The Microbiome and Immune System in Environmental Risk of Infectious Disease

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Appreciation

• To the workshop organizers for my inclusion in the program
• To my editor and wife, Janice Dietert
Disclosures

Recent and Current Positions Held and Financial Support:

• Professor of Immunotoxicology at Cornell University
  (Now Professor Emeritus)
• Consultant – in Education and Translational Research for Seed (a 2018 start-up company)
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Disappearing Dogmas of the 20\textsuperscript{th} Century

1. The newborn is fully prepared immunologically to fight all diseases.
   - (The newborn must postnatally co-mature with the microbiome to be immunologically balanced and prepared to fight diseases).

2. Species barriers are chromosomally gene driven.
   - (Immune-microbiome incompatibility can also determine species barriers)

3. Most microbes are a threat to human health.
   - (Some microbes are required for human health.)

4. The human mammal is the target of environmental health risk assessments (e.g., toxicological safety).
   - (The human superorganism is the most relevant target for assessment/evaluation/safety determinations).
The Complete Human: Three Domains of Life

Domains of Life
- Eukaryota
  - Mammalian
  - Microbial
    - Eukaryotes
- Bacteria
- Archaea

Genomes
- First
  - ~25,000 genes
- Second
  - ~10 million genes
  ~ 3.3 million microbial genes in an individual

Superorganism
- Majority-Microbial Humans
  (based on cell and gene numbers)

Approximately 57%-90% microbial by cell number

Adapted from:
Dietert and Dietert Healthcare
3(1), 100-129; 2015.
Routes of Exposure, Portals of Entry, and Microbiome Sites Converge

Main Toxicological Routes of Exposure

Dermal  Oral  Inhalation

Skin Break  Urogenital

Infectious Agents - Major Portals of Entry

Major Body Sites for the Microbiome

Nasal  Oral  Skin  Gastro-intestinal  Urogenital

See: Damalas and Kourtoubas, Toxics 2016, 4(1), 1; doi:10.3390/toxics4010001;
Hologenomic Speciation Determined by the Microbiome and Immune System

Nasonia sp. wasp

House Mouse in Europe

(note: generalized wasp depicted)

Flintoft, L. Nature Reviews Genetics 2013; 14: 598 (Photo: Bordenstein Lab)
Wang et al. Nature Comm 2015; 6, Article number: 6440 doi:10.1038/ncomms7440
Postnatal Immune Maturation
(Note: 1,000 day concept on postnatal developmental windows)

- Environmental exposures and adaptations are required for full immune maturation (the newborn does not equal adult immunologically). The prenatal environment has a Th2 preferential bias.
- Gut microbes at mucosal surfaces drive the newborn’s stereotypic immune development. Microbial dysbiosis impairs immune maturation.
- Some aspects of inflammation must be ramped down and others made more selective as per innate immune responses. Macrophage polarization and regulation must be altered to better protect the infant from infections (e.g., via cell signaling factors - IRF5).
- Peripheral T cell helper and regulatory populations must change for balanced responses
- B cell, Natural killer cell, and dendritic cell maturation is affected during first 3 months of life
- Specialized innate immune populations (e.g., microglia, invariant NKT cells) must mature, expand, contract in tissues to provide immune homeostasis

Examples of Neonatal “Critical Windows”
Involving the microbiome and immune system


• Neonatal timed influx of FoxP3+ T regulatory cells (Tregs) into the skin (determines tolerance to skin commensals) (Scharschmidt et al. Immunity 43, 1011–1021, 2015)
A Systems Biology Unit: the Microimmunosome

Barrier integrity and bi-directional communication leading to immune homeostasis is critical.

2/3rds of your immune cells are in the gut near the gut barrier.

Adapted from Dietert, Reprod. Toxicol. 2017
Responses of the Microbiota to Environmental Exposures

Environmental pollutants (e.g., metals, organics)

Diet

Drugs

1. Sequestration
2. Avoidance/Exclusion
3. Metabolism
4. Specific Signaling
5. Selective Microbe Death
6. Selective Microbe Expansion
7. Translocation

Gut Microbiota and Xenobiotics

- Increase or decrease drug available for absorption
- Directly metabolize drug
- Inhibit detoxification
- Biotransform common food components, drugs, and xenobiotics
- Generate aryl-hydrocarbon receptor agonists
- Convert a pro-drug into an active drug
- Respond to one drug/xenobiotic by inactivating host enzymes for an unrelated drug
- Regulate host metabolism

From: Klaassen and Cui, Drug Metab Disp. 2015; 43(10): 1505-1521
Microbiome Destruction – What happens next?

- Elective Cesarean delivery
- Prophylactic use of antibiotics for growth promotion in food-producing animals
- Howler monkeys

Altered infant cytokine production → More hospital-associated microbes seeding the neonatal gut → Increased antimicrobial resistance and zoonotic risk from pathogens (e.g., *Campylobacter* spp., *Salmonella* spp., *Escherichia coli* and *Staphylococcus aureus*)

Captivity (Food and lifestyle restricted) → Reduced microbiota diversity → Humanized microbiome - from animal handlers

Elevated risk for several diseases associated with the mucosal immune system → More hospital-associated microbes seeding the neonatal gut → Increased antimicrobial resistance and zoonotic risk from pathogens (e.g., *Campylobacter* spp., *Salmonella* spp., *Escherichia coli* and *Staphylococcus aureus*)

Current Biomarkers Model for Health Risk Assessment (1987)

From:
National Research Council,
Environ Health Perspect,
74: 3-9, 1987
The Microbiome Filters Virtually All Exposures and Directly Participates in Epigenetic Alterations

Proposed New Environmental Health Assessment Model

Adapted from: Dietert and Silbergeld, Toxicol. Sci. 2015 Apr;144(2):208-16.
Colonization Resistance

**General factors:** competitive exclusion (Gauses’ Law in ecology, Nurmi Concept), host gut motility, mucus layer regulation, epithelial barrier integrity

**Specific processes:** Inter-bacterial interactions

- Nutrient limitation (e.g., need to block simple sugar availability for pathogens)
  - Including blocking inflammation-associated nutrient shifts (e.g., nitric oxide)
- Bile salts metabolism (secondary bile salt inhibition of pathogens)
- Short chain fatty acid (SCFAs) production (note: loss of butyrate production triggers increased oxygen and nitrate release in the lumen)
- Bacteriocin production
- Cell-cell contact-dependent inhibition
  - Type VI secretion systems (e.g., *B. fragilis* blocks enterotoxigenic *B. fragilis*)
  - LgX proteins

Importance of Commensal Microbes to Block Pathogens

Information adapted from: Keith and Pamer, J. Exp Med.DOI: 10.1084/jem.20180399 Published October 11, 2018
Pathogens: Minimum Microbiota Necessary for Effective Competitive Resistance

• Metagenomic tools were used to construct a minimum consortium of gut microbiota that would protect mice from infection with the human enteric pathogen *Salmonella enterica serovar* Typhimurium (S. Tm).

• An installed combination of 15 specific gut bacterial strains were equivalent to a complete microbiome in effective colonization resistance.

Utility of Biomarkers
From Altered Microbiota to Disease

Altered Gut Microbiota

- Loss of Colonization Resistance
- Barrier Function
- Physiological System/Immune Dysbiosis

Clinical Disease

- Infectious Disease
- Non-communicable Disease

(Is it useful to Flip this information?)
Arsenic Presystemic Metabolism via the Microbiome

• Sulfate-reducing colon microbiota can thiolate methylated arsenic producing highly toxic metabolites.

• There is individual human variation in the presence of these bacteria potentially affecting individual risk.

• Arsenic exposure can also change gut microbiome composition and microbial genes.

• Arsenic exposure is associated with increased risk of certain human infections (e.g., hep B). - NHANES

• Infections can change both microbiome composition and arsenic metabolism (mouse study).

• Components of the gut microbiome can protect the immune system from arsenic toxicity (mouse study)

Arsenic “Ages” the Immune System

1. Prenatal and early childhood arsenic exposure is inversely associated with telomere length and signal joint T-cell receptor excision circle (sjTREC) at 9 years of age. Fewer naive T cells with aging.
   

2. Low to moderate levels of arsenic disrupt T cell development. Both genotoxic (oxidation) and non-genotoxic (IL-7 signaling are involved) processes are involved. The earliest T cells are the least capable of pumping out arsenic and are at the greatest risk. - Xu et al. Toxicity of environmentally-relevant concentrations of arsenic on developing T lymphocyte. Environ Toxicol Pharmacol. 2018 Sep;62:107-113.
Case Scenario for Cumulative Environmental Health Risks
Childhood Incompleteness of the Microbiome

Bereavement
- Maternal stress
  - PAHs, others
  - Environmental tobacco smoke
  - Air pollution/urbanization

Cesarean delivery
- Antibiotics administered
  - F1 immune programming
  - Reduced Tregs
  - Elevated risk of allergy, autoimmunity, obesity, CVD

Formula feeding
- Reduced microbial seeding
  - Missing prebiotics and microbes
  - Altered metabolites & immune development

BPA, heavy metals, certain food additives
- Depleted microbiome
  - Reduced colonization resistance; increased risk of infection

Adapted from: Dietert, R. NeoReviews 2018 19(2):e78-e88.
Summary

• The microbiome is the lens through which we see our external environment (chemicals and pathogens). It is also our first line of defense from external threats and it is malleable.

• The microbiome and immune system must be sufficiently matched and must co-mature together to ensure host integrity and effective immune function (e.g., self tolerance and host defense against infectious diseases). The immune system, absent a “healthy” microbiome, is a disease inflictor rather than a protector.

• Optimizing colonization resistance is a key to improved health protection even as we work to reduce external health threats (chemical and microbiological).

• Managing the microbiome-immune interface should be a significant part of future preventative and therapeutic health.