Mechanisms of Conjugated Linoleic Acid in Health and Disease

J. Bassaganya-Riera, DVM, PhD
Veterinary Medical Research Institute
Iowa State University
Outline

- Immune and anti-inflammatory effects
- Factors maximizing the immunological impact
- Controversy
- Potential Mechanisms
- Gaps in CLA research
CLA in Immune and Inflammatory Dysfunction

- Anti-inflammatory
  - TNF-α and nitric oxide are suppressed
  - IL-1 and IL-6 expression

- Enhances adaptive immune responses
  - IL-2 production
  - Numbers and effector functions of CD8^+ cells
Amelioration of Colonic Inflammation by CLA

H & E stained sections of porcine colonic tissue, × 63.
Immunological Mechanisms

- Modulation of cytokine expression
  - Down-modulation of T helper 2 cytokines
    - IL-10 and IL-4
  - Down-modulation of T helper 1 cytokines
    - IFN-γ and IL-12
  - Possible inhibition of helper T cell polarization

- Proliferative responses of T cells
Modulation of the T helper cell polarization

T helper 1 cytokines
- IFN-\( \gamma \)
- IL-12

T helper 2 cytokines
- IL-4
- IL-5
- IL-10

Dendritic Cells
Antigen-specific IFN-γ

Non-stimulated

ORF2-stimulated

CLA

Control
IFN-γ mRNA Expression

RT-PCR using RNA recovered from colonic lymph nodes
Immunological Benefits

- CLA fed early in life
  - Development of the immune system
- Requirement for a period of accumulation
  - Thymus size and composition at d 28
  - Numbers of peripheral lymphocytes at d 42
- Optimized in disease states
  - Autoimmune
  - Inflammatory
Dietary Regulation of Numbers of CD8⁺ lymphocytes

**Graph Description:**
- X-axis: Day
- Y-axis: TCR αβCD8 αβ cells/mL Blood ($\times 10^{-6}$)
- Two lines represent:
  - CLA Diet
  - Control Diet
- Days 20-80 are shown, with marked days showing significant differences.
- Significant differences indicated by asterisks (*).
Antigen-specific Proliferation of PBMC

Ex vivo Antigenic Stimulation

A  Control Diet

B  CLA-supplemented Diet

- Non-vaccinated
- B. hyodysenteriae
- Pseudorabies virus
- B. hyodysenteriae & Pseudorabies virus
Controversy

- Enhanced immune function
  - Animal models (mice, rats, and pigs)
  - In vitro (lymphocyte cultures)

- No effects
  - Human trial (Kelley et al., 2000)
  - CLA does not affect the immune status
  - Poor CLA source
Potential Explanations for the Immunological Effects of CLA

- **Endoplasmic Pathway**
  - Decreased eicosanoid synthesis

- **Nuclear Pathway**
  - Enhanced expression and activation of PPAR-γ
Endoplasmic Pathway

Linoleic Acid → Arachidonic Acid

- cPLA2
- S-LO FLAP
- 5-LO

COX1, COX2

- PGE2
- PGD2
- PGI2
- LTB4

CD4 + T cell

CLA

PMNN

Colonic Epithelial Cell

EP 4

B-LT2

EP 4
Endoplasmic Pathway

- CLA decreases eicosanoid production
- Eicosanoids
  - Modulate cytokine production
  - Involved in inflammation
  - Involved in cancer
Nuclear Pathway

- PPAR-\(\delta\)
- SMRT
- RXR tetramers
- NCoR

- PPAR-\(\gamma\)

mRNA transcription

- SRC1
- PBP
- 9-cis RA
- cis-9, trans-11 CLA
Nuclear Pathway

- CLA enhances PPAR-\(\gamma\) expression in vivo
- CLA enhances PPAR-\(\gamma\) activation in vitro
- Both known PPAR-\(\gamma\) agonists and CLA
  - Prevent mucosal inflammation
  - Similar modulation of cytokine production
  - Are anti-diabetic
  - Are anti-carcinogenic
Gaps in CLA research

- Poor mechanistic understanding in physiologically relevant models
  - Nuclear pathway
  - Endoplasmic pathway
  - Synergies and/or antagonisms

- Limited number of studies using specific isomers

- Limited number of human studies