Interactions of Inflammation and Metabolism in Transition Dairy Cows

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OUTLINE
- Transition inflammation: the evidence
- Physiological roles for inflammation
- Metabolic impacts of inflammatory signaling
- Mammary and lactation responses
The transition period

Infections increase ketosis risk

Ingvartsen, 2006

Gröhn et al., 1989
Ketosis increases infection risk

Risk of metritis
Risk of mastitis

Odds ratio, relative risk following ketosis

Duffield et al., 2009; Doohoo and Martin, 1984

Inflammation

Acute inflammation
- Associated with immune activation or tissue damage
- Swelling
- Pain
- Fever
Inflammation

Chronic inflammation
- No outward signs
- Slightly elevated inflammatory mediators
- Alterations in signaling

Acute phase proteins
Subacute liver inflammation is common in postpartum cows

Keski-Nisula et al., 1997

...and in women, even in the absence of complications

Keski-Nisula et al., 1997
Inflammation is associated with transition disorders

% of cows with one or more transition disorders

Degree of inflammation

Plausible causes of postpartum inflammation

Bradford et al., 2015

Bertoni et al., 2008
What’s the role of “normal” peripartum inflammation?

Parturition

Immediate postpartum anti-inflammatory

- Flunixin meglumine given 2 h and 24 h after calving
- Over 1,300 cows enrolled

Blocking inflammation on the day of calving can interfere with inflammatory signals needed to expel the placenta

Newby et al., 2017
Inflammatory signals are essential for parturition

1. Stimulate release of proteases
2. Promote contractions
3. Interact with prostaglandin synthesis pathways

Are there metabolic implications of postpartum inflammation?
Classification of cows according to BW loss postpartum

In retrospect, cows were divided according to % of BW loss during the first month postpartum:

1) **HWL** – High weight loss, lost more than the average of %BW loss (> 6%, on average 9%).

2) **LWL** – Low weight loss, lost less than the average of %BW loss (≤ 6%, on average 5%).

Zachut et al., 2013, 2015, 2017

Increased abundance of TNFα in adipose tissue of HWL cows at 7 d postpartum

Zachut and Moallem, 2017
Response to glucose tolerance test

Lipolysis and inflammatory proteins higher in IR (HWL) adipose

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<tr>
<th>function annotation</th>
<th>P value</th>
<th>no. of molecules</th>
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- Mono-glyceride lipase (MGLL)
- Perilipin-1 (PLIN)
- Hormone-sensitive lipase (HSL, LIPE)
- IR adipose → increased lipolysis
Alpha-1 acid glycoprotein (AGP)

TRANSITION DAIRY COWS:

Feed intake

AGP?

Acute phase proteins

Week relative to calving

AGP in transition cows

AGP (μg/mL)

Week relative to calving

n = 426

Unpublished data, Bradford et al.
AGP associated with reduced intake

- AGP explained 20% of variation in within-farm DMI during weeks 1-4 postpartum ($P < 0.001$)
- Rising from the 25th percentile to the 75th is associated with a 1 kg/d drop in DMI

Unpublished data, Bradford et al.

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Do repeated inflammatory signals alter metabolism?

- 33 Holstein cows were assigned to 1 of 3 treatments ($n = 11$) at calving.
- 3 treatments: 0, 1.5, or 3.0 μg TNFα/kg BW.

Yuan et al., 2013
**Inflammation suppresses intake**

![Graph showing the effect of inflammation on dry matter intake during lactation.](image)

- **Control**
- **1.5 µg/kg TNF**
- **3.0 µg/kg TNF**

*Subclinical Ketosis*

- 9%
- 27%
- 27%

*P = 0.02, TNFα vs. control (18% decrease)*

**Yuan et al., 2013**

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**A vicious cycle?**

- Excessive lipid stores
- Cytokines
- Pathogen challenge

**Metabolic disorders promote Infections**

**Metabolic disorders promote altered metabolism**

**Metabolic disorders**

**NEFA**

**BHBA**

**Cytokine receptor**

**Inhibited function**

**Pathogen challenge**

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Anti-inflammatory drug salicylic acid

- The parent compound for aspirin
- Interrupts central inflammatory pathways found in most cells

Salicylate induces mild hypoglycemia

![Graph showing plasma glucose levels over lactation days](image_url)

*Farney et al., 2013*
Is salicylate-induced hypoglycemia driven by enhanced insulin sensitivity?

Garcia, Ylioja, et al., 2018 (abstract)
Inflammatory pathways can promote gluconeogenesis

The saturated fatty acid palmitate promotes transcription of gluconeogenic genes by activating TLR4 (the LPS receptor).

Mamedova et al., 2013

Transition metabolism is a balancing act

- Inflammation may help promote homeorhetic mechanisms to promote glucose synthesis and conservation
- Excessive inflammation impairs feed intake, drives lipolysis
Inflammatory biomarkers predict lost milk

- Plasma concentrations of haptoglobin >1.1 g/L were associated with a 947 kg decrease in 305-day mature equivalent milk yield (Huzzey et al., 2015)
- Cows with haptoglobin concentrations greater than 0.1 g/L a week after calving produced 11% less milk in the first 2 months of lactation than those below that threshold (Shin et al., 2018)
Processes activated on day 1 of lactation

Ylioja et al., 2017 (Abstr.)

Orange = up-regulated vs. day 45 by RNA-Seq

Postpartum NSAID study

1. Na salicylate
2. Meloxicam
3. Placebo

- Administered orally starting 24 h postpartum
- 51 multiparous cows per treatment

Carpenter et al., 2016
Anti-inflammatories in early lactation

Meloxicam +12% P < 0.05 1 dose
Salicylate +11% P < 0.05 3 doses

Carpenter et al., 2016

Herd survival analysis

Con vs. Melox: P = 0.06

Carpenter et al., 2016
Chinese skullcap (Scutellaria baicalensis)

- Used in traditional Chinese medicine
- Liver-protective effects
- In vitro anti-tumoral effects
- Anti-inflammatory effects
- Effects in dairy cows?

Scutellaria baicalensis extract experiment

- 40 multiparous cows per treatment
- Randomized block design
- Commercial dairy farm with an Automatic Milking system (AMS)
- Treatment pre-mixed in concentrate pellet
Whole-lactation response

Con v. SBE60: \( P = 0.07 \)

Con v. SBE60: \( P = 0.04 \)

Decreased somatic cells point to reduced mammary inflammation

\( P = 0.02 \)

**Milk yield, lb/d**

Olagaray et al., 2019

Carpenter et al., 2016

Olagaray et al., 2019
Hypothetical impacts of unresolved inflammation

Bradford et al., 2015

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Any questions?