes, particularly in children born just prior to or during the pandemic.**[16] Utilizing approaches known to enhance microbial diversity and support a healthy microbiota balance may prevent the negative health impacts associated with the enhanced hygiene practices implemented to prevent the spread of COVID-19.

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Targeting the gut microbiota to optimize vaccine efficacy?

by Dr. Genelle Healey

Since the COVID-19 pandemic started, the need for a robust and long-lasting immunity induced by vaccines has never been more apparent.[20] However, vaccine-induced immune responses are highly variable between individuals and many factors have been suggested that may alter vaccine immunogenicity and efficacy[21] **(Fig 8)**.

Therefore, gaining a better understanding of the factors driving variations in vaccine efficacy is critically important. **One factor known to control vaccine efficacy is the gut microbiota.**[21]

Interestingly, certain gut microbiota profiles (i.e. higher abundance of Actinobacteria, *Clostridium cluster* XI and Proteobacteria) are associated with greater vaccine responses against other viral infections such as HIV and rotavirus.[22-26]

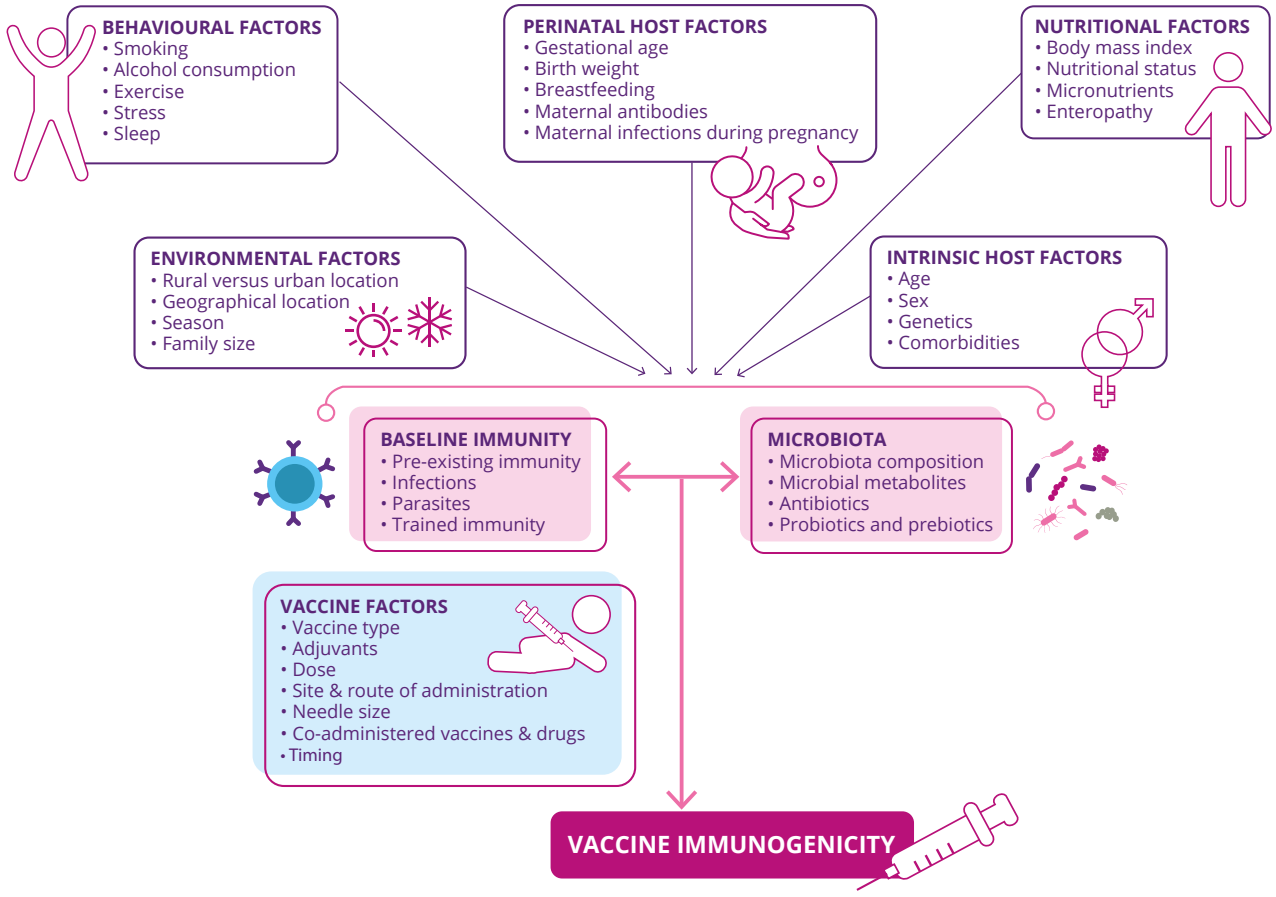
Additionally, a recent study reported that antibiotic-induced intestinal microbiota dysbiosis led to impaired vaccine responses against influenza, such as a reduced antibody-based neutralization of the virus, as well as lower concentrations of antibodies produced in responses to vaccination.[27]

This and other similar studies provide evidence of **the important role that the gut microbiota plays in vaccine efficacy.**[23,28]

To date no studies have investigated what impact the gut microbiota may have on SARS-CoV-2 vaccine efficacy, but it seems likely that individuals with gut microbiota dysbiosis may be at increased risk of developing relatively poor vaccine responses. Thus, future research which examines whether specific gut microbiota signatures affect SARS-CoV-2 vaccine efficacy will be critically important.

FIGURE 8: Factors suggested to alter vaccine immunogenicity and/or efficacy, including intrinsic host factors, behavioural, environmental, nutritional and perinatal factors.

Most of these factors have also been shown to influence the composition of the gut microbiota and baseline immunity. Vaccine immunogenicity is also dependent on vaccine intrinsic factors. Adapted for Lynn DJ *et al,* 2021[20]



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ROLE OF THE MICROBIOTA in skin immunity and atopic dermatitis

By Pr. Brigitte Dréno

WHAT IS ATOPIC DERMATITIS?

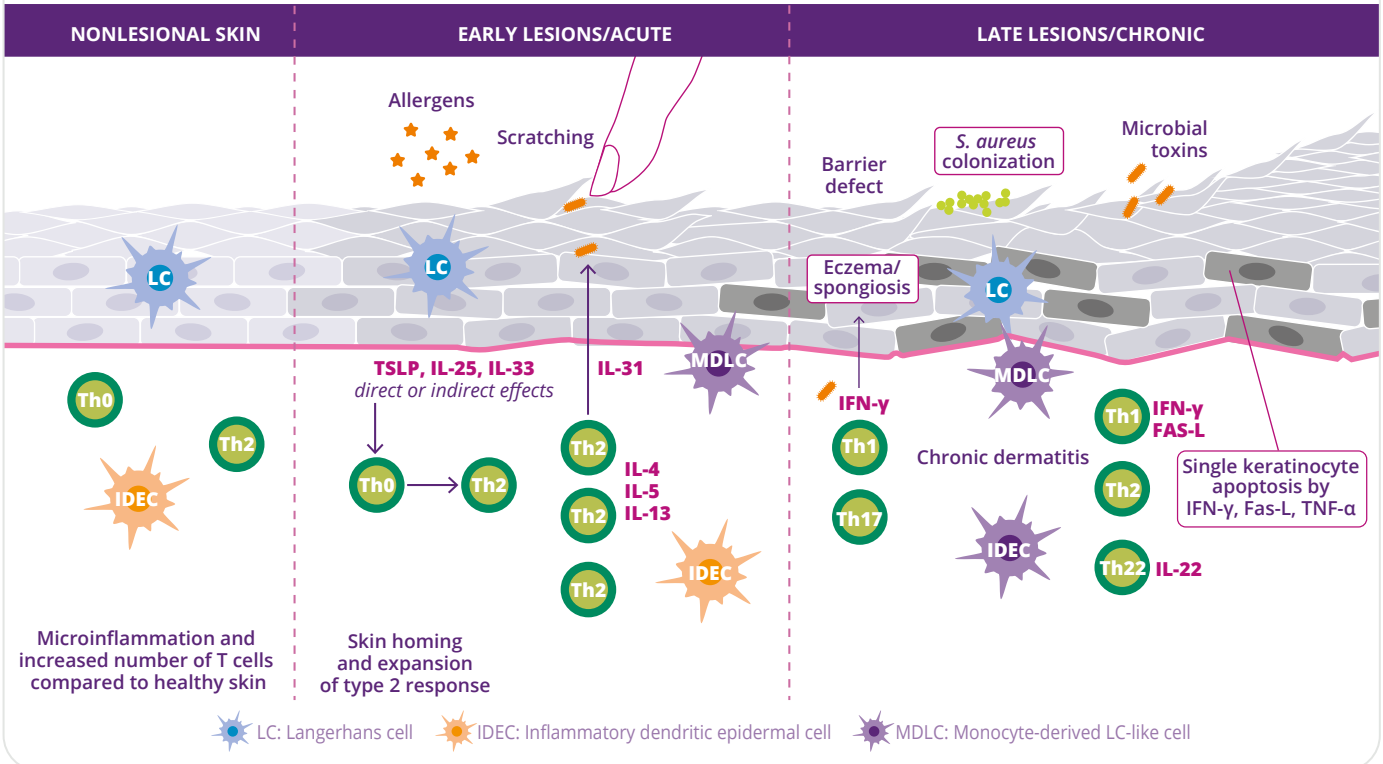
Atopic dermatitis (AD) is a chronic inflammatory skin disease that appears in periodic flare-ups. Like asthma, hay fever or allergic conjunctivitis, it is classified as an allergic disease. The disease causes very poorly defined oozing red lesions to appear in specific locations on the skin, such as in the folds of the elbow or behind the knees, but at times also on the face or the rest of the body. AD usually appears in early childhood, and may persist into adulthood. The causes are multifactorial and complex and include a genetic predisposition (mutation of the skin protein, filaggrin), an alteration of the skin barrier, a dysbiosis of the skin and gut microbiota, and immune dysregulation. AD affects 15%-20% of children and 10% of adults in "developed" countries. The number of cases has increased significantly in recent decades due to pollution and contact with allergens.[1]

WHAT FACTORS CAUSE FLARE-UPS?

Inflammatory outbreaks can be triggered by multiple factors, including stress, pollution, cold, humidity, certain allergens (pollen), certain medications, woolen clothing, and certain cosmetics containing plants or essential oils.

> *« The causes of atopic dermatitis are multifactorial and complex and include a genetic predisposition, an alteration of the skin barrier, a dysbiosis of the skin and gut microbiota, and immune dysregulation. »*

FIGURE 9: Pathogenesis, main mechanisms and pathophysiology of atopic dermatitis.
Adapted from Sugita K *et al*, 2020[4]



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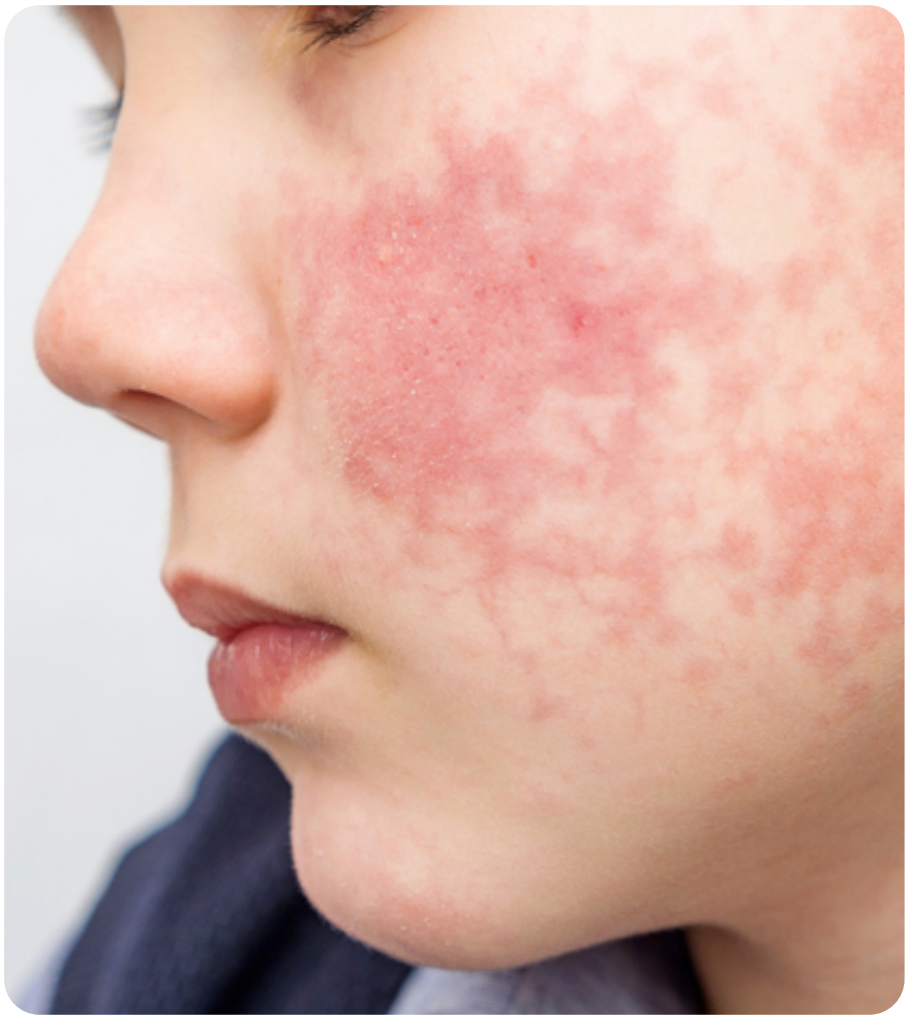

WHAT DO WE KNOW ABOUT THE LINKS BETWEEN ATOPIC DERMATITIS, THE MICROBIOTA AND IMMUNITY?

On a pathophysiological level, AD is characterized by an alteration of the skin barrier, a skin and gut dysbiosis, and immune dysregulation with the activation of Th2 lymphocytes. This immune dysregulation leads to a major cytokine surge, which in turn causes the inflammatory reactions.[2] An alteration of the skin barrier is the starting point for a dysbiosis of the skin microbiota characterized by a reduction in bacterial diversity and the proliferation of *Staphylococcus aureus*. Allergen penetration leads to the activation of keratinocytes and the production of interleukin (IL-33, IL-25, TSLP), resulting in the differentiation of Th2 lymphocytes. These in turn secrete pro-inflammatory cytokines (IL-4, IL-5 and IL-13) characteristic of Type 2 inflammation **(Fig 9)**. These cytokines directly activate the sensory nerves, provoking pruritus. With chronic lesions, the skin barrier repairs itself poorly and becomes thicker, since it is subject to chronic inflammation. There is also a progressive increase in cytokines and Th-cells (Th1, Th2, Th22) which secrete cytokines that contribute to the destruction of keratinocytes. Lastly, a gut dysbiosis may play a role in the disease's pathophysiological mechanism.[3]

> *« The immune dysregulation in atopic dermatits leads to a major cytokine surge, which in turn causes the inflammatory reactions.[2] »*

WHAT HAVE RECENT DISCOVERIES ABOUT THE MICROBIOTA TAUGHT YOU? HAS YOUR PRACTICE CHANGED?

Recent discoveries about the microbiota have led me to better understand the importance of maintaining and repairing the skin barrier to control inflammation. As a systemic treatment, I advise my patients to use a cleansing gel that preserves the skin's pH (pH ~5, avoid products with a basic pH), as well as a moisturizer and tailored cosmetic products. The findings also help us to better understand the skin's immunological system and how to respect the skin's microbiota.

WHAT ARE YOUR THOUGHTS ON THE USE OF PROBIOTICS TO TREAT AD OR PREVENT RELAPSE?

There are many ways to rebalance the skin microbiota in case of AD (probiotics, prebiotics, symbiotics, etc.)[5] but the postbiotic approach seems to me the most interesting. Postbiotics are preparations of inanimate microorganisms and/or their components that confers a health benefit on the host.[6] They can restore the skin barrier via an anti-inflammatory action that allows bacteria to recolonize, therefore having a long-term impact on the microbiota. Oral probiotics or prebiotics are another interesting approach to regulating the intestinal system, which itself plays a general immunomodulatory role in the immune system.[7]

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WHAT TO TAKE AWAY?

INTESTINAL

- The microbiota plays critical roles in the development and education of the host's innate and adaptive immune system components, while the immune system orchestrates the maintenance of key features of host-microbe symbiosis. **Maintaining homeostasis between the gut microbiota and the immune system is essential,** determinants interfering with neonatal gut establishment (antibiotics…) may potentially lead to negative health outcomes.[1]
- At least **80%** of the body Ig-producing cells are located in the gut.[2]
- **Mucus**: the intestinal mucus layer is at the crucial interface between host and gut microbiota. Its disruption leads increased penetration or passage of potentially harmful bacteria that can eventually cause inflammation and infection.[3]

RESPIRATORY

- The bidirectional communication axis between the gut and lungs, called **the "gut–lung axis" influences the immune status of both organs.** Lung and gut microbiota influence each other and may have an impact on respiratory diseases.[4]
- **1** factor known to control vaccine efficacy can be gut microbiota.[5]
- **Dysbiosis**: Lung and gut dysbiosis are observed during viral respiratory infections.[6] Common definition of dysbiosis describes it as a compositional and functional alteration in the microbiota that is driven by a set of environmental and host-related factors that perturb the microbial ecosystem.[7]

SKIN

- **Skin and gut dysbiosis, as well as immune dysregulation,** have been observed in the development of atopic dermatitis, a complex disease with multifactorial causes.[8]
- Atopic dermatitis is characterized by the activation of type **2** lymphocytes resulting in an overactive and exaggerated immune response.[9]
- **Inflammation**: atopic dermatitis is a chronic inflammatory skin disease that appears in periodic flare-ups.[9] The inflammation observed is the result of an immune dysregulation.[9]

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