Health, immune function and energy metabolism

Nutrition 202
Animal Energetics
R. D. Sainz
Lecture 13

Immune Response

• How the body recognizes and defends itself against bacteria, viruses, and other foreign substances harmful to the body

• Antigen – a substance capable of producing an immune response
Innate vs. Adaptive Immunity

- **Innate**
  - 1st response
  - nonspecific
  - phagocytosis
  - proinflammatory cytokines
    - IL-1
    - TNF-α

- **Adaptive**
  - delayed response
  - specific
  - memory

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**Table 17-1. Major effector-cell types of the immune system**

<table>
<thead>
<tr>
<th>White blood cells (leukocytes)</th>
<th>Neutrophils</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Plasma cells</th>
<th>Macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphonuclear granulocytes</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
</tr>
</tbody>
</table>

- Present of total leukocytes: 50-70%
- Primary site of production: Bone marrow
- For each known function:
  - Neutrophils: Phagocytosis of bacteria, cell debris, and antibody-primed foreign matter; release of chemotactic and degranulating factors, etc.
  - Eosinophils: Release of histamine and other chemotactic factors (similar to tissue mast cells)
  - Basophils: Release of histamine and other chemotactic factors (similar to tissue mast cells)
  - Lymphocytes: Production of antibodies (atherogenicity), phagocytosis, and T cell-mediated immunity
  - Monocytes: Production of antibodies
  - Plasma cells: Derived from B lymphocytes
  - Macrophages: Derived from monocytes

Table 1  Different types of immune response

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Innate immunity</th>
<th>Acquired immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Diversity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Specialisation</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Memory</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood proteins</td>
<td>Complement</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Cells</td>
<td>Phagocytes, NK cells</td>
<td>Lymphocytes</td>
</tr>
</tbody>
</table>

From: Stenger & Röllinhhoff, 2001
**Sequence of events in infection**

1. Antigen enters the body (circulation)
2. Macrophages scan for 'self' and detect 'non-self'; antigens are ingested and degraded
3. Macrophages coordinate all subsequent reactions to the invaders (if the immune system is an army, they are the generals)
4. Depending on the nature of the antigen, as determined by its binding to receptors or products of proteolysis, macrophages will interact (via dendritic cells) with B-lymphocytes (humoral immunity) or T-lymphocytes (cellular immunity)

**Immune Response**

- Antigen infects host
- Recruitment of phagocytic cells to site of infection
- Macrophages and dendritic cells present antigen to T cells
  - Th1 cells
  - Th2 cells
  - Cytotoxic T cells
    - Macrophage phagocytosis
    - Activation of B cells
    - Killing of infected cells
    - Antibody production
From: Takeda & Akira, 2005

**Fig. 3.** Innate and adaptive immunity. Innate immune cells, such as dendritic cells and macrophages, engulf pathogens by phagocytosis, and present pathogen-derived peptides antigens to naïve T cells. In addition, TLRs recognize pathogen-derived components and induce expression of genes, such as co-stimulatory molecules and inflammatory cytokines. Phagocytosis-mediated antigen presentation, together with TLR-mediated expression of co-stimulatory molecules and inflammatory cytokines, instruct development of antigen-specific adaptive immunity, especially Th1 cells.

From: Parker et al., 2006

**Fig. 5.** Innate immune response. TLR activation, innate immune response, and adaptive immune responses. TLR activation results in the stimulation of both the innate and adaptive immune responses. Mononuclear cells (MNCs) in the tissue damage and inflammatory cytokines such as IL-1 and TNF-α can induce the production of IL-1 and TNF-α. These cytokines can activate the innate immune response, which can be mediated by TLR activation. The innate immune response is mediated by macrophages and dendritic cells, which can present antigens to T cells. The adaptive immune response is mediated by T cells and B cells, which can produce antibodies and cytokines.

From: Parker et al., 2006
Fig. 1. TLRs and their ligands. TLR2 is essential in the recognition of microbial lipopolysaccharides. TLR1 and TLR6 cooperate with TLR2 to discriminate salicylic acid from lipopolysaccharides, respectively. TLR4 is the receptor for LPS. TLR9 is essential in CpG DNA recognition. TLR5 is implicated in the recognition of viral dsRNA, whereas TLR7 and TLR8 are implicated in viral-derived siRNA recognition. TLR8 recognizes flagella. Thus, the TLR family members recognize specific patterns of microbial components.

From: Takeda & Akira, 2005

Fig. 4. TLR signaling pathway. TLR signaling pathways originate from the cytoplasmic TIR domain. A TIR domain-containing adaptor, MyD88, associates with the cytoplasmic TIR domain of TLRs, and recruits IRAK to the receptor upon ligand binding. IRAK then activates TRAF6, leading to the activation of the IκB kinase (IKK) complex consisting of IKKα, IKKβ, and NEMO/IκKγ. The IKK complex phosphorylates IκB, resulting in nuclear translocation of NF-κB which induces expression of inflammatory cytokines. TRIF, a second TIR domain-containing adaptor, is involved in the MyD88-independent signaling pathway via TLR2 and TLR4. In TLR3 and TLR4-mediated signaling pathways, activation of IRF-3 and induction of IFN-β are observed in a MyD88-independent manner. A third TIR domain-containing adaptor, TRAM, is specific to the MyD88-independent/TRIF-dependent pathway.

From: Takeda & Akira, 2005
FIG. 2. Ligand specificities of TLRs. Ten different mammalian TLRs have been described, but as yet no function is known for TLR8 and TLR10 (see the text). TLR1 and TLR4 do not signal as separate entities but act in cooperation with TLR2. TLR4 acts in a complex with several other molecules, such as CD14 and MD-2. TLR3, TLR5, and TLR9 exhibit the strongest ligand specificity. No natural ligands have been described yet for TLR7. LPS, lipopolysaccharide; RSV, respiratory syncytial virus; EDA, extra domain A; HSP60, heat shock protein 60; dsRNA, double-stranded RNA. References are indicated.

From: Janssens & Beyaert, 2003

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Cell type (reference)</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR1</td>
<td>Umbilicox (63)</td>
<td>No significant regulation except for downregulation in T cells after exposure to PHA (55)</td>
</tr>
<tr>
<td>TLR2</td>
<td>Restricted expression, undetectable in lymphoid cells, expressed in PMNLs, DCs, and monocytes (53)</td>
<td>Induced by LPS (53, 85)</td>
</tr>
<tr>
<td>TLR3</td>
<td>Expressed in DC and NK cells (24, 53)</td>
<td>Absent in precursors, monocytes, induced by differentiation, decreased upon maturation (53)</td>
</tr>
<tr>
<td>TLR4</td>
<td>Expressed in a variety of cell types, such as macrophages, DCs, ECs, not in lymphocytes (48, 53)</td>
<td>Expression enhanced by proinflammatory cytokines and bacterial products, downregulated by anti-inflammatory cytokines (53)</td>
</tr>
<tr>
<td>TLR5</td>
<td>Expressed in monocytes, immature DCs, epithelial, NK, and T cells (14, 28, 56)</td>
<td>No significant modulation by cytokines or LPS (21, 53)</td>
</tr>
<tr>
<td>TLR6</td>
<td>High expression in B cells, lower in monocytes and NK cells (24)</td>
<td>Not induced by proinflammatory cytokines or LPS (24)</td>
</tr>
<tr>
<td>TLR7</td>
<td>B cells, plasmacytoid precursor DC (24, 32)</td>
<td>Highly induced by IL-6, moderately by other cytokines (86)</td>
</tr>
<tr>
<td>TLR8</td>
<td>Monocytes, low in NK and T cells (24, 32)</td>
<td>Highly induced by gamma interferon and LPS, moderately by other cytokines (85)</td>
</tr>
<tr>
<td>TLR9</td>
<td>Plasmacytoid precursor DCs, B cells, macrophages, PMNLs, NK cells, and microglial cells (3, 32)</td>
<td>Induced by gamma interferon and LPS (3, 36)</td>
</tr>
<tr>
<td>TLR10</td>
<td>B cells, low in plasmacytoid precursor DCs (24)</td>
<td>No significant modulation by cytokines or LPS (86)</td>
</tr>
</tbody>
</table>

*Abbreviations: DC, dendritic cell; DC, osteoblastic cell; PMNL, polymorphonuclear leukocytes; NK, natural killer cell; PHA, phytohemagglutinin. References are indicated.

From: Janssens & Beyaert, 2003
Humoral immunity (antibodies)

1. Antigen fragments are transported to the macrophage cell surface, and presented to T-H2 cells, which 'turn on' the B cells

2. B-lymphocytes react to antigenic sequences on macrophages by shuffling and combining sections of DNA to produce antibodies specific for the antigen

3. B-lymphocytes can also recognize antigens on their own, and produce an antibody response

4. Antibodies (immunoglobulins) are released into the circulation, bind and remove antigen
Antibodies

• Antibodies are composed of two identical heavy chains and two identical light chains

• Each chain has a constant and a variable region

• The variable region confers the specific binding sites (idiotypes)

**Figure 2.2 BIFUNCTIONAL NATURE** of an antibody is reflected in its structure, as is seen in this schematic diagram of the molecule modeled in Figure 2.1. Each protein chain has a variable region and a constant region. In the variable region the sequence of amino acids is different in each antibody; the constant regions are the same in every antibody of a given type. The variable regions recognize and bind to a specific antigen; the constant regions thereby carry out some immunologic task. The chains are folded so that their hypervariable regions, where the amino acid sequence is particularly variable, come together to form a highly specific antigen-combining site.


**Figure 2.3 ANTIBODY MOLECULE** is an assembly of four protein chains, which are folded and interconnected to form a split I. There are two identical heavy chains (red and dark blue) and two identical light chains (yellow and light blue). In this model, generated with the aid of a computer by Richard J. Feldmann, the spheres represent amino acids, the subunits of the protein chains.

Cellular immunity

- Macrophages present antigens to T-H1 cells, which 'turn on' T-cytotoxic lymphocytes
- T-cytotoxic cells leave the bone marrow & spleen, cruise around killing anything that is not 'healthy'

**Figure 7.6** HUMORAL IMMUNE SYSTEM forms pores much like those inflicted by the cellular system's killer myocytes. Binding of antibodies to a target cell triggers a cascade in which successive proteins of the complement stem are activated. Eventually the protein C3b-6 binds to the target's surface membrane, after which C7, C8 and a number of C9 proteins aggregate to form a pore (left). In contrast, the pores made by killer cells are formed by the self-aggregation of one kind of subunit: the perforin monomer (right).

Cytokines

- Substances produced by various cells of the immune system that transmit instructions to each other and to other body cells, coordinate immune and metabolic responses
- Typically glycosylated monomeric peptides, ~150 amino acids; also homo- and hetero-dimers and –trimers
- Pro-inflammatory and anti-inflammatory (with considerable overlap)

Pro-inflammatory cytokines

- Interleukin 1 (IL-1: α, β, γ) – main pro-inflammatory cytokine; induces antibody response, also other inflammatory responses (fever, etc.)
- Tumor necrosis factor (TNF)
- Interleukin 6 (IL-6)
- Interferons
- Many others
Anti-inflammatory cytokines

- IL-1 receptor antagonist (IL-1ra)
- IL-4
- IL-6 (mainly anti-)
- IL-10
- IL-11
- IL-13
- TGF-β
- Interferons
- Many others

Acute Phase Response

- Complex series of reactions initiated in response to infection

- Sickness behavior
  - ↓ Feed intake: meal frequency, size, duration
  - Taste aversion
  - Lethargy
  - Malaise
Effect of Immune Response on Chick Body Weight

![Graph showing the effect of immune response on chick body weight. The graph compares the average body weight (g) over time (days post injection) for control and LPS groups.](graph1)

Effect of Immune Response on Daily Gain

![Graph showing the effect of immune response on daily gain. The graph compares daily gain (g) over time (days post injection) for control and LPS groups.](graph2)
Decreased feed intake only accounts for 70% of the decline in growth rate. The other 30% is due to metabolic changes occurring within the body.
**Effect of Immune Response on Feed Efficiency**

- **Day Post Injection**
  - Gain:Feed
  - Control
  - LPS

**Infection**

- ↑ heat production
- ↓ food intake (due to IL-1, not high temperature)
- activation/proliferation of lymphocytes & phagocytes
- induction of acute phase proteins in liver

- So: negative energy balance
Fever

• ↑ body temperature due to pyrogenic stimuli (thermoregulation at a higher set point)

• van’t Hoff / Arrhenius equation:
  \[ R_2 = R_1 \cdot Q_{10}^{(T_2 - T_1)/10} \]

• Where \( R_1 \) and \( R_2 \) are rates occurring at temperatures \( T_1 \) and \( T_2 \), and \( Q_{10} \) is the relative increase in rate caused by a 10°C rise in temperature.

• For most biological phenomena, \( Q_{10} \) lies between 2 and 3. This means that metabolic rate would increase by 7 to 12% for each 1°C rise in temperature.


Fever

• Dubois (1921)
  – Clinical human studies; linear regression analyses
  – Heat production ↑ by ~13% for each 1°C of fever

• Baracos et al. (1987)
  – Sheep given E. coli endotoxin +/- naproxen (to block prostaglandin synthesis)
  – Biphasic responses of HE and temperature; peaks at 45 and 200 min
  – Average HE = 133 ± 2 % of controls (+ 24 ± 2%/°C rise in temp.)
  – Naproxen abolished the fever and increased HE
Fever

- Caused by release of IL-1
- Metabolic rate increases $\sim$10-15% per $^\circ$C of fever
- Decreased feed efficiency
- Temperature enhances immune response and provides a less suitable environment for pathogen survival
Fever

- Hasselgren et al. (1997)
  - Catabolic conditions – e.g., trauma, cancer, fasting
  - ↑ ubiquitin mRNA
  - ↑ protein degradation (proteasome; also lysosomal)
  - Sepsis – only energy-dependent pathways activated
  - Mediated by interleukin-1, tumor necrosis factor α, glucocorticoids

- What is the purpose?
  - Possibly, presentation of degradation fragments to the surface of macrophages, with major histocompatibility complex I
  - Also, lymphocyte proliferation increases 4X  \((37°C \rightarrow 40°C)\)

Lipid Metabolism

Hyperlipidemia: NEFA

- ↑ Lipolysis in adipose tissue

- Decreased hepatic FA oxidation
  - IL-1 and TNF-α increase malonyl CoA levels which inhibits CPT-I

- Decrease in FA oxidation leads to the suppression of ketone body production
Lipid Metabolism

Hyperlipidemia: VLDL

- ↓ LPL activity

- ↑ Hepatic FA and TAG synthesis
  - TNF-α increases intracellular concentrations of citrate which activates acetyl CoA carboxylase

Overall decrease in FA utilization by the body

Glucose Metabolism

- During infection, there is an increase in gluconeogenesis and glycogenolysis

- IL-1 and TNF-α influence plasma glucose levels

- An increase in glucose utilization is common
Protein Metabolism

- Protein metabolism is affected differently in each tissue

- Overall negative whole body N balance
  - N loss exceeds what is to be expected from anorectic conditions

\[ \text{Intake} \quad \dot{\text{Amino Acids}} \quad \text{Synthesis} \quad \dot{\text{Protein}} \quad \text{Degradation} \quad \text{Oxidation} \]
Liver Protein

- Overall increase in protein synthesis
- Increase in amino acid uptake
- Acute phase protein synthesis
  - Large increase in plasma within 24-72 hours
- No alteration in protein degradation

Skeletal Muscle Protein

- Overall decrease in protein synthesis and increase in protein degradation
- Activation of proteolytic systems
- Supplies amino acids to visceral organs and immune cells
Glucocorticoids

- IL-1 induces ACTH release
- Decrease feed efficiency
- Anabolic effect on liver
- Catabolic effect on skeletal muscle
# Effect of Antigen on Corticosterone Concentration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IL-1 (SI&lt;sub&gt;max&lt;/sub&gt;)</th>
<th>Cort (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>1.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LPS</td>
<td>2.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


# Effect of Corticosterone on Feed Efficiency and Growth

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Feed</th>
<th>Gain (g/d)</th>
<th>Feed (g/d)</th>
<th>Gain: Feed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>Ad lib</td>
<td>17.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.61&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Saline</td>
<td>Equal-fed</td>
<td>15.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.59&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-1</td>
<td>Ad lib</td>
<td>14.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.56&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cort</td>
<td>Ad lib</td>
<td>15.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.53&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Effects of sanitation and antibiotics on chick growth

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average daily gain, g/d</th>
<th>Gain:feed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean</td>
<td>12.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.66&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unsanitary</td>
<td>12.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.54&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clean + antibiotics</td>
<td>12.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.67&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unsanitary + antibiotics</td>
<td>12.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.63&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


**FIGURE 1** The influence of environment and antibiotics on plasma interleukin-1 (IL-1) of chicks. Plasma IL-1 levels were measured in chicks raised either in a clean or an unsanitary environment and fed a corn-soybean-based diet with or without 100 mg/kg of streptomycin and 100 mg/kg of penicillin. Each bar represents the mean ± SEM (p > 0.05) for each treatment. Asterisk indicates significant difference from the other means (p < 0.05).

Health and growth

• Exposure of animals to microorganisms creates an environmental stress
• Animals in a germ-free environment grow more rapidly and efficiently than animals reared conventionally
• Poor sanitation ↓'s growth rate (15%) and gain:feed (10%), even with no clinical signs of infection
• Vaccination can reduce morbidity, without overcoming the growth depression
• Antibiotics can alleviate the immunological stress and growth depression associated with environmental pathogen load

• BOTTOM LINE:
  – The body’s response to infection helps fight off disease, but
    • these endogenous mechanisms have a substantial energy cost and therefore
      • a negative impact on performance.
  – Approaches to mitigate these effects include
    • sanitation
    • antibiotics
    • anti-inflammatory agents
    • nutrition