Dysbacteriosis: Gut Microflora Imbalance and Hypersensitivities

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Background

Gastrointestinal Tract & Microflora

- The GI tract is comprised of the; Oral Cavity, Esophagus, Stomach, Duodenum, Jejunum, Ileum, Cecum, Colon, Rectum
- The GI tract houses the largest diversity and abundance of bacteria in the body, especially the large intestine
- Dominant bacterial groups; *Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Cyanobacteria, Fusobacteria* (1)

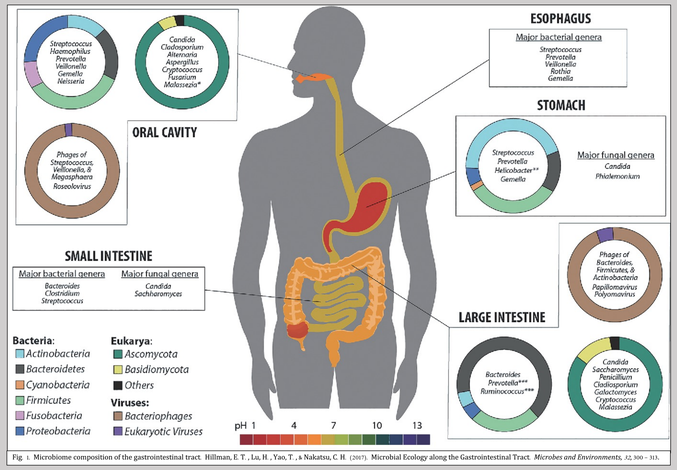

Fig. 1 Microbiome composition of the gastrointestinal tract. Hillman, E. T. , Lu, H. , Yao, T. , & Nakatsu, C. H. (2017). Microbial Ecology along the Gastrointestinal Tract. *Microbes and Environments*, *32*, 300 – 313.

Risk Factors of Gastrointestinal Dysbacteriosis

- Environment (rural vs. urban)(2)
- Antibiotic exposure(2)
- Method of delivery (vaginal vs. Caesarian section)(3)
- Breast feeding (present or absent)(3)
- Diet (high fat content)(2)

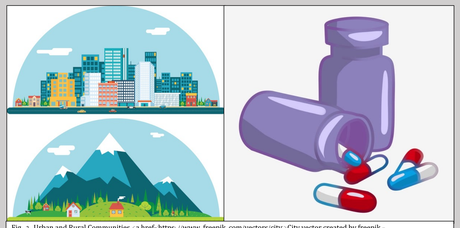

Fig. 2 Urban and Rural Communities City vector created by freepik - www. freepik. com Fig. 3. Antibiotics Chemical png from pngtree. com/

Dysbacteriosis Related Hypersensitivities

The most prevalent allergic diseases in children and adults include:

- Allergic Rhinitis (7.2%)* – inflammation of the nose occurring from immune system overreaction to airborne allergens
- Atopic Dermatitis (12.6%)* – chronic inflammation, redness, irritation of the skin
- Asthma (9.6%)* – inflammation and excess mucous production of the airways

*Percentage of children under the age of 18 in the United States of America (CDC 2018).

(1) : Hillman, E.T., Lu, H., Yao, T., & Nakatsu, C.H. (2017). Microbial Ecology along the Gastrointestinal Tract. *Microbes and Environments, 32*, 300 - 313.
(2) The Microbiota in Gastrointestinal Pathophysiology : Implications for Human Health, Prebiotics, Probiotics, and Dysbiosis, edited by Martin H. Floch, et al., Elsevier Science & Technology, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/ufvca/detail.action?docID=4745403.
(3) Kim, C. C., Parkar, S. G., & Gopal, P. K. (2020). Developing infant gut microflora and complementary nutrition. Journal of the Royal Society of New Zealand, 50(3), 384–396.
(4) CDC, Summary Health Statistics: National Health Interview Survey, 2018. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-2.pdf

Normal Immunological Tolerance

Effects of Intestinal Microbiota(5)

- Organize Peyer's patches, and intestinal epithelial cells
- Modulate type humoral Immunity
- Regulate basophil homeostasis
- Promote intestinal barrier health
- Induce regulatory tone of mucosal immune system

Immunological Tolerance Mechanisms

Intestinal Epithelial Cells

- Integrate microbial–associated molecular patterns (MAMPs) into either antimicrobial or immunoregulatory responses (5)
- Toll–like receptors (TLR), nucleotide binding oligomerization domain receptors (NOD– like receptors), leucine–rich repeat (LRR)–containing proteins, and RIG–I–like receptors are stimulated by MAMPs to promote homeostasis (6)
- Receptors induce intracellular signaling pathways, cytokine release, and chemokine release

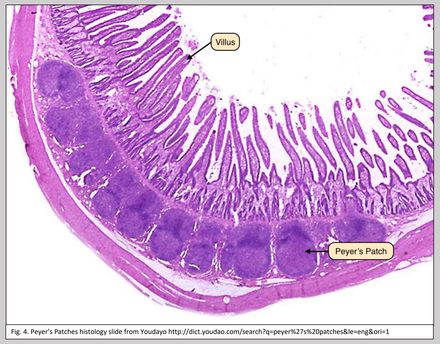

Fig. 4. Peyer's Patches histology slide from Youdayo http://dict.youdao.com/search?q=peyer%27s%20patches&le=eng&ori=1

Peyer's Patches (7)

- Isolated lymphoid follicles found in the small intestine
- Contain B–cells, T–cells, macrophages, phagocytes, dendritic cells, microfold (M) cells
- M cells transport antigens and proteins into Peyer's patches for immunocyte screening, initiating an inflammatory response
- Different forms of dendritic cells (DC) transport antigens to T–cells to convert them to regulatory T– cells (T_{reg})* to maintain anti–inflammatory responses through IL–10 secretion (immunological tolerance) (8)

*T_{reg}–cells regulate and suppress immune responses of other T–cells through the expression of the transcription factor Forkhead box P3 (FoxP3)

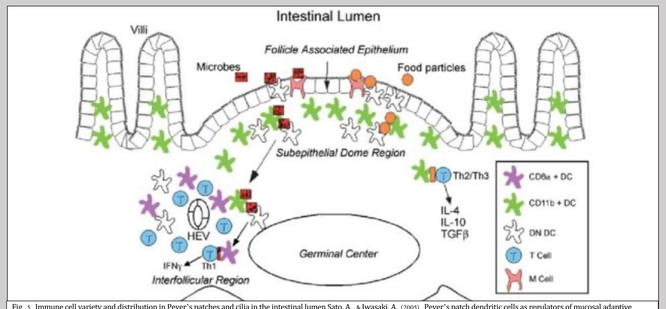

Fig. 5. Immune cell variety and distribution in Peyer's patches and cilia in the intestinal lumen Sato, A. , & Iwasaki, A. (2005). Peyer's patch dendritic cells as regulators of mucosal adaptive immunity. *Cellular and Molecular Life Sciences : CMLS*, *62*(12), 1333–1338. https: //doi-org. proxy. ufv. ca: 2443/10.1007/S00018-005-5037-Z

(5) The gut microbiome in food allergy Zhao, William et al. Annals of Allergy, Asthma & Immunology, Volume 122, Issue 3, 276 – 282
(6) Neutra, M. R., Mantis, N. J., & Kraehenbuhl, J.-P. (2001). Collaboration of epithelial cells with organized mucosal lymphoid tissues. *Nature Immunology*, *2*(11), 1004. https://doi-org.proxy.ufv.ca:2443/10.1038/ni1101-1004
(7) Jung, C., Hugot, J. P., & Barreau, F. (2010). Peyer's Patches: The Immune Sensors of the Intestine. International journal of inflammation, 2010, 823710. https://doi.org/10.4061/2010/823710
(8) Hilligan, K. L., & Ronchese, F. (2020). Antigen presentation by dendritic cells and their instruction of CD4+ T helper cell responses. *Cellular & molecular immunology*, *17*(6), 587–599. https://doi.org/10.1038/s41423-020-0465-0

Impaired Immunological Tolerance

Germ–Free Animal Models (9)(10)

Germ–free animal models raised in sterile environments are used in dysbacteriosis studies to mimic that of human dysbacteriosis and display:

- Smaller Peyer's patches
- Fewer plasma cells, and intraepithelial lymphocytes
- Impaired T–cell differentiation
- Elevated IgE* secretion
- Less functional antimicrobial peptides and IgA* secretions

*IgE trigger mast cells and basophils to release inflammatory chemicals
*IgA neutralizes and agglutinates antigens

Changes in Immunity Leading to Hypersensitivities

A loss or reduction of beneficial bacterial species effects the mucosal immune system in the following ways, all increasing the likelihood of developing hypersensitivity

- Decreased T_{reg} stimulation, a T–cell that that plays a role in maintaining immune tolerance, which reduces the risk of hyperresponsiveness (11)
- Decreases in segmented filamentous bacteria (SFBs) leads to T helper type 17 cells expression, resulting in proinflammatory responses (14)
- Reduction in *Lactobacillus* leads to increased IgE production/secretion (12)
- Tolerance, immune suppression, molecules TGF–β and Thymic Stromal lymphopoietin (TSLP) are depleted (13)
- Tolerogenic CD103+ dendritic cell functions are suppressed (14)

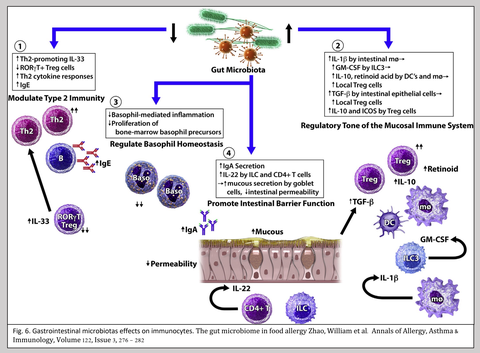

Fig. 6. Gastrointestinal microbiotas effects on immunocytes. The gut microbiome in food allergy Zhao, William et al. Annals of Allergy, Asthma & Immunology, Volume 122, Issue 3, 276 – 282

Treatment of Dysbacteriosis

Dysbacteriosis, especially during the first years of life, can have long–lasting effects on the immune system leading to conditions such as allergic diseases Treatment of dysbacteriosis has been shown to reduce this risk

- Administration of prebiotics and probiotics to replenish diversity and quantity of resident bacteria (1)
- Antibiotics to eliminate pathogenic bacterial species
- Fecal transplantation (15)
- Vaginal seeding following a Caesarean birth (16)

(9) Lee, Y. K., & Mazmanian, S. K. (2010). Has the microbiota played a critical role in the evolution of the adaptive immune system?. *Science (New York, N.Y.)*, *330*(6012), 1768–1773. https://doi.org/10.1126/science.1195568
(10) Hill, D. A., & Artis, D. (2010). Intestinal bacteria and the regulation of immune cell homeostasis. *Annual review of immunology*, *28*, 623–667. https://doi.org/10.1146/annurev-immunol-030409-101330
(11) Azza Abdel-Gadir, Amir H. Massoud, & Talal A. Chatila. (2018). Antigen-specific Treg cells in immunological tolerance: implications for allergic diseases [version 1; referees: 3 approved]. *F1000Research*, *7*, F1000 Faculty Rev-38. https://doi-org.proxy.ufv.ca:2443/10.12688/f1000research.12650.1
(12) Jakubczyk, D., & Górska, S. (2021). Impact of Probiotic Bacteria on Respiratory Allergy Disorders. *Frontiers in microbiology*, *12*, 688137. https://doi.org/10.3389/fmicb.2021.688137
(13) Gauvreau, G. M., Sehmi, R., Ambrose, C. S., & Griffiths, J. M. (2020). Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert opinion on therapeutic targets*, *24*(8), 777–792. https://doi.org/10.1080/14728222.2020.1783242
(14) Ness, S., Lin, S., & Gordon, J. R. (2021). Regulatory Dendritic Cells, T Cell Tolerance, and Dendritic Cell Therapy for Immunologic Disease. *Frontiers in Immunology*, *11*, N.PAG.
(15) Ademe, M. (2020). Benefits of fecal microbiota transplantation: A comprehensive review. Journal of Infection in Developing Countries, 14(10), 1074–1080. https://doi-org.proxy.ufv.ca:2443/10.3855/jidc.12780
(16) Hoang, D. M., Levy, E. I., & Vandenplas, Y. (2021). The impact of Caesarean section on the infant gut microbiome. *Acta Paediatrica*, *110*(1), 60–67.

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