MICROBIOME AND IMMUNE FUNCTION

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Symbiogenesis is the result of the permanent coexistence of various bionts to form the holobiont (namely, the host and its microbiota)

Ricardo Guerrero et al, Aug 2013

A NEW PERSPECTIVE: HUMAN IS MERELY A COLLECTION OF SYMBIONTS OR BIONTS WHO FORM A HOLOBIONT – A SUPER ORGANISM

“Symbiogenesis is the result of the permanent coexistence of various bionts to form the holobiont (namely, the host and its microbiota)”

Ricardo Guerrero et al, Aug 2013
• Human immune system begins to develop in the embryo.
• Starts with hematopoietic (from Greek, "blood-making") stem cells.
• Stem cells differentiate into major cells in the immune system
  • granulocytes, monocytes, and lymphocytes
• The only major system in the body designed to protect us
• Immune system is an army with no general – requires training.
• Takes at least 6 months for the immune system to start working on its own
• Stem cells continue to be produced and differentiate throughout ones lifetime.
INNATE IMMUNITY (our first line of cellular defense)

➢ **ANTIGEN PRESENTING CELLS** – Macrophages and Dendritic cells – find and present potential problems.

- These APCs are produced by the thymus and other lymphoid centers but are recruited to the gut mucosa by our commensal organisms.
- The microbiome helps these cells by expressing something called Toll-like receptors (TLRs) – These TLRs neutralize immune response to offer “tolerance”.
- The microbiome also goes as far as producing ATP (energy) to help these cells differentiate and function.

➢ **NEUTROPHILS** – Key part of first line of defense

- Killer cells that directly target harmful organisms. Very important to maintain infection free in the cold and flu season.
- Dependent on the microbiota to stimulate their expression and even to equip them with the tools to perform their killing function – nitric oxide, super oxides, etc.
INNATE VS. ADAPTIVE IMMUNITY

INNATE IMMUNITY (our first line of cellular defense)

- **NATURAL KILLER CELLS** – Highly important in viral infections. These cells identify infected tissue and eliminates it. With dysfunction in NK cells, an individual would face chronic, consistent infections.
  - The microbiota stimulates the production of NK cells.
  - The microbiota effects the potency of the cells as well.

- **MAST CELLS** – Highly important regulatory cells in the lamina propria.
  - They control blood flow and coagulation in the LP.
  - They control smooth muscle cell peristalsis.
  - Fight against gut permeability
  - Control electrolyte exchange
  - Poor microbiota and low diversity leads to fewer mast cells in the gut and more in circulation – one mode of action for increasing allergies.

- **INTESTINAL EPITHELIAL CELLS (IEC)** – The barrier cells that have some immune function
  - Releases key antimicrobials to protect the barrier
  - Releases chemokines and cytokines to recruit immune cells to the location
  - The microbiota stimulates the IEC to release these antimicrobials and chemical messengers.
ADAPTIVE IMMUNITY — The second line of defense and the long term protection

B-Cells: (antibody secreting cells)

- Gut associate B-cells primarily secret IgA – this is the antibody that is made in the highest concentration and we make about 7g of it each day!
- B-cells originate in the Peyers patches
- The amount of B-cells/Peyers patches and their potency is directly controlled by commensal bacteria.
- IgA, unlike IgM, has low “memory” and mostly recognizes current crop of commensals and invading organism. It requires constant stimulation and up-regulation to provide new IDs and protection.
- Low microbiota diversity, low microbial exposure, low antigenic species in our environment leads to low levels of IgA production and actually higher IgE production!
ADAPTIVE IMMUNITY – The second line of defense and the long term protection

T-Cells – (Our Immune Orchestrators)
CD4+ T cells are the T cells that can differentiate into Th1, Th2, Th17 or Treg cells.

HAVING BALANCE IN THESE 4 SUB-TYPES IS CRITICAL TO HEALTH

- Th1 protects against intracellular microbial infections
- Th2 protects against parasites
- Th17 is pro-inflammatory and acts in the heat of battle
- Uncontrolled Th expression causes disease: Too much Th1 and Th17 is linked to autoimmune conditions. Too much Th2 is linked to allergic and sensitivity reactions.
- Treg regulates the balance and favors tolerance. When Treg expressions are low, it leads to autoimmune conditions and severe allergies
- A weak microbiome leads to Th1/Th2 imbalance and typically leans towards Th2
- The microbiota is responsible for stimulation and maturation of Tregs, when the microbiota is weak we see increased colitis risk. We find a low level of colonic Treg cells and so T-cells in the colon attack the tissue and commensals.
Largest surface area in the body, about 400 sq meters – the skin is 2 sq meters
Largest portion of the immune system, most found in the gut
Lines areas of entry into the body – respiratory, digestive, reproductive, skin, etc.
Largest site of immune sampling
Covered with microbes
40 Trillion or more microbial cells

About 200 Million Immune cells

200,000 Times More Microbial Cells Than Immune Cells Available to Monitor the system
Small intestine
Gut lumen
Mucus layer
Intestinal epithelial layer
Mucosal healing
Enterocyte proliferation
Wound healing

Microbiome – Immune Crosstalk
MICROBIOME AND LYMPHOID ORGANS

The microbiome promotes the maturation of secondary lymphoid organs
• During **Norovirus Infection** – lactobacilli and other commensals trigger the release of IFN-beta and IFN-gamma, which alerts the innate immune system to the presence of the virus. (Vitamin A, provides substrate for commensal bacteria to make these interferons)

• During a **Rotavirus infection**, bacterial flagellin from commensal bacteria activates the expression of Pattern Recognition Receptors (PRR) – this triggers expression of TLR5 which then stimulates the release of IL-22 (helps repair the damaged epithelium) and IL-18 (induces apoptosis in infected epithelial cells)

• Bifidobacterium breve and GOS/FOS – have been shown to prevent **Rotavirus Infection** by increasing IFN-gamma, IL-4, TNF-alpha and TLR-2, which increases mucosal immune defense

• Commensal bacteria produce SCFAs which is required to increase and maintain mucus production, which creates a stronger barrier against pathogens. In addition, commensals also increase the synthesis of antiviral compounds like ROS and Defensins which prevent local viral replication

• During **Influenza Infection**, commensal bacteria trigger the release of inflammasome, which is a potent defense against influenza replication. These inflammasomes induce dendritic cell migration to the local lymph nodes to stimulate influenza specific T-cell response in the lungs – shuttling the response to the more potent and less damaging early adaptive response.
The gut microbiota regulates the respiratory mucosal immune response in respiratory *Influenza Infection* through stimulation of IgA secretion, Th1 activation and Cytotoxic T-Cell priming.

When *Influenza virus* is present in the lungs, gut commensal bacteria increase the presence of innate immune cells in the lungs by causing the release of cytokines like IL-33, IL-1 alpha, IL-1 beta, IL-12 and INF-gamma. This causes more NK cells, dendritic cells and macrophages to end up in the lungs.

When virus is low or not present, gut commensals do the opposite by stimulating the release of anti-inflammatory IL-10.

This balancing act is an example of the Gut-Lung Axis, where microbes in the lung communicate with microbes in the gut to inform on the presence of a pathogen.

*S. aureus* on airway surface recruits monocytes that mature to macrophages through activation of TLR2 during lung infection – this leads to a reducing in damage to lung tissue in acute infections.

Respiratory commensal bacteria *Corynebacterium* modulates TLR-3 antiviral response to Respiratory *Syncytial Virus Infection* (RSV) by enhancing the production of TNF-alpha, IL-6, IFN-gamma and IFN-beta through increasing T-cell proliferation.

Butyrate from commensal bacteria lower inflammatory damage post-early innate by activating GPR on cell surfaces and stimulation of IL-22

*Lactobacillus crispatus* (when dominant), decreased *HIV-1 infection* in South African women by inhibiting viral function.
B. subtilis produces Levan, an antimicrobial compound which inhibits various forms of adenovirus, including respiratory adenovirus (HSN1) and enteric adenovirus type 40 (DNA virus).

Study showed that B. subtilis and the surfactin it produces prevents invasion from a specific type of coronavirus, known as transmissible gastroenteritis virus.

B. subtilis produces a powerful antiviral compound called P18 that completely neutralizes influenza virus in vitro. Other studies have demonstrated this strains in vivo antiviral effects.

B. subtilis produces antimicrobial lipopeptides, which effectively inactivate viruses such as Containing surfactin and fengycin (showing strong antiviral effect), Porphine Parvovirus (PPV), Porcine Pseudorabies Virus (PRV), Newcastle Disease Virus (NDV) and Infectious Bursal Disease Virus (IBDV) in vitro.
Collectively, these data indicate that commensal-derived signals provide tonic immune stimulation that establishes the activation threshold of the innate immune system required for optimal antiviral immunity.
DISRUPTION TO IMMUNE RESPONSE DUE TO DYSBIOSIS

**Science News**

**Antibiotics found to weaken body’s ability to fight off disease**

**Date:** August 17, 2017

**Source:** University of Virginia Health System

**Summary:** Adding another reason for doctors to avoid the overuse of antibiotics, new research shows that a reduction in the variety of microbes in the gut interferes with the immune system's ability to fight off disease.

**Abstract:**

Antibiotics can weaken flu defenses in the lung, leading to significantly worse infections and symptoms, finds a new study. The research discovered that signals from gut bacteria help to maintain a first line of defense in the wiring of the lung. When mice with healthy gut bacteria were infected with the flu, around 80% of them survived. However, only a third survived if they were given antibiotics before being infected.

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**Related Topics:**

- Health & Medicine
- Immune System
- Infectious Diseases
- Gastrointestinal Problems

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**Collateral Damage: Detrimental Effect of Antibiotics on the Development of Protective Immune Memory**

Joseph M. Danes, Carrie L. Lands, and Jennifer A. McCleary

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**ABSTRACT:**

Antibiotic treatment is an effective treatment strategy for many bacterial infections and lifelong bacterial antigens and commensal bacteria that can induce an inflammatory response. Despite the opportunity for bacterial killing to enhance the development of adaptive immunity, patients treated successfully with antibiotics can suffer from maladaptation. Studies in mice modelled S. aureus and Group A Streptococcus also demonstrate that early antibiotic intervention reduces host protective immunity to subsequent infections. This heightened susceptibility to rechallenge correlates with poor development of Th1 and antibody responses in antibiotic-treated mice but can be overcome by delayed antibiotic interventions, thus suggesting a requirement for sustained T cell memory for protection. Although the contribution of memory T cell subsets is imperfectly understood in both of these infection models, a protective role for non-naïve T cell subsets is supported by recent studies. Together, these data propose a model where antibiotic treatments specially attenuate naïve but elicit memory T cell responses. Greater understanding of the mechanistic basis of this phenomenon might suggest therapeutic interventions to reinvigorate protective memory responses in antibiotic-treated patients, thus reducing the incidence of reinfection.

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**Editors’ Choice**

**FOCUS AREA:**

**Antibiotics bug the immune response**

Sarah E. Flaxman

**Abstract:**

Changes in the gut microbiome caused by antibiotics can impair immune responses to influenza vaccination.

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**Annual address:**

Many facets of the immune system have been shown to be affected by the bacteria that live on us and within us. However, the mechanisms of these effects remain unclear, especially in human immunology. Prior investigations highlighted the potential impact of commensal microorganisms on vaccine responses but have left many questions. Hagan et al. recruited a cohort of healthy adults (n = 220) and vaccinated for influenza (on day 0). Half of the participants were pretreated...
"The gut microbiota plays a critical role in the anti-tumor immune response. There is increasing data showing that antibiotics (ATBs) change the composition of the gut microbiota and affect the efficacy of immune checkpoint inhibitors (ICIs)."

"Therefore, the findings of our meta-analysis indicated that ATB use is negatively associated with OS and PFS in cancer patients treated with ICI immunotherapy."
LANGUAGE USED BY THE MICROBIOME TO COMMUNICATE WITH THE IMMUNE SYSTEM

- IFN-Beta
- IFN-Gamma
- IL-1 alpha
- IL-1 beta
- IL-12
- INF-gamma
- TNF-alpha
- IL-6
CHRONIC DISEASES
Leading Causes of Death, Disability, and Health Care Costs

- Heart Disease
- Cancer
- Chronic Lung Diseases
- Stroke
- Alzheimer's Disease
- Type 2 Diabetes

1 in 2 Adults in the US has a chronic disease & 1 in 4 Adults in the US has two or more chronic diseases.

DIABETES
CANCER
CARDIOVASCULAR
PANCREATITIS
AUTOIMMUNE DISEASES
IBD
ARTHRITIS
RENAL DISEASE

- IFN-Beta
- IFN-Gamma
- IL-1 alpha
- IL-1 beta
- IL-12
- INF-gamma
- TNF-alpha
- IL-6
- Segmented Filamentous Bacteria – Increases Inflammatory Damage of tissues and can drive autoimmune development.
- HSV and CMV – Infects T-Cell, monocytes/macrophages
- EBV – Infects B cells
- Free LPS can be used by viral pathogens to gain entry into cells
- Chronic Inflammation can drown out immune signals
**INVADING PATHOGEN**

**DISRUPTION TO THE ECOSYSTEM**

**MICROBIOME**

**CYTOKINES AND INTERLEUKINS – IL-1, IL-6, INF, TNF, etc.**

**IMMUNE SYSTEM**

**CHRONIC LOW-GRADE INFLAMMATION**

**CYTOKINES AND INTERLEUKINS – IL-1, IL-6, INF, TNF, etc.**

**MICROBIOME**

**CYTOKINES AND INTERLEUKINS – IL-1, IL-6, INF, TNF, etc.**

**INVADING PATHOGEN**

**LOST**
Pre-existing medical conditions and COVID-19

COVID-19 death rate by pre-existing medical condition

- Cardiovascular disease: 10.5%
- Diabetes: 7.3%
- Chronic respiratory disease: 6.3%
- Hypertension: 6.0%
- Cancer: 5.6%
- No pre-existing conditions: 0.9%
CONCLUSIONS

• A healthy, diverse microbiome provides critical signaling and energetics to the immune system to elicit proper immune function
• Higher pathogen load disrupts immune response
• A disrupted microbiome leads to improper and attenuated immune response against pathogens
• A disrupted microbiome is also the most prevalent source of chronic low-grade inflammation through endotoxemia and barrier dysfunctions
• Immune support ingredients, as important as they are (vitamin C, D, zinc, etc.) cannot overcome a dysfunctional microbiome and so must be used in conjunction with microbiome modulation
• The success of preventative measures like vaccines will depend on one's immune capabilities
• Simple measures can make a big difference:
  • Diversify diet
  • Lower stress
  • Get outdoors
  • Use a spore-based, researched probiotic
  • Focus on leaky gut solutions
  • Bring down inflammation
  • Prebiotics (oligosaccharides) have a major impact on immune function
  • Polyphenols and Omega fatty acids can be powerful support tools