Immunology in the Animal: Microbial Interaction, Stress and Nutrition

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Credits

- Kuby Immunology
- Immunobiology, 9th edition
- Bruns et al, 2010 PLoS Pathog
- David Topham, University of Rochester
- Mike Kogut, ARS
- Lance Baumgard, Iowa State
Topics

- Three Levels of Immune Protection
- Mucosa-Barrier- New Frontier, Good
- Innate Immunity-Good, Bad, Ugly
- Acquired Immunity-Good, Bad
What is gut health?

“I Know It When I See It”

Supreme Court Justice Stewart Potter
to describe his threshold test for
Obscenity in *Jacobellis v. Ohio* (1964)

*Gut Health Symposium Dec. 3-5, 2012*
The "Gut"

- The largest interface between the external environment & the internal host milieu

- Constitutes the major barrier through which molecules can either be absorbed or secreted

- Largest residence of immune cells in body; acts as a physical & immune barrier to pathogens

- Natural habitat for a large & dynamic community of microbes that participate & regulate gut & systemic functions
Components of a Healthy GI System

1. Effective digestion/food absorption
2. Stable microbial population
3. Effective immune status
4. Effective gut barrier
5. Effective neuroendocrine system
Think of the body as a hollow plastic tube…

The food is digested within the hole in the tube, but it never actually enters into the solid plastic material.
Immune responses

1\(^{st}\) Line of Defense
- **Barriers**
  - mucous, tears, gastric pH, saliva, skin

2\(^{nd}\) Line of Defense
- **Cellular and humoral defenses**
  - interferon, cytokines (pro-inflammatory and T stimulatory), complement proteins, phagocytosis, NK cells

3\(^{rd}\) Line of Defense
- **Cellular and humoral defenses**
  - Antibodies, cytokines, T helper cells, cytotoxic T cells

From David J. Topham, Introduction to Viral Immunology: Part I
Stressors at the Farm

- Co-mingling
- Injury
- Water - palability and supply
- Feed - time to first
- Pen density
- Pen total number
- Heat Stress
- Handling and movements
- Fear and Flight
- New “add-ons”
- Weather extremes
- Dust
- COMPETITION
- Vaccination
Mucosal Immune Responses

• 1\textsuperscript{st} Line of Defense
  • Barriers
    Skin & Mucous membranes and secretions
    Barrier, rapidly regenerating surfaces, peristaltic movement, lysozyme, sebaceous/mucous secretions, stomach acid, commensal organisms

• 2\textsuperscript{nd} Line of Defense
  Humoral and Cellular Defenses
  Cellular, cytokine and protein defenses
  Interferons, defensins, chemokines, cytokines (pro-inflammatory and T stimulatory), complement proteins, TLRs, phagocytosis, NK cells

• 3\textsuperscript{rd} Line of Defense
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  Cellular and humoral defenses
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Epithelial Cells and First Line of Defense

Decrease water intake - dehydration barrier
Epithelium and Kill Zone
Epithelial Cells

- Location
  - GI tract
  - Respiratory tract
  - Reproductive tract
  - Skin
Epithelium and Immune Function
Microbiota (Microflora)

- The collection of organisms found in and on our body- very location specific and individual specific (genetic component)

- Gastrointestinal microbiota is the most diverse and has the largest interaction both with mucosa and ingesta- “superorganism”
Commensal Organisms

- $10^{14}$ organisms—eukarya, archae and bacteria
- $10^{12}$ commensal bacteria/ml - 10X higher than the combined somatic and stem cells in man

- Commensals are essential for immune development
- Composition of commensal bacteria influenced by the host immune status
Microbiota and Immune Development

Commensal Bacteria

The gut microbiome and its potential role in the development and function of newborn calf gastrointestinal tract
Commensals Mucosal Barrier and Immunity

Microbes and Regulating Innate Immunity

Commensals Mucosal Barrier and Immunity

Anti-inflammatory response is key for healthy mucosa

Adapted from Cell 156, Issues 1–2, 2014, Pages 7
Stress and Dysbiosis

Commensals and their Induced Immune Changes

Khosravi and Mazmanian, Current Opinion in Microbiology 2013, 16:221–227
Microflora, Diet and Stress

- Nutrition isn’t just feeding the “animal” it is also feeding the “microbes”
- Production of vitamins
- More efficient bacteria- increase opportunity for obesity
• **Innate Immunity - 2nd Line of Defense**

• the troops are called to battle...
  - injury & infection
  - macrophages are on patrol
  - cytokine chemicals attract other “troops”
  - Absolutely essential for vaccine responses
Inflammatory Response
Neuro-Immune Interaction

Epithelial Cells- Immunomodulation

- Pro-inflammatory cytokines-
- Epithelial Cell Enemy# 1
  - Tumor necrosis factor-alpha
Leaky Gut

- Leaky gut explains the negative consequences of heat stress and off-feed events (all farm animals)
Leaky Gut Mucosa

Inflammatory Response

First Immune Organ

Systemic response
Neutrophils-Blowing Up-Collateral Damage

Tissue Damage - Overactive Immune System
Overactive Inflammatory Response
Heat Stress and Gut Health

- Diversion of blood flow to skin and extremities
- Coordinated vasoconstriction in intestinal tissues
  - Reduced nutrient and oxygen delivery to enterocytes
  - Hypoxia increases reactive oxygen species (ROS)
- Reduced nutrient uptake increases intestinal osmolarity
Cytokine Storm

Cytokine Storm

- High Temps- 104°-106°F
- Respiratory Disease-
  - Acute Lung Injury
  - Acute Respiratory Disease Syndrome
- Is BRSV???
- Is Vaccination or Aspirin the Answer?
Acute Respiratory Disease Syndrome

Acute

Chronic

Brain-Gut-Microbiota axis
Inflammation and Obesity- Overconditioned Weaned Calves, Fat Cattle, Transition Cow

Documented Causes of Increased Intestinal Permeability ("leaky gut")

- Transition Period
- Heat Stress
- Large Intestine Acidosis
- Distant Inflammation
- Weaning
- Large Intestine PTN Fermentation
- Small Intestine Bacteria Overgrowth
- Feed Restriction
- Psychological Stress

Baumgard L, International Symposium on Dairy Cattle Nutrition, Wageningen NL October 26, 2017
Inflammation and Production

- Proinflammatory Cytokines
  - Tumor Necrosis Factor-α (TNF-α)
  - Interleukin 1-β (IL-β)
  - Interleukin 6 (IL-6)

- Proinflammatory Cytokines- Turn on Acute Phase Proteins
Inflammation and Effect on Production Parameters

- Increase Sickness Behavior-listlessness
- Decrease feed intake- Inappetence-
- Increase body temperature sweats
- Decreased feed conversion
- Decrease gain
- Decrease milk production
- Increased Mastitis
- Increased Metritis
- Increased BRD
Consequences of Leaky Gut and LPS

Overactive Inflammatory Response

Tissue Damage
Proinflammatory Summary

• Innate Pro-inflammatory response
  • Cell Recruitment
  • Neutrophil Migration
  • Acute Inflammation
  • Humoral Immunity IgG
  • Cell mediate immunity-Memory
Anti-inflammatory Summary

- Innate Anti-inflammatory response
  - Maintains gut homeostasis
  - Humoral immunity-IgA
  - Cell Mediated Regulatory T cells- Helps to Control Acute Inflammation-
Innate Immunity Interventions

- **NSAIDS**
  - Aspirin-
  - Meloxicam

- **Cytokine**
  - Imrestor (pegbovigrastim injection)- Granulocyte Colony Stimulating Factor (PEG bG-CSF)- Elanco- Off the Market

- **Immunomodulators**
  - Immunoboost- MCWF Amplimune Bioniche- Nova Vive
  - Zelnate- Liposome-DNA- CpG-Bayer-

- **Gut Health- Nutriceuticals**
  - Prebiotics
  - Probiotics
Mucosal Vaccine Responses

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Where Does The Intranasal Vaccine Response Occur?

Danger and Activation of the Acquired Immune System

3rd Line of Defense
“mucosal immune system”
Take Home: A Healthy Gut is a Necessity—What About Nutriceuticals?

- Essential Oils, Organic Acids, Bioactives (Plasma Proteins, colostrum), Bacterial cultures, yeast, cell wall products, metabolites

- Problem: how do we measure it

- Do we need them all the time? Depends- times of stress
Summary

- Immune System is the Body’s Defense System - 3 lines of defense
  - Mucosa-Barrier - New Frontier,
    - Good - Antimicrobial proteins, IgA, cytokines
    - Bad - inflammatory cells - leaky gut
  - Innate Immunity -
    - Good - Primary “reactive” defense, necessary for acquired
    - Bad - leaky gut
    - Ugly - collateral damage
  - Acquired Immunity -
    - Good - specific immunity, duration
    - Bad - allergy, chronic inflammation
Harvey Dunn (1884-1952) Prairie is My Garden, South Dakota Art Museum