The immune system

- **Leukocyte**: White blood cells; cells of the immune system
- **Innate**
  - Non-specific
  - Neutrophils and macrophages
  - Macrophages:
    - Recruit neutrophils (PMN)
    - Phagocytose (i.e., engulf and kill)
    - Antigen presentation
  - PMN:
    - Chemotaxis
    - Phagocytose
- **Adaptive**
  - Specific
  - Vaccine development
  - Lymphocytes
    - T and B (antibody [Ig] production)

**Outline**

- Overview of immune response
  - Innate and Adaptive
- Impact of stress on immune function
  - Heat
  - Crowding + Transport
  - Malnutrition
  - **Parturition**
  - Disease
- Nutrient utilization during inflammation
  - **Glucose**
  - Amino Acids
  - Lipids
- Impact of Vitamin/mineral supply on immune response
  - Vitamin E + Selenium
  - **Chromium**
- Take-home messages

**Stress the Immune System: Parturition**
Dysfunctions observed in periparturient dairy cows
(Nielsen, 2002 and Ingvartsen, 2005)

<table>
<thead>
<tr>
<th>Leukocytes (PMN)</th>
<th>Dysfunction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative metabolism <em>in vitro</em></td>
<td>Detilleux et al., 1995</td>
<td></td>
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<tr>
<td>Neutrophil chemotaxis <em>in vitro</em></td>
<td>Kehrli et al., 1989a</td>
<td></td>
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<tr>
<td>Antibody dependent cell-mediated cytotoxic reaction <em>in vitro</em></td>
<td>Cai et al., 1994</td>
<td></td>
</tr>
<tr>
<td>CD62L and CD18* expression <em>in vivo</em></td>
<td>Lee &amp; Kehrli, 1998</td>
<td></td>
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<tr>
<td>Phagocytosis</td>
<td>Paape et al., 1981</td>
<td></td>
</tr>
<tr>
<td>Saad et al., 1989</td>
<td></td>
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</tbody>
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<tr>
<th>Monocytes/Macrophages</th>
<th>Dysfunction</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>TNF-α production induced by LPS**</td>
<td>Sordillo et al., 1995</td>
<td></td>
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<tr>
<td>TNF-α production</td>
<td>Røntved, 2000</td>
<td></td>
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<th>Lymphocytes</th>
<th>Dysfunction</th>
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<td>Cell division</td>
<td>Kehrli et al., 1989a</td>
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<tr>
<td>I. Ishikawa et al., 1994</td>
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</tbody>
</table>

* CD62L and CD18: adhesion molecules involved in the migration from blood into tissue.
** Lipopolysaccharide (LPS) constitutes a part of the cell surface of gram negative bacteria.

What causes periparturient immunosuppression?

- Cumulative effect of a multitude of factors, including endocrine changes?
- Cortisol – not a major contributor
- Milk yield?
- Physiological imbalance?
- Nutrition
- Genotype?
- Others?

Major Diseases During the Periparturient Period:
Mastitis

- An inflammation of the mammary gland
- Most costly of all diseases in the dairy industry
  — > $2 Billion annually (Cha et al., 2011)
Neutrophils (PMN) and the Immune Response

- Macrophages detect + recruit PMN
- ↑ somatic cells (SCC) indicator of mastitis
- During mastitis, 90% PMN in milk
  - Released from bone marrow
  - Short half-life
  - Few mitochondria
  - Utilize little oxygen
  - 1° phagocytose + kill
- Improving Macrophage + PMN function vital

Garnsworthy, 1988

Energy Balance During Early Lactation

Rastani et al., 2001

Non-Esterified Fatty Acid (NEFA) Concentrations During the Transition Period

Rastani et al., 2001
Major Diseases During the Periparturient Period: Ketosis and Fatty Liver

- Ketosis
  - ↑ ketones (i.e. BHBA); >1.2 mM
- Fatty liver (i.e. hepatic lipidosis)
  - NEFA uptake >>> oxidation + export
  - Liver triacylglyceride (TAG)

<table>
<thead>
<tr>
<th>Liver Category</th>
<th>Liver TAG (% wet wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Mild</td>
<td>1-5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-10%</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

Adapted from Bobe et al., 2004

Fates of Energetic Fuels in Leukocytes

Krebs’ Cycle

Overall Effect

Qu et al., 2014; J. Dairy Sci. 97 (Suppl. 1):180.

Nutrient Utilization During Inflammation
Proposed Mechanism

Qu et al., 2014; J. Dairy Sci. 97 (Suppl. 1):180.

Nutrients and Leukocyte Function

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Effect on Immunity</th>
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</thead>
<tbody>
<tr>
<td>Glutamine</td>
<td>Cytokine and ROM production; phagocytosis; CD4 T cell adherence</td>
</tr>
<tr>
<td>Glucose</td>
<td>Proliferation, survival, differentiation; chemotaxis/phagocytosis</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>Phagocytosis; IgM secretion; cytokine production; cell viability; diapedesis; antigen presentation</td>
</tr>
<tr>
<td>Ketones (BHBA)</td>
<td>Chemotaxis; phagocytosis; PMN trap formation; oxidative burst; ROM production; IgM secretion</td>
</tr>
<tr>
<td>Energy Balance</td>
<td>Chemotaxis; phagocytosis; diapedesis; antigen presentation; acute phase response; oxidative burst; cytokine production</td>
</tr>
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Adapted from Ingvartsen and Moyes, 2013

Vitamin/E (alpha-tocopherol)

- General Aspects:
  - Most important fat-soluble antioxidant
  - Protects membrane lipids from oxidative damage
Dietary vitamin E ↓ the rate of clinical mastitis\(^1\) (\(P < .09\)).

\[
\begin{align*}
\text{Rate of Clinical Mastitis}\% &= 0.58 - 0.01x \\
R^2 &= 0.36
\end{align*}
\]

\(\text{Rate of clinical mastitis} = \left[\frac{\text{# cases}}{305}\right] + 0.001\)

Adapted from Weiss et al., 1990

The Effect of Vitamin E on Mammary Gland Health During the Transition Period

- Plasma Vitamin E suppression coincides with incidence of disease around calving
- Reducing the suppression of plasma vitamin E may help incidence of disease during transition period

Adapted from Weiss et al., 1990

Percent intracellular kill of \textit{Staph. aureus} in blood PMN with vitamin E (VE), Selenium (Se) or both.

Means with different letters (a,b) differ (\(P < 0.05\))

<table>
<thead>
<tr>
<th></th>
<th>% Intracellular Kill of Staph. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE+ Se</td>
<td>a</td>
</tr>
<tr>
<td>VE</td>
<td>a</td>
</tr>
<tr>
<td>Se</td>
<td>a,b</td>
</tr>
<tr>
<td>Control</td>
<td>b</td>
</tr>
</tbody>
</table>

Note: VE = 90 mg/kg concentrate DM; Se = 0.45 mg/kg concentrate DM

Adapted from Hogan et al., 1990
Mechanistic Action of Chromium (Cr)

- Cr and glucose metabolism
  - Modulates tissue response to insulin (Vincent, 2004)
- Cr and stressors
  - Stress reduces Cr excretion + Cr status (Yasui et al., 2014)
    - Gestation
    - Lactation
    - Infection
- Unclear role Cr supplementation for periparturient cows

Cr supplementation in lactating dairy cows

- Improves insulin sensitivity during periparturient period (Subiyatno et al., 1996) and glucose tolerance (Hayirli et al., 2001)
- DMI (Smith et al., 2005; Yasui et al., 2014)
- Milk yield + components (Hayirli et al., 2001; Smith et al., 2005; Vergas-Rodriguez et al., 2014)
- Improves energy metabolism during early lactation
  - NEFA (Bryan et al., 2004; Soltan, 2010; Yasui et al., 2014)
  - Loss in body condition (Hayirli et al., 2001; Soltan, 2010)
  - Energy balance (Soltan, 2010)
  - Cytological endometritis (Yasui et al., 2014)
- Improves reproductive performance (Bryan et al., 2004; Soltan, 2010)
- Role of Cr on mammary epithelial cells in vitro (Garcia et al., unpublished)

Chromium Modulates Innate Immune Response

- Circulating monocytes
  - Antibody response around calving (Burton et al., 1993)
  - TNF-α and IL-2 production during peak lactation (Burton et al., 1996)
  - Monocytes, glucose, IGF1 and SLC2A3; TNF-α production; Primi- > multi-parous cows mid-lactation (Garcia et al., 2016 under review)
- Circulating PMN
  - TNFA during peak lactation (Yuan et al., 2014)
  - % PMN in early lactation (Yasui et al., 2014)
- Cr improves anti-inflammatory response for heat-stressed cows in mid-lactation
  - IL-10 and IκBα (Zhang et al., 2014)

Mechanistic Action of Chromium (Cr)

- Cr and glucose metabolism
  - Modulates tissue response to insulin (Vincent, 2004)
Serum concentration of insulin around calving (Adapted From Ingvartsen et al., 1995)

Insulin receptors on leukocytes in cows

- Leukocytes use insulin-independent receptors (GLUT-1 and GLUT-3) for glucose uptake
- Insulin receptors are present on bovine monocytes with low expression on PMN (Nielsen et al., 2003)
  - Insulin receptors stimulate leukocyte functions (Spagnoli et al., 1995)
- Suggests insulin plays a role in PMN recruitment??
- Cr supplementation improve bovine monocyte insulin response?

Take-Home Messages

- Most cows immunosuppressed around calving
- Major nutrients that change around calving alter immune response
  - Glucose + glutamine =  
  - Ketones =  
  - Fatty acids = ??
- Vitamins/Minerals alter immune response
  - VE + Se =
  - Chromium =  
    - Altered by age, physiological state, stage of lactation, other stressors

Questions?

“Yes…I believe there is a question in the back”