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Feeding the Immunity Defenders:

The Evolving Field of Nutritional Immunology

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Department of Animal Science

Michigan State University

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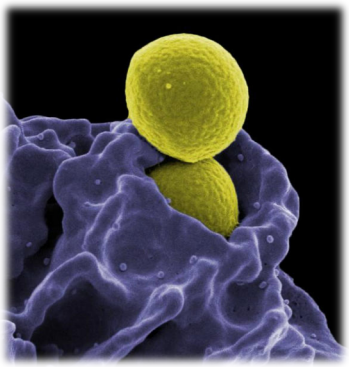
Outline

- Immune system primer
- Immunometabolism
- Nutrient impacts on immunity
- Impact of immune response on metabolism
- Integration and applications



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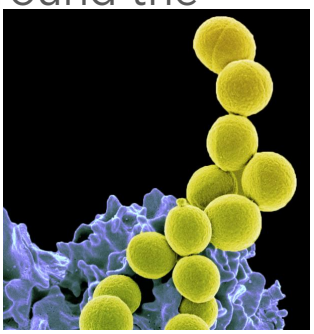
Roles of the immune system

- Monitors and manages the normal and pathogenic microflora found in and around the body
  - Bacteria
  - Viruses
  - Fungi
  - Multicellular parasites
- Detects and clears rogue and compromised cells, tissue debris
- Many emerging regulatory roles



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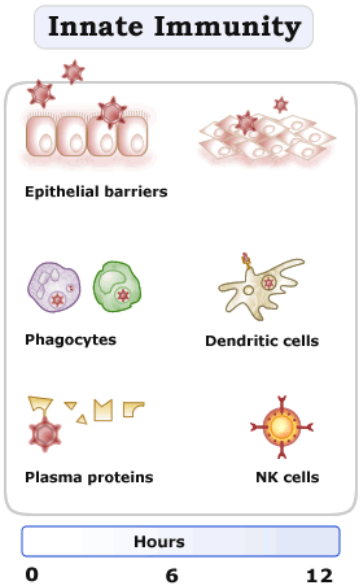

drrajivdesaimd.com

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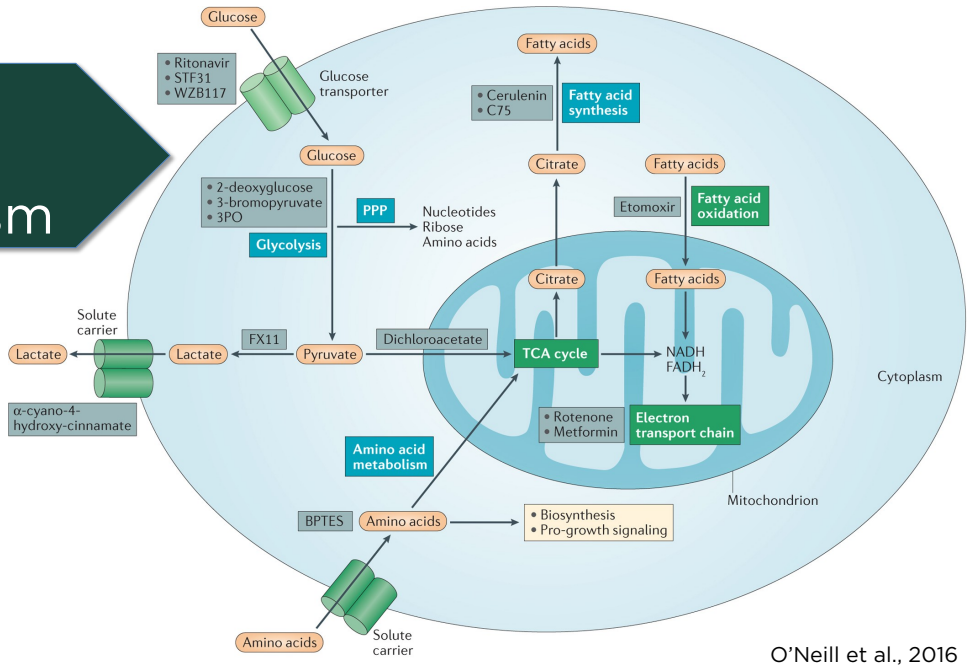
Intrinsic immuno-metabolism



O'Neill et al., 2016
Nature Reviews | Immunology

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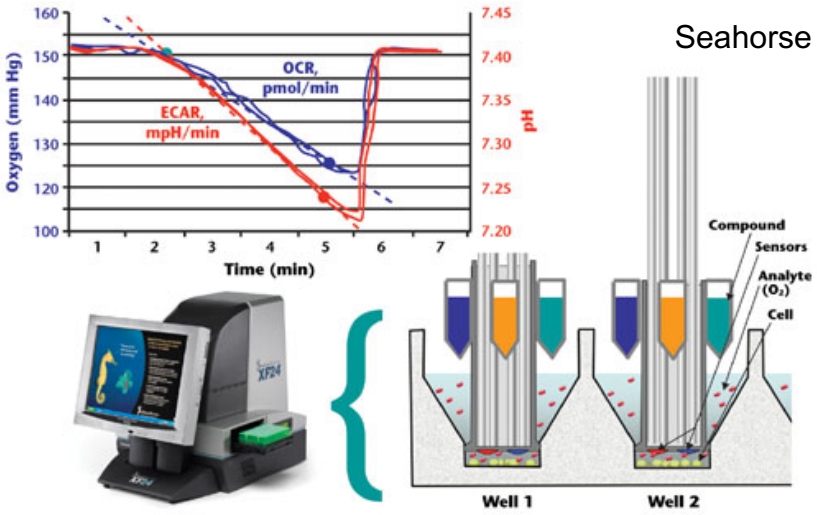
Measuring cellular energetics



Seahorse XF Analyzer

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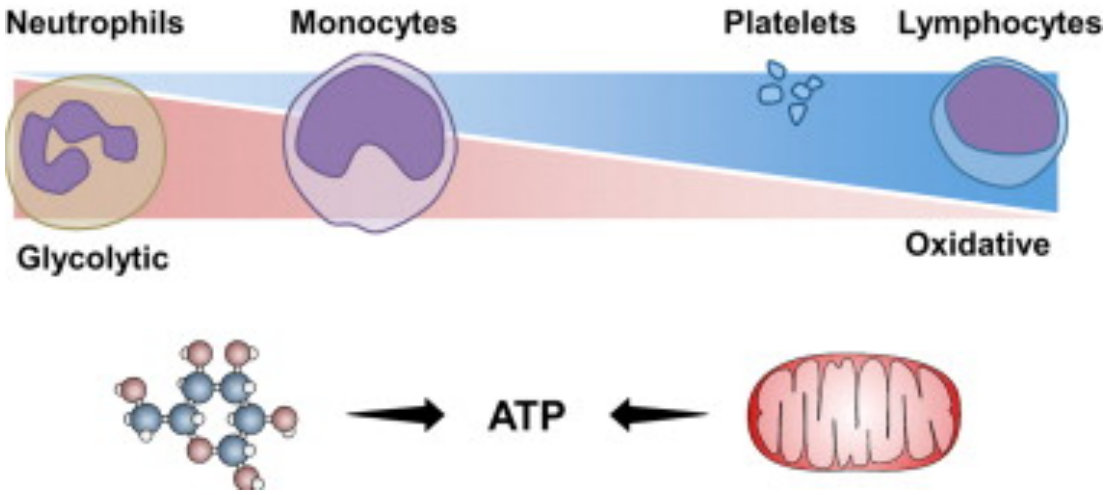
Differential Metabolism in Leukocytes and Platelets



Kramer et al., 2014

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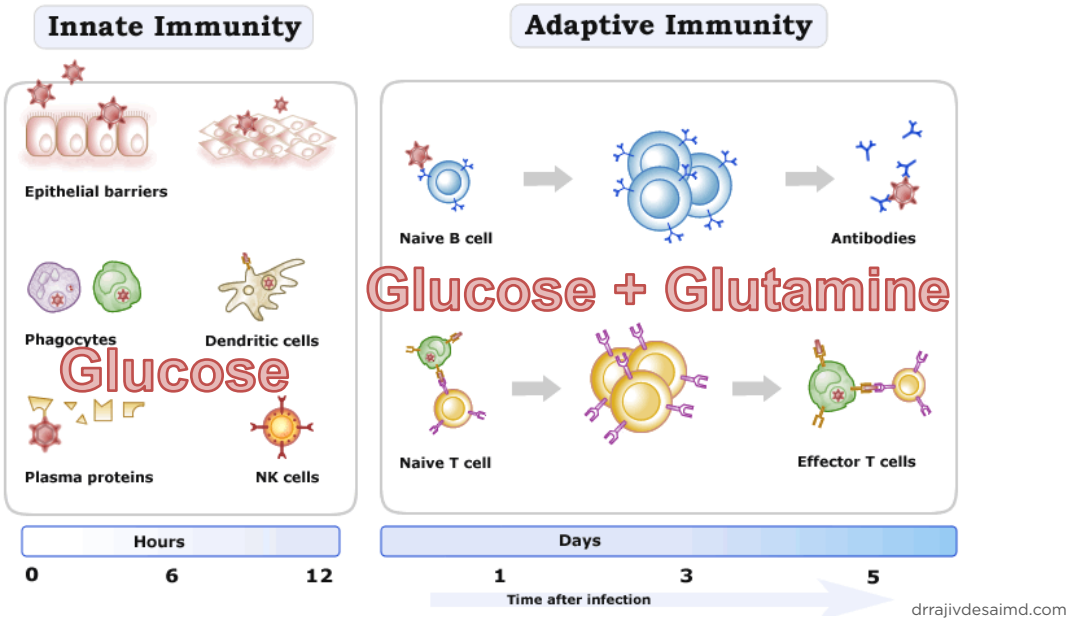

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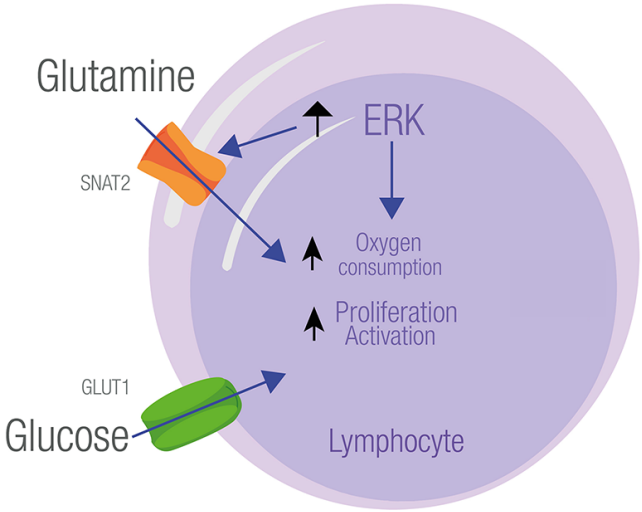
Critical roles of AA in immune cells

- Glutamine is required for lymphocyte activation (adaptive immunity)



Leguina-Ruzzi and Cariqueo, 2017

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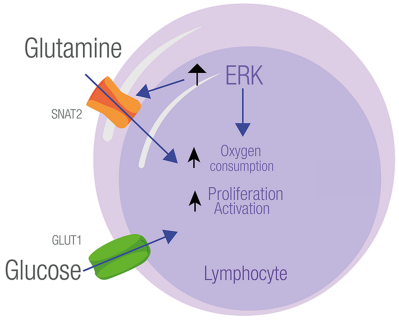
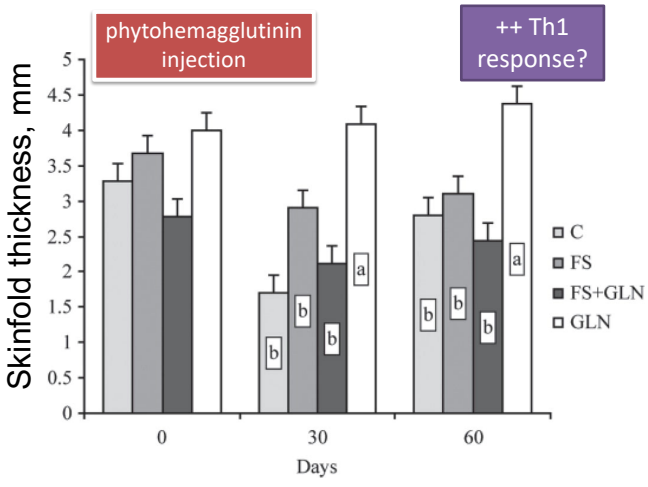
RP Glutamine enhanced cell-mediated immunity

- 24 mid-lactation Friesian cows in heat stress





Caroprese et al., 2013

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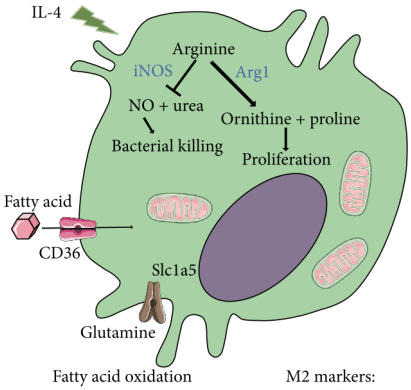
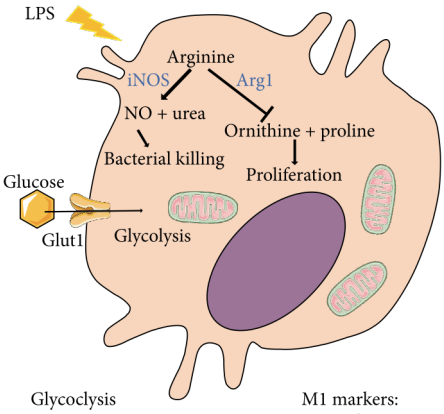
Critical roles of AA in immune cells



Fatty acid oxidation
Lipolysis
Glutaminolysis

M2 markers:
CD206$^+$
CD301$^+$
Arg1$^+$
Chi3l3$^+$
Relm-α^+

Arginine fuels the switch between calm and activated macrophages



Glycoclysis
ROS production
Itaconate production

M1 markers:
CD11c$^+$
iNOS$^+$
Marco$^+$

Stunault et al., 2018

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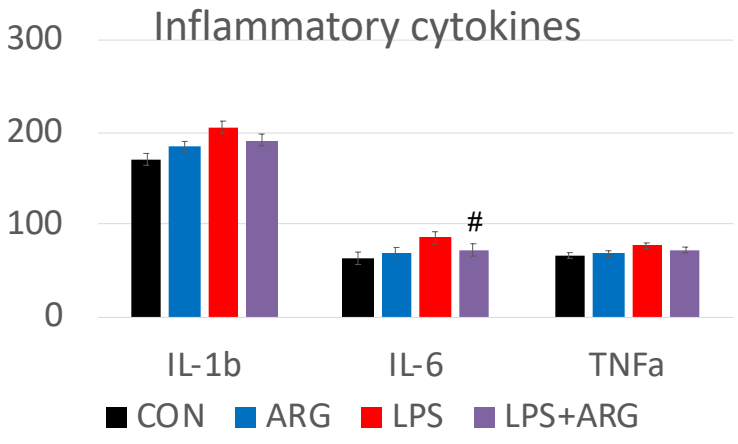
IV Arginine quells LPS inflammation

- 8 Holstein cows in late lactation used in a Latin square
- Low-grade LPS challenge for 15 d



Zhao et al., 2018

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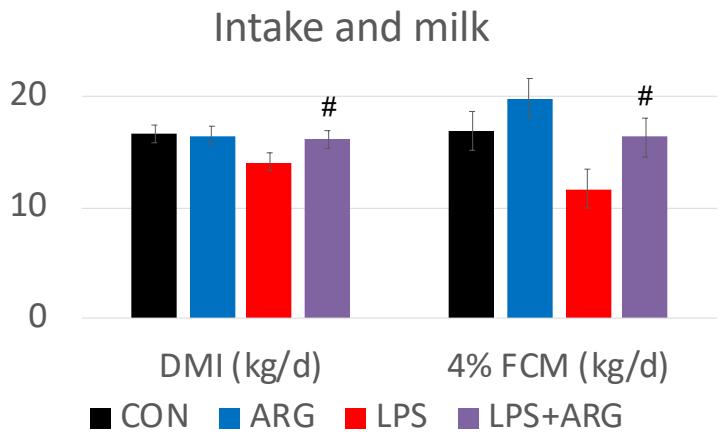

Zhao et al., 2018

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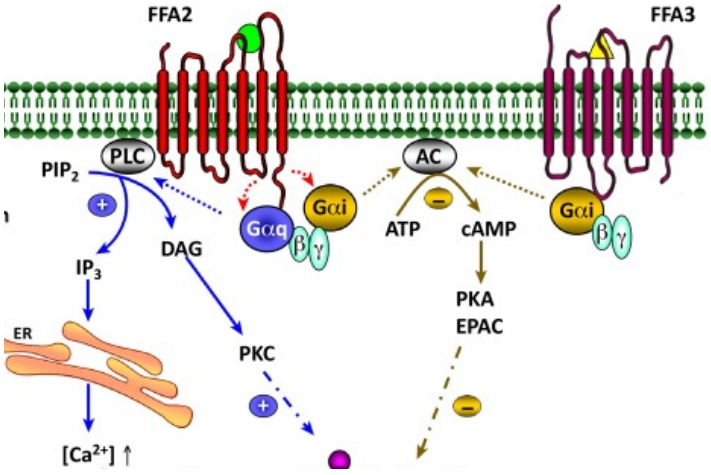
Nutrients are signals!

Including:

- Volatile fatty acids
- Long-chain fatty acids
- Sugars
- Amino acids
- Minerals
- Intermediary metabolites



Priyadarshini et al., 2016

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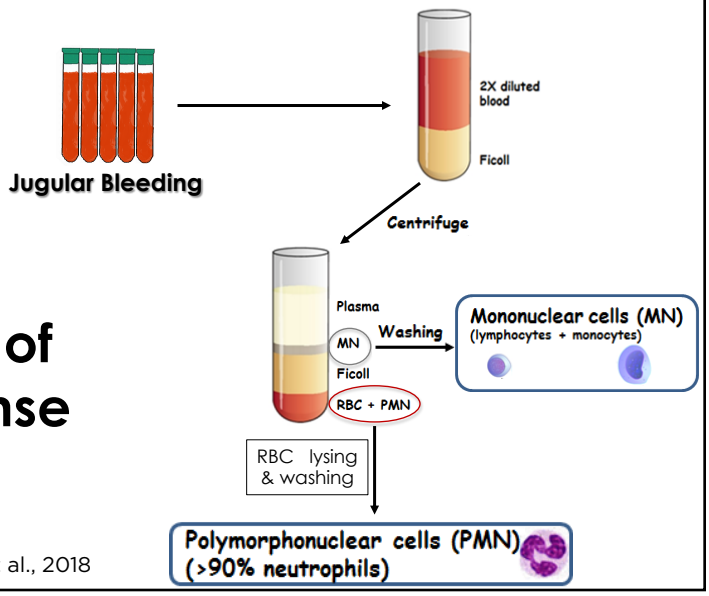

Ex vivo evaluation of immune cell response to nutrients

Garcia et al., 2018

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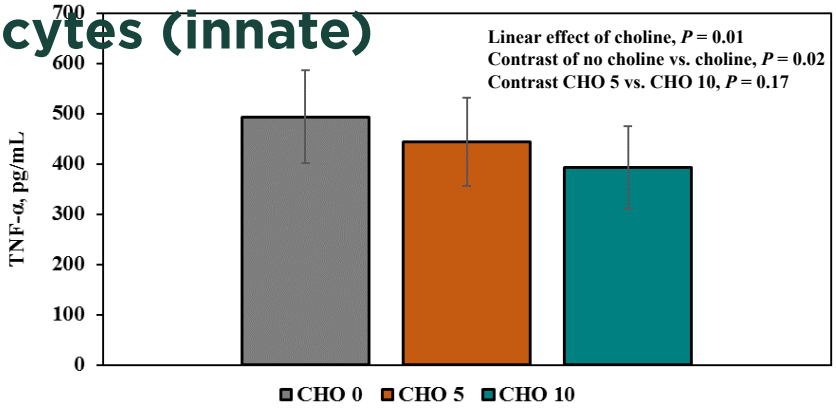
TNF-α in spent media from LPS-challenged monocytes (innate)



The decrease in TNF-a in spent media, coupled with downregulation of NFKB1 and TLR4 mRNA abundance, supports an anti-inflammatory effect of choline in monocytes.

Garcia et al., 2018

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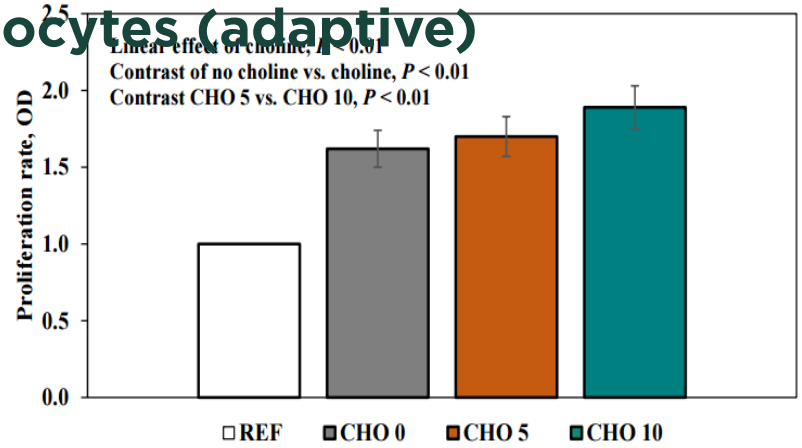
Proliferation of ConA-stimulated lymphocytes (adaptive)



REF: Cells without choline and without Concanavalin A (mitogen that enhances proliferation of T-cells)

Garcia et al., 2018

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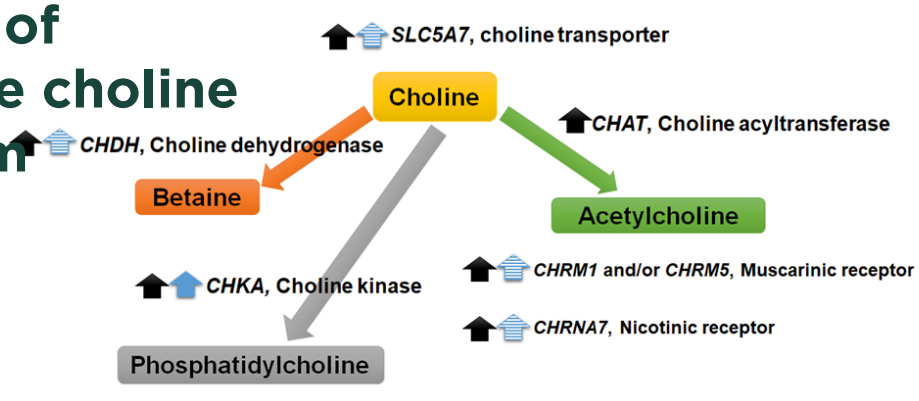
"Feed-forward" regulation of progressive choline metabolism



Neutrophil: Mild anti-inflammatory response
Monocyte: Strong anti-inflammatory response
Lymphocyte: Enhanced proliferative response

Garcia et al., 2018

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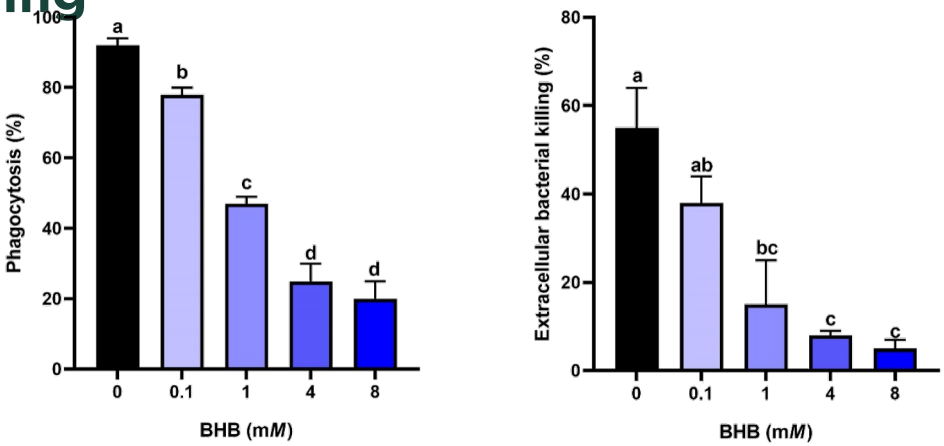
BHB impaired neutrophil bacterial killing



Different letters denote significance; Grinberg et al., 2008

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Infusion study

- Late lactation cows (n = 12) continuously IV infused with either BHB (target: 1.8 m*M*) or isotonic saline for 72 h
- Challenged with *Strep uberis* in two quarters at the start of BHB infusion

Swartz et al., unpublished data

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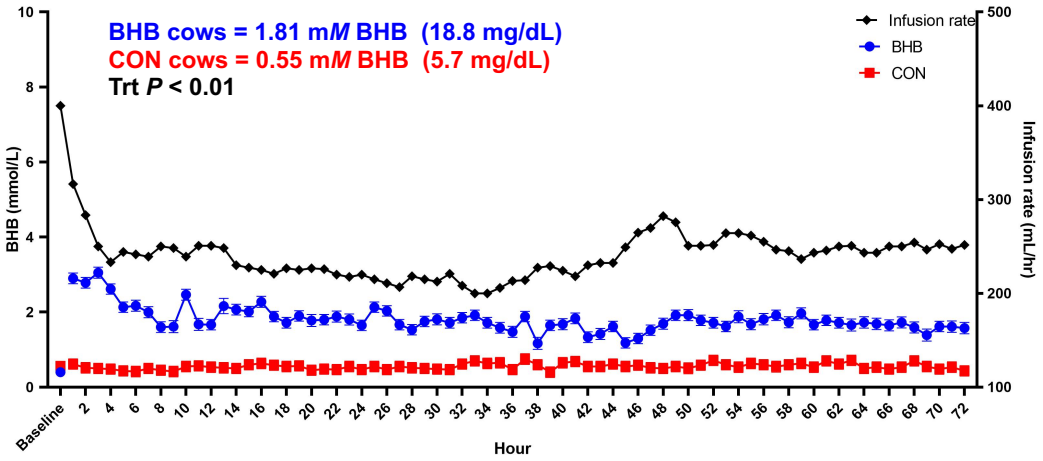
BHB clamp successful



Swartz et al., unpublished data

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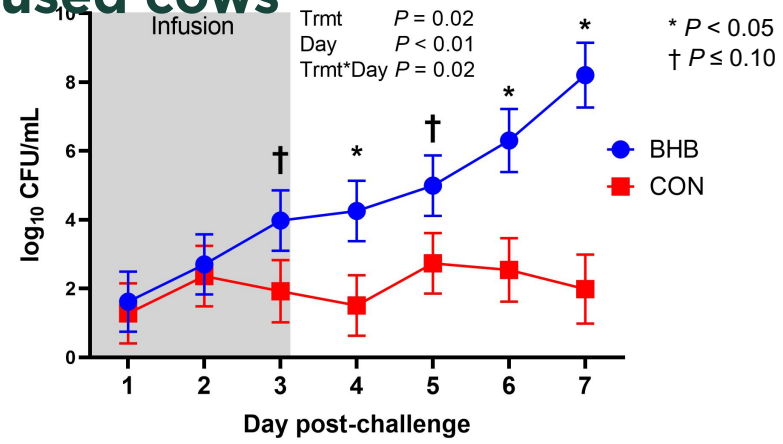
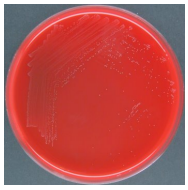
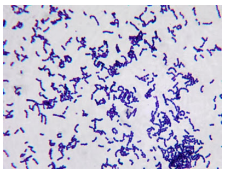
S. uberis growth enhanced in BHB-infused cows







Swartz et al., unpublished data

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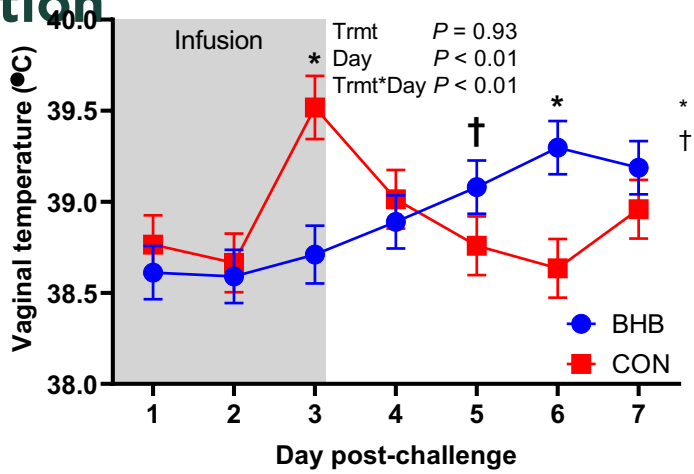
BHB delayed the febrile response to infection



Swartz et al., unpublished data

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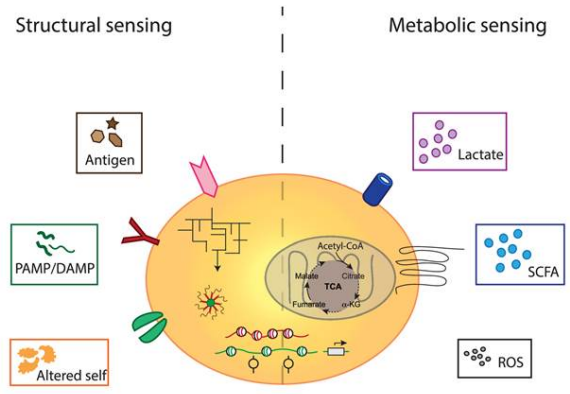

- surface or cytosolic receptors
- activation of signalling cascades
- activation of transcription factors
- effector response (proliferation, cytokine-production)

- solute channels, diffusion, GPRs, other?
- fuel into metabolic pathways
- alteration of cellular metabolic state
- direct effects (protein- or histone modification)
- effector response (cytokine production, polarization)

Intrinsic immunometabolism – many nutrients can influence immune function

Lötscher and Balmer, 2019

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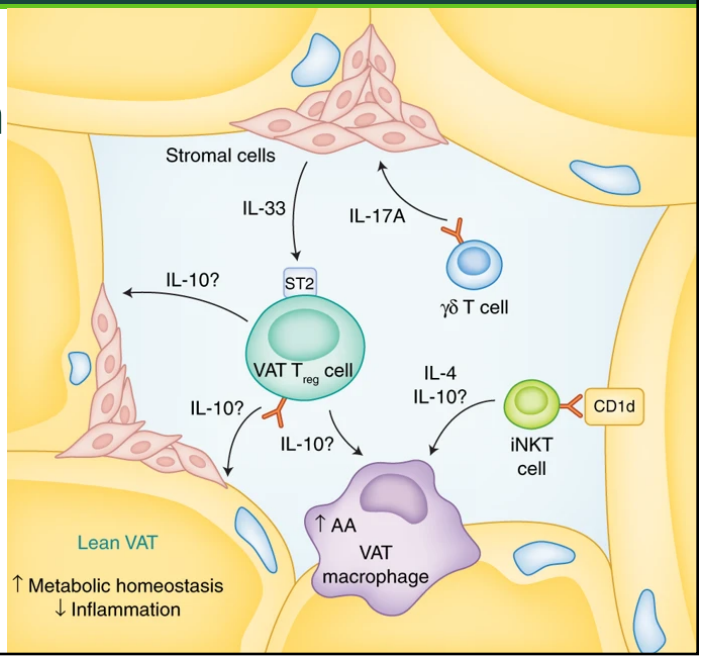
Extrinsic immunometabolism

- Local and distant immune cells greatly influence tissue metabolism



Caputa et al., 2019

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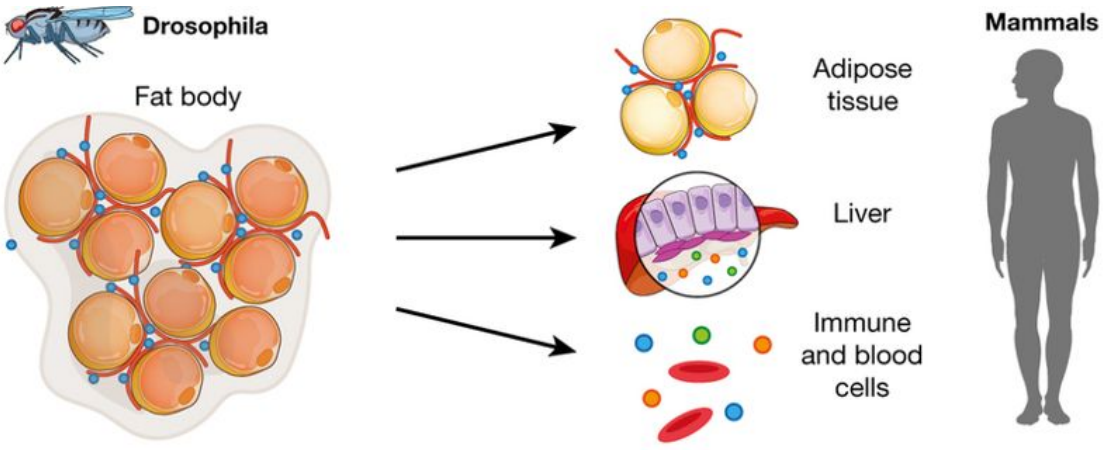
Evolution of organ systems



Hotamisligil, 2017

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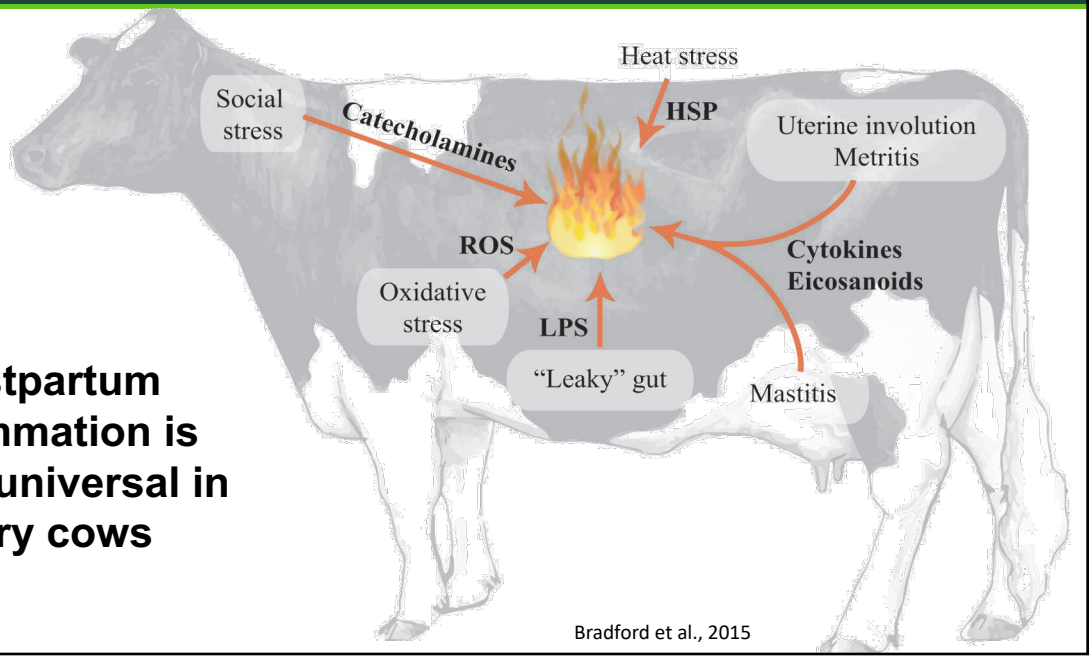
Postpartum inflammation is nearly universal in dairy cows



Bradford et al., 2015

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Does mild inflammation directly alter liver metabolism?

- 15 late lactation Holstein cows
- Treatments administered by s.c. injection once daily for 7 days
  - Control (saline) CON
  - TNFα at 2 µg/kg BW daily rbTNF
  - Pair-fed controls (saline) PFC

Bradford et al. 2009

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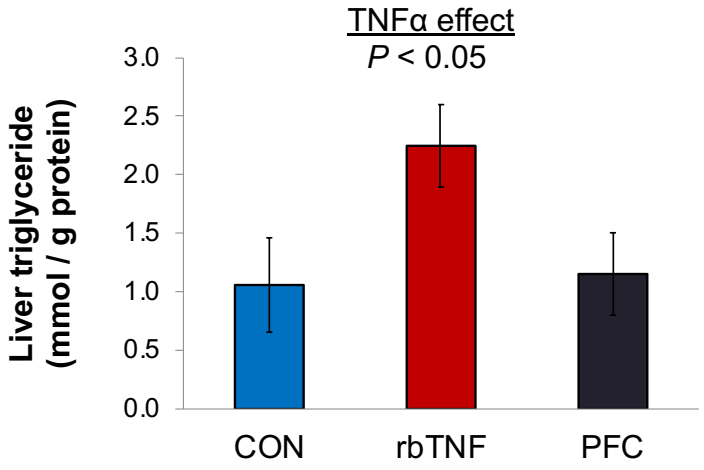
TNFα increases liver TG content



Bradford et al. 2009

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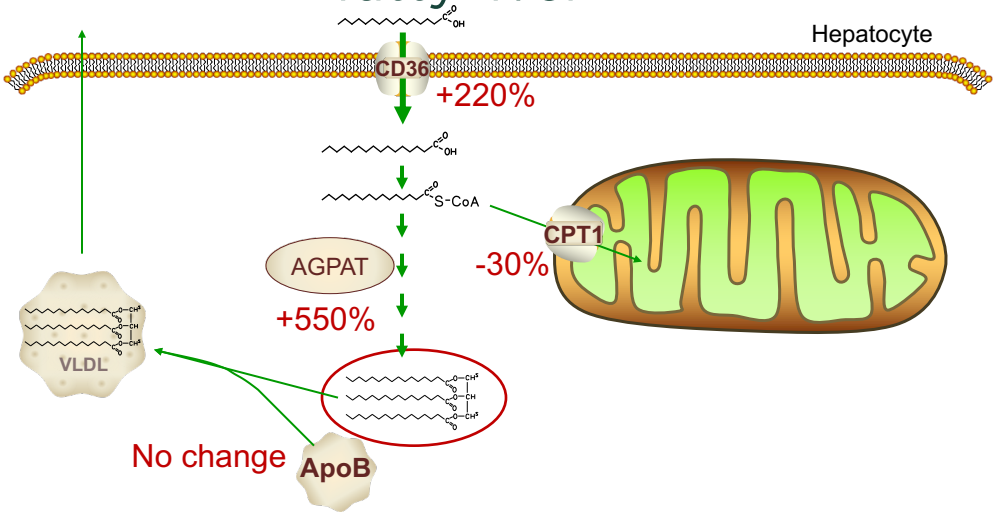
TNF effects on mRNA are consistent with fatty liver



Bradford et al. 2009

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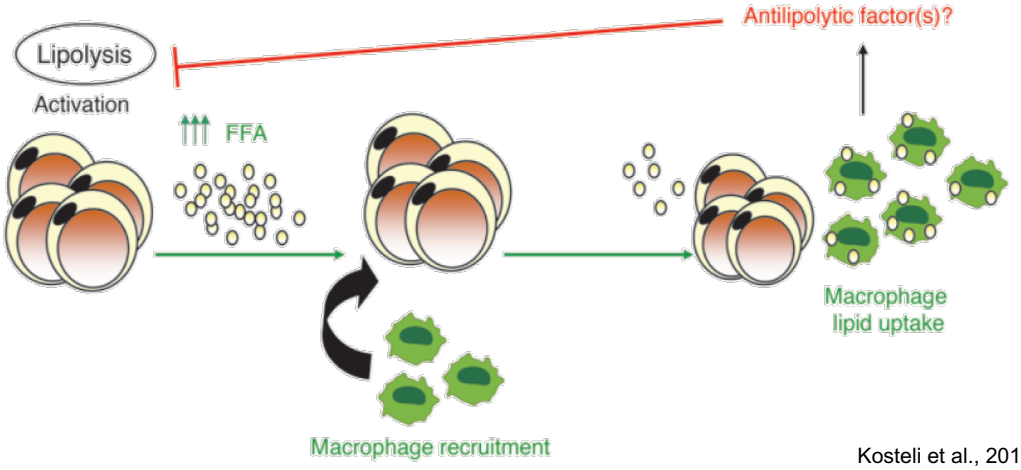
Immune cells regulate lipolysis



Kosteli et al., 2010

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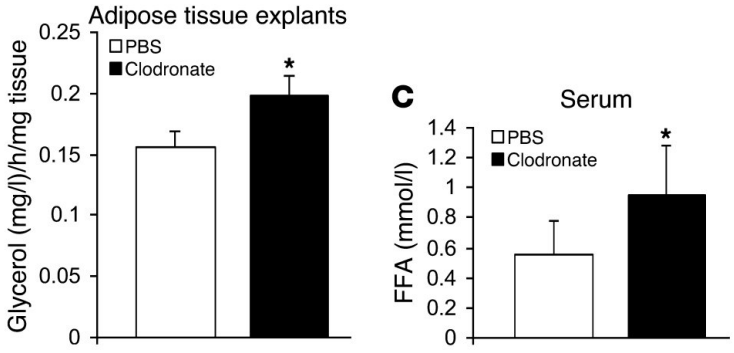
Lipolysis

- Clondronate kills macrophages
- Increased lipolysis



Kosteli et al., 2010

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Metabolic costs of disease

1. Increased metabolic activity
2. Reduced nutrient availability
3. Altered priorities for nutrient utilization
4. Increased turnover rates in the immune system
5. Damage to host tissues
6. "Genetic cost" - to offspring

Colditz et al., 2008

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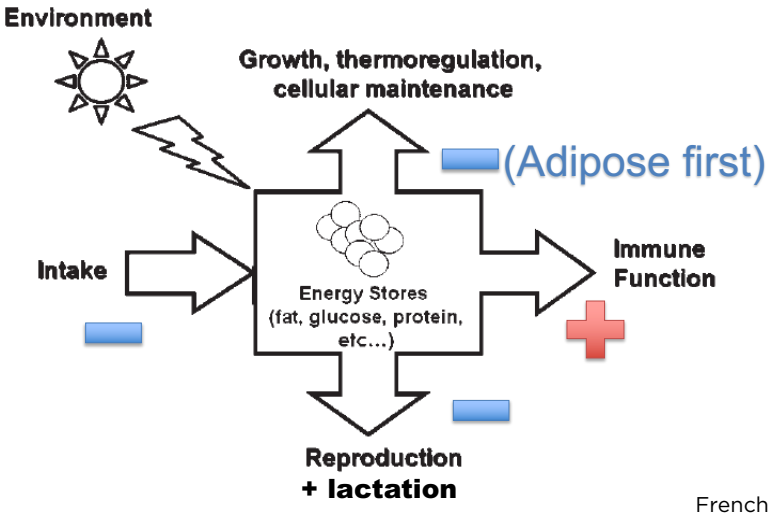
Resource allocation with immune activation



French et al., 2009

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What is the energetic cost of immune responses?

Species	Immune challenge	Cost	Reference
Human		30%	Kreymann et al. (1993)
		30%	Carlson et al. (1997)
		57%	Clark et al. (1996)
		16%	Cooper A. L. et al. (1992)
		15%	Borel et al. (1998)
Laboratory rat		18%	Tocco-Bradley et al. (1987)
		28%	Cooper et al. (1994)
Laboratory mouse		30%	Demas et al. (1997)
Sheep		28%	Fewell et al. (1991)
		10–49%	Baracos et al. (1987)

[a] Keyhole limpet hemocyanin injection.

10 – 40% increase in BMR

Lochmiller and Deerenberg, 2000

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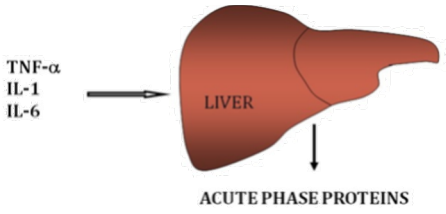
Estimated EAA costs of immune responses

2% for proliferation of immune cells

1% for increased immune activity

9% for liver acute phase response



(Relative to baseline requirements)

Klasing, 2007

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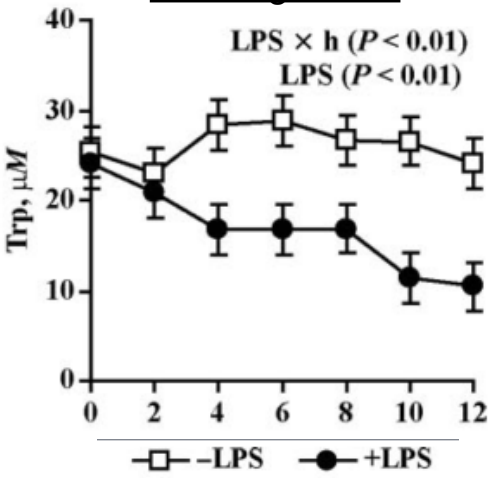
AA depletion after LPS

Growing steers



Similar effects for:
Leucine
Isoleucine
Phenylalanine
Threonine
Serine
Alanine
Glycine
Asparagine
Ornithine
Glutamate

Waggoner et al., 2009

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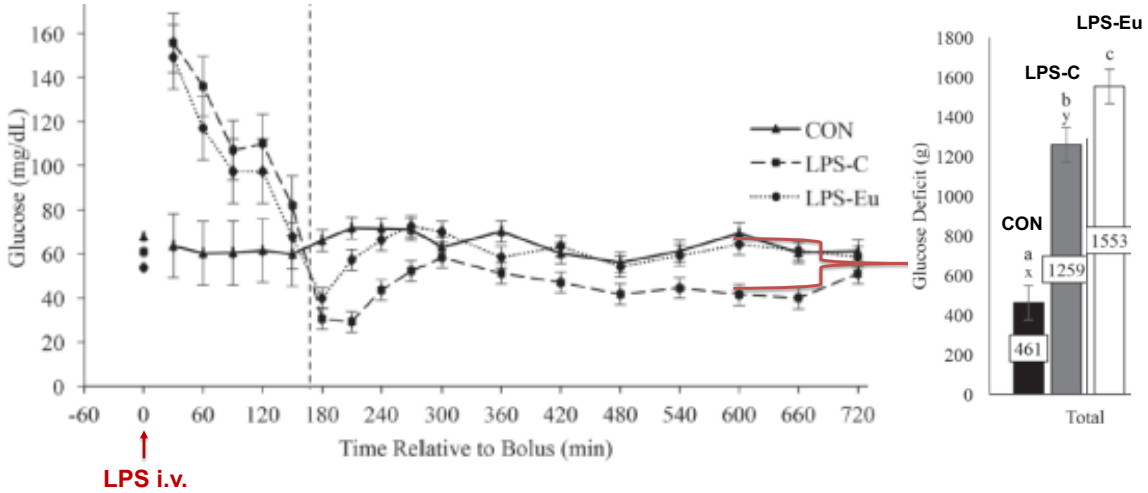
What is the glucose drain?



Kvidera et al., 2017

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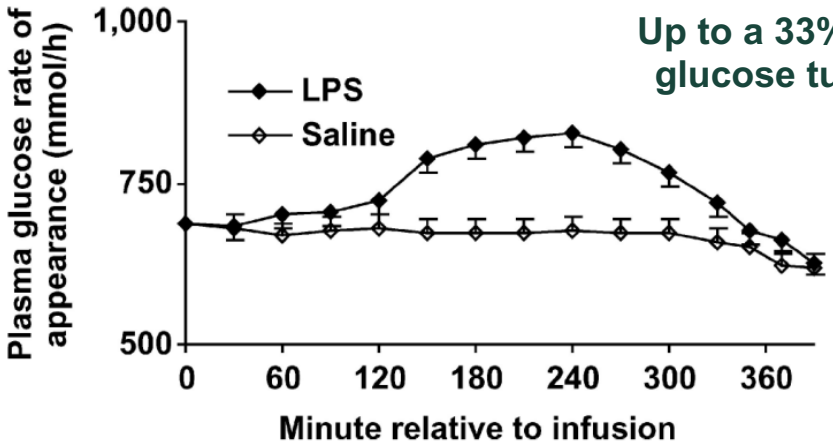
What is the glucose drain?



Up to a 33% increase in glucose turnover rate

Waldron et al., 2006

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Assessing adequacy

- Nutritional support of health can be difficult to assess
- Requirements are altered by physiological state: "conditionally essential"
- Suboptimal nutrition may only cause problems during challenging scenarios

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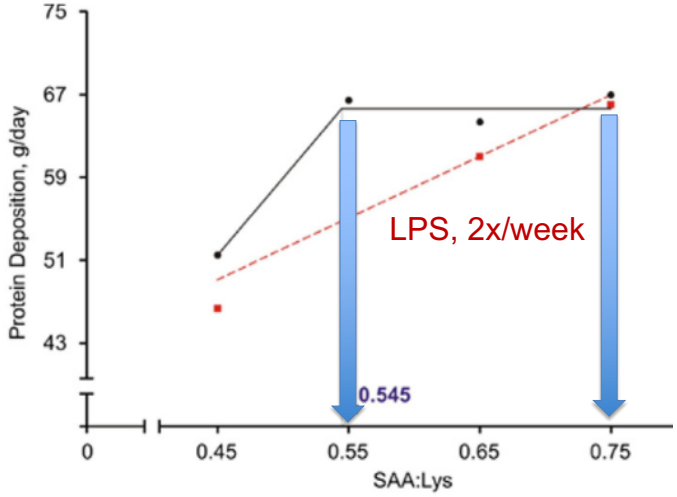
Inflammation may alter AA requirements

Growing pigs:



Kim et al., 2012

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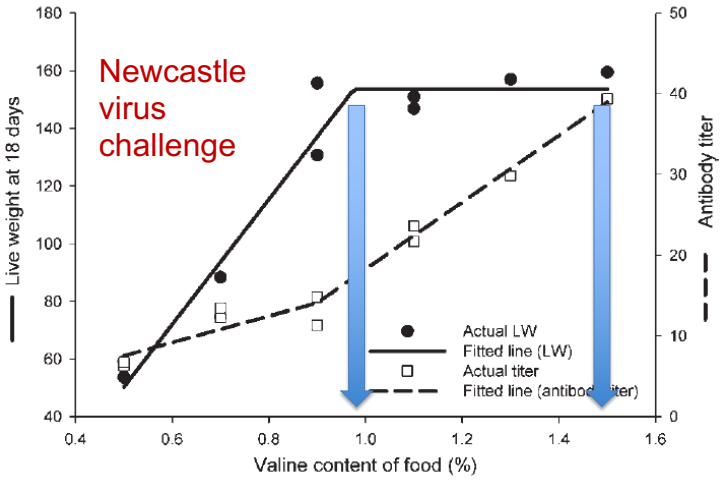
AA requirements may differ considering immunity

Growing chicks:



Sandberg et al., 2007 from Bhargava et al. 1970

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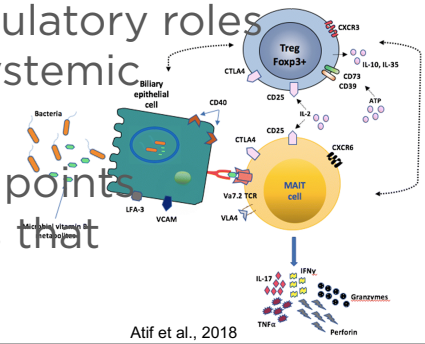
Overall conclusions

- Intrinsic metabolism seeks to understand how nutrient use influences immune cell phenotype and function
- Extrinsic metabolism explores regulatory roles of immune signals in tissue and systemic metabolism
- The interactions of these vantage points may point to nutritional strategies that improve resilience and efficiency of livestock



Atif et al., 2018

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