Mechanisms of Regulation of Inflammation and Immunity by ABA

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Outline

- Background and introduction
- Mouse models
  - Insulin resistance and adipose tissue inflammation
  - Intestinal inflammation
  - Influenza virus-driven pulmonary inflammation
- Molecular mechanisms of action
  - Peroxisome proliferator activated receptor γ
 - Lanthionine synthetase C-like 2
- Future directions

ABA in Biomedicine

- – Generated through the carotenoid pathway

- – Produced in brain and immune cells

- – Secreted by pancreatic beta cells in response to hyperglycemia

- – Anti-inflammatory and immune modulatory
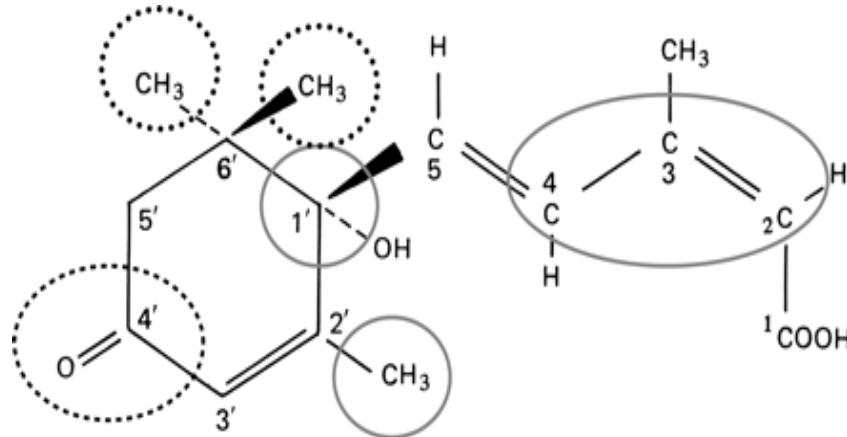
# Peroxisome Proliferator-Activated Receptor γ

- Regulates fatty acid storage and glucose metabolism

- Suppresses the expression of pro-inflammatory cytokines and chemokines

- Full agonists: Thiazolidinedione (TZD) class

- Side effects: hepatotoxicity (troglitazone); congestive heart failure (rosiglitazone); weight gain

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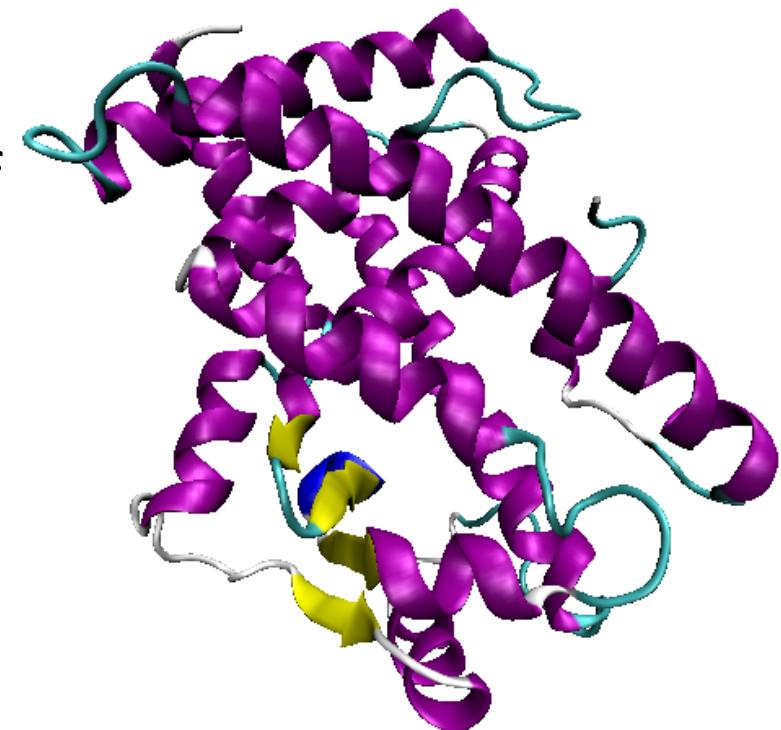
ABA Increases PPARγ Reporter Activity
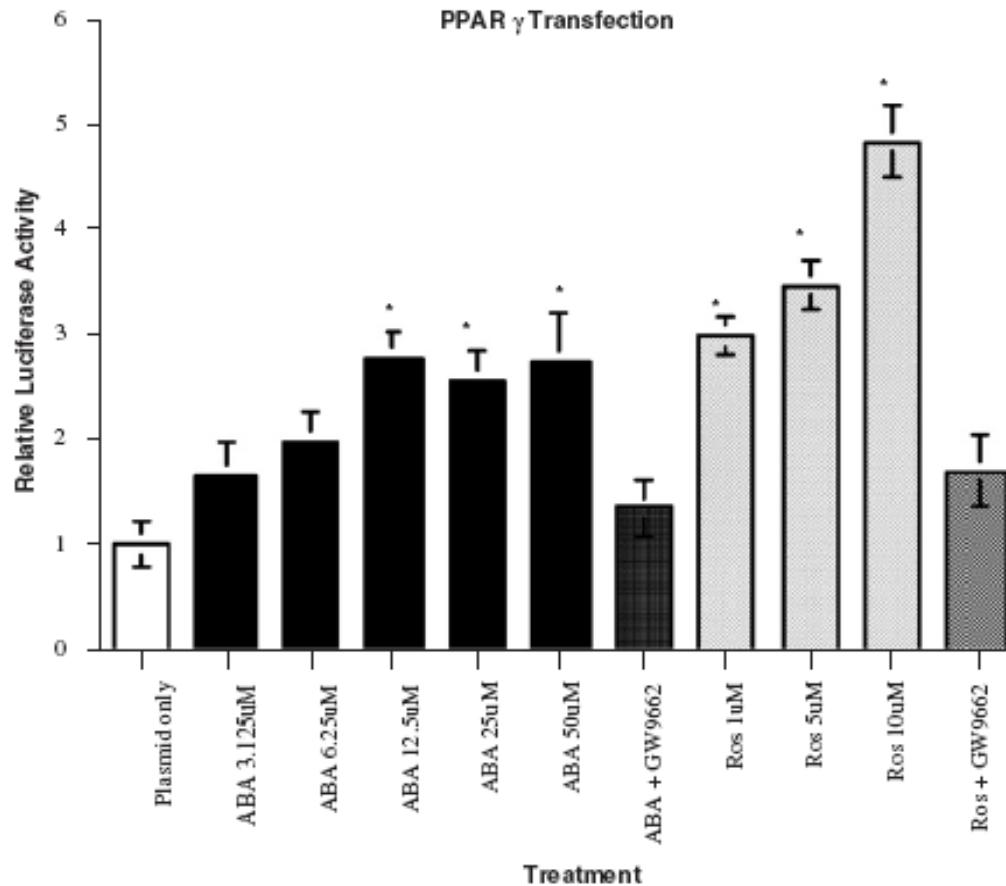
Metabolic Parameters
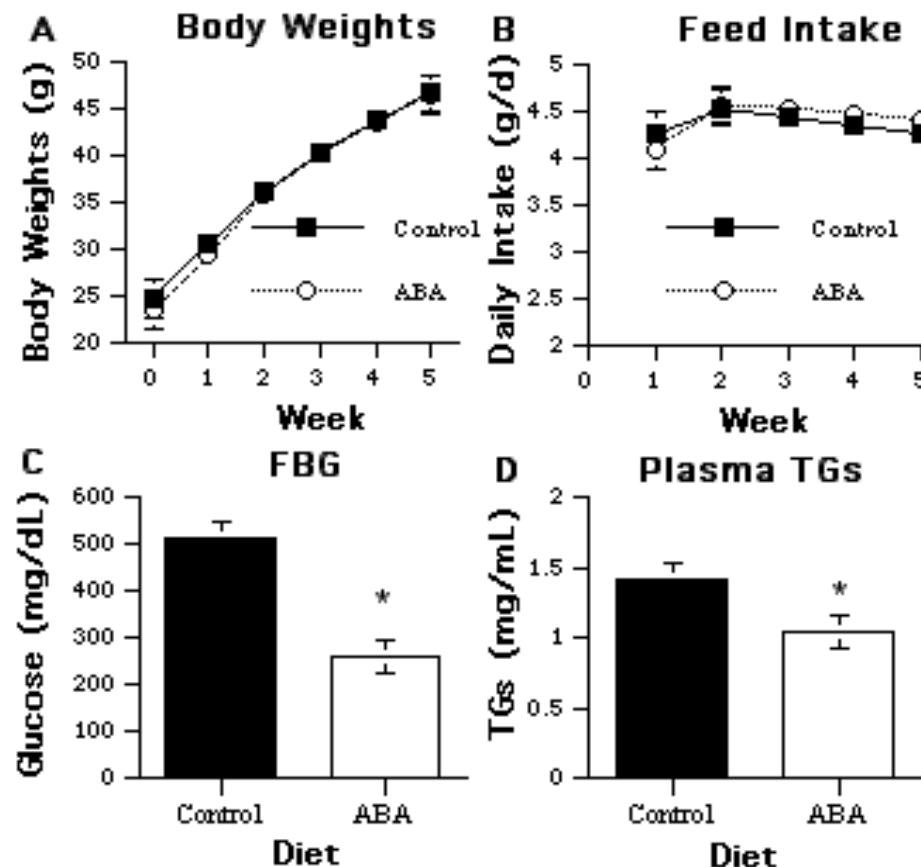
Glycemic Control and Diabetes

- ABA reduces glucose levels in diabetic mice equivalent to prescription Avandia without side effects

- Increased PPARγ and responsive genes

Glucose Tolerance Test

PPARγ Adiponectin aP2 CD36
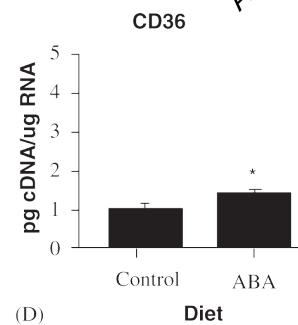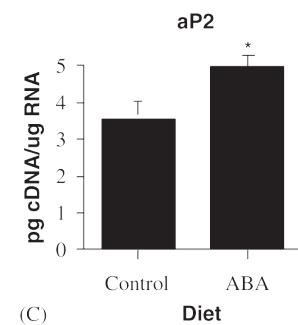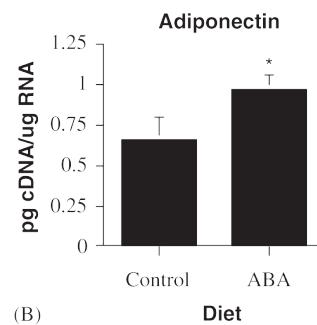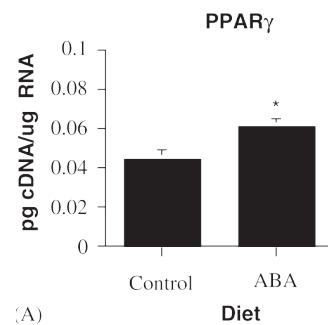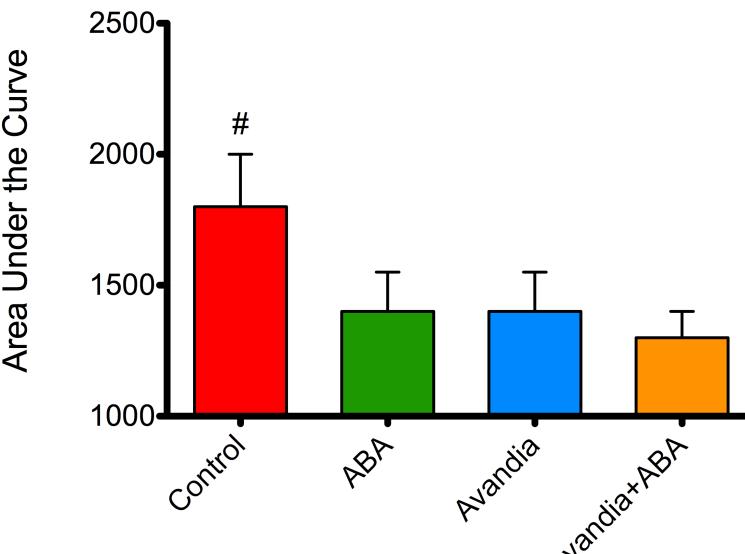
Adipose Tissue Inflammation

- ABA downregulates MCP-1 expression and reduces infiltration of macrophages into adipose tissue through a PPAR γ-dependent mechanism

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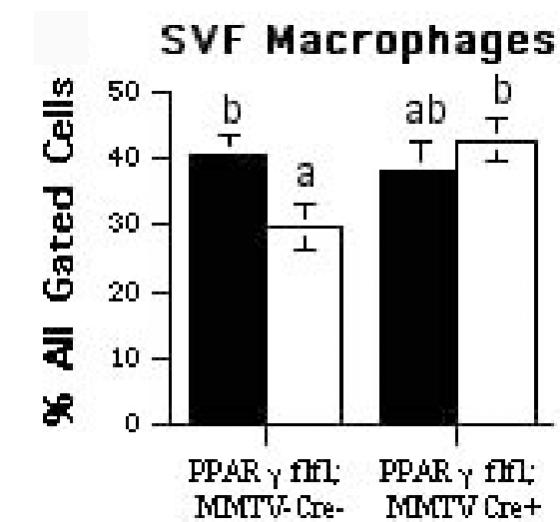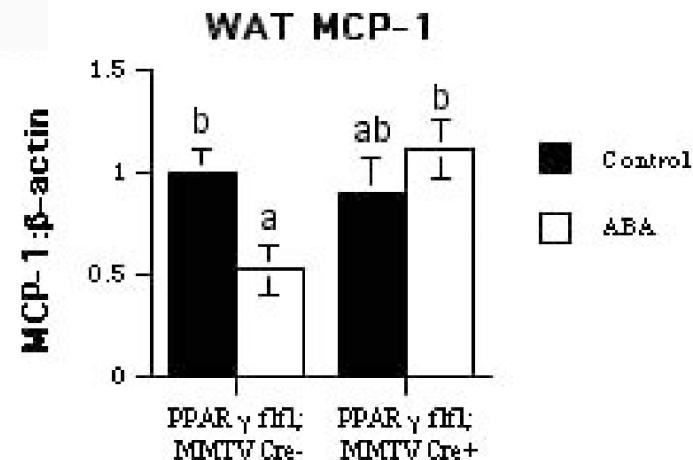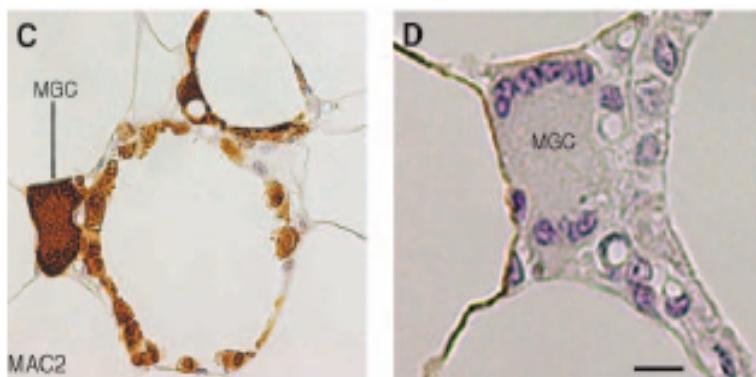
Modulation of Diabetes by ABA

- Induced transactivation of PPARγ in 3T3-L1 pre-adipocytes *in vitro*

- Upregulated PPARγ and its responsive genes

- Decreased fasting blood glucose concentrations, ameliorated glucose tolerance

- Attenuated adipocyte hypertrophy, TNF-α and MCP-1 expression, and macrophage infiltration in WAT through PPARγ

Health vs. Disease

- Microbiome
- Diet
- Inflammation & Immunity
- Genes RNA Proteins

UNTREATED — Greater Microbial Diversity

PROBIOTIC TREATED — Lower Microbial Diversity

Local CLA production

INCREASED COLITIS

DECREASED COLITIS

Macrophage Activated PPARγ

Firmicutes

Family
Lachnospiraceae
Incertae-Sedis-XIV
Erysipelotrichaceae
Veillonellaceae
Ruminococcaceae
Clostridiaceae
Other
Eubacteriaceae
Incertae-Cedis-XIII
Porphyromonadaceae
Peptostreptococcaceae
Prevotellaceae
Enterococcaceae
Streptococcaceae
Rikenellaceae
Bacteroidaceae
Alcaligenaceae
Coriobacteriaceae
Pasteurellaceae
Enterobacteriaceae

IBS Children
Healthy Children

Verrucomicrobia
Actinobacteria
Proteobacteria (Gammaproteobacteria)
Bacteroidetes

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# Inflammatory Bowel Disease

- Chronic immunoinflammatory illness
- Afflicting over 1,200,000 in North America
- Two clinical manifestations
  - Crohn's Disease
  - Ulcerative Colitis
- Current therapies are modestly successful and with significant side effects (steroids/NSAIDs)
 - Immunosuppression and delayed wound healing

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Mucosal Immune System

Kunisawa et al., Trends in Immunol (2008)
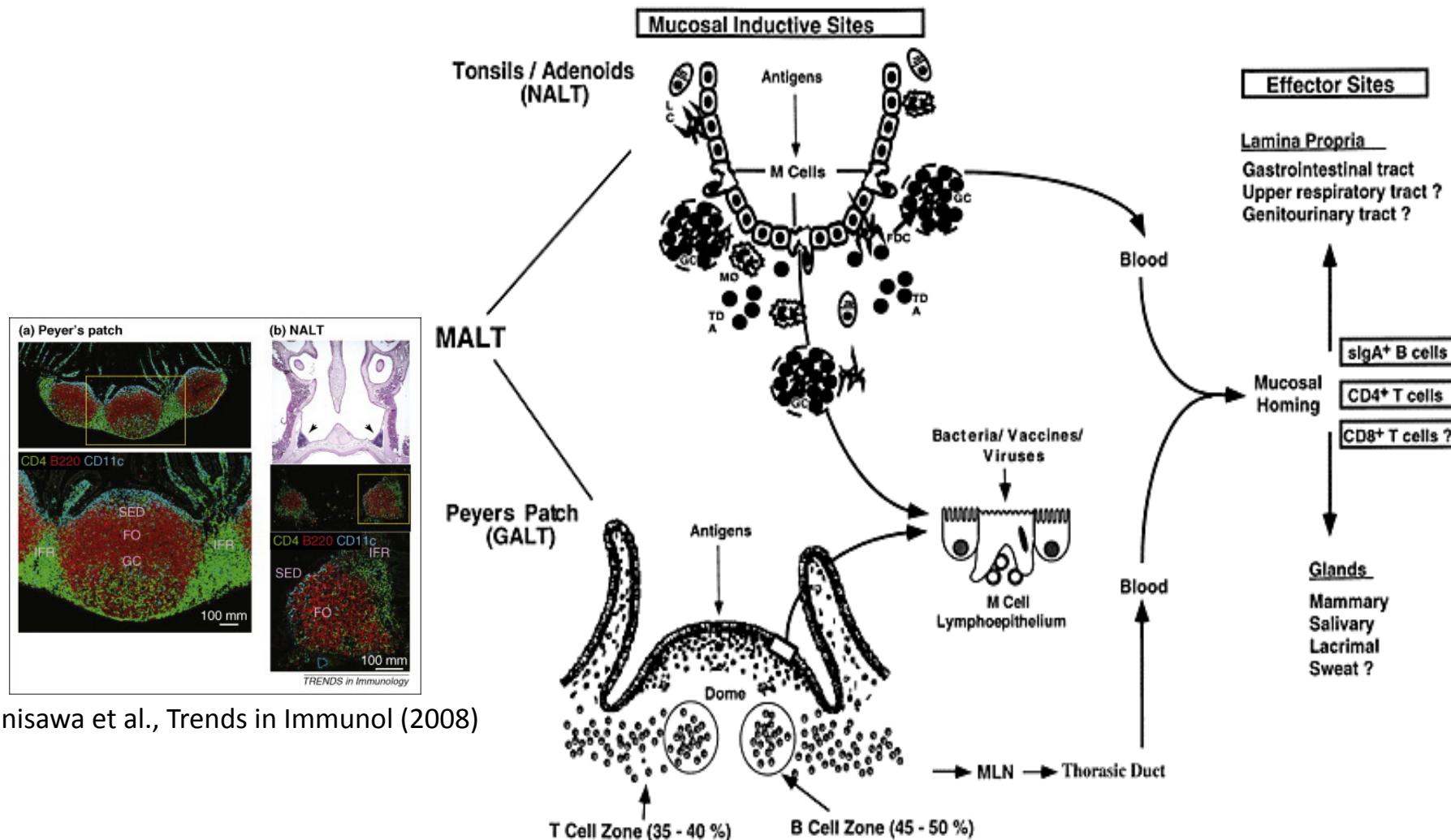
Effector and Regulatory Pathways

No DSS   DSS

Control

ABA

E   Epithelial Erosion

F   Mucosal Thickening

G   Lymphocyte Infiltration

no DSS
DSS

Score

Control   ABA
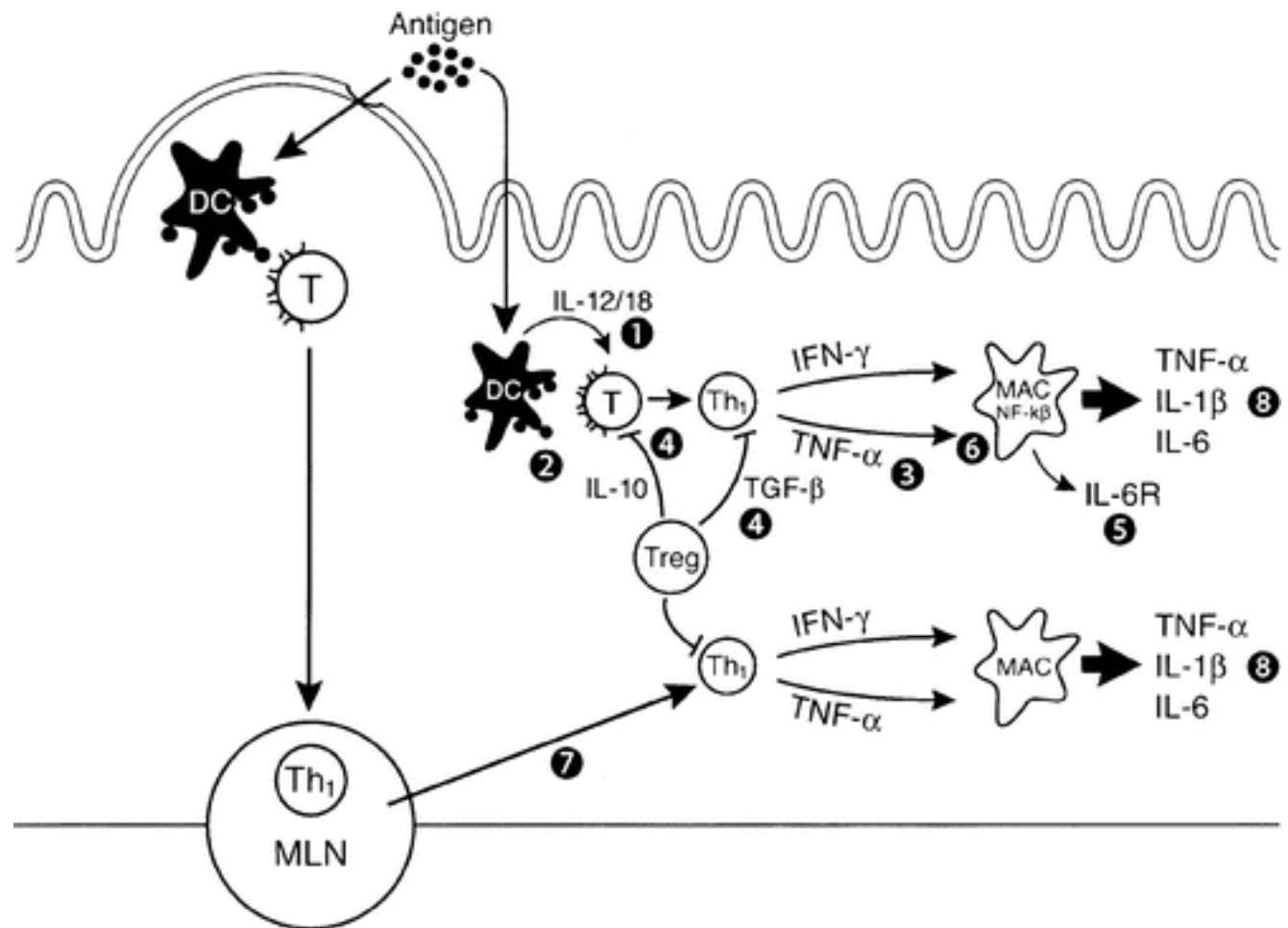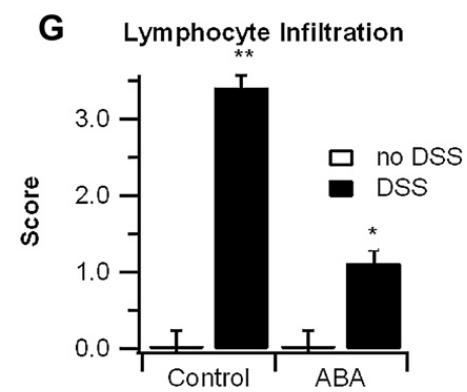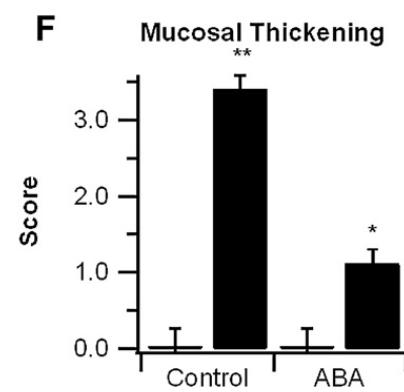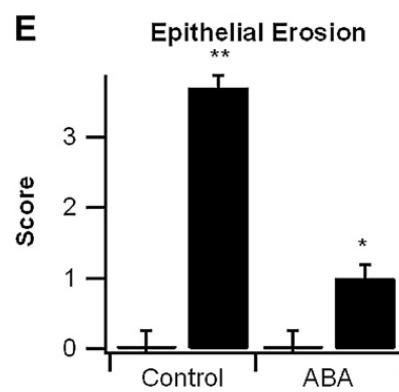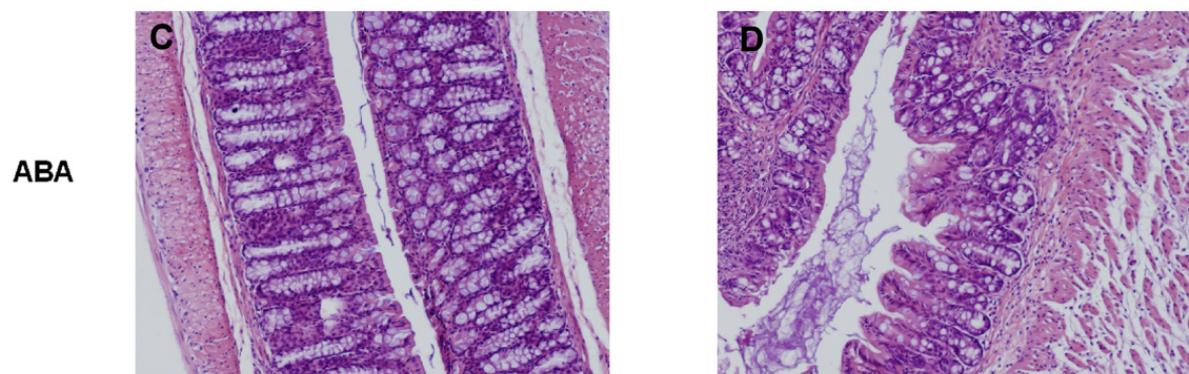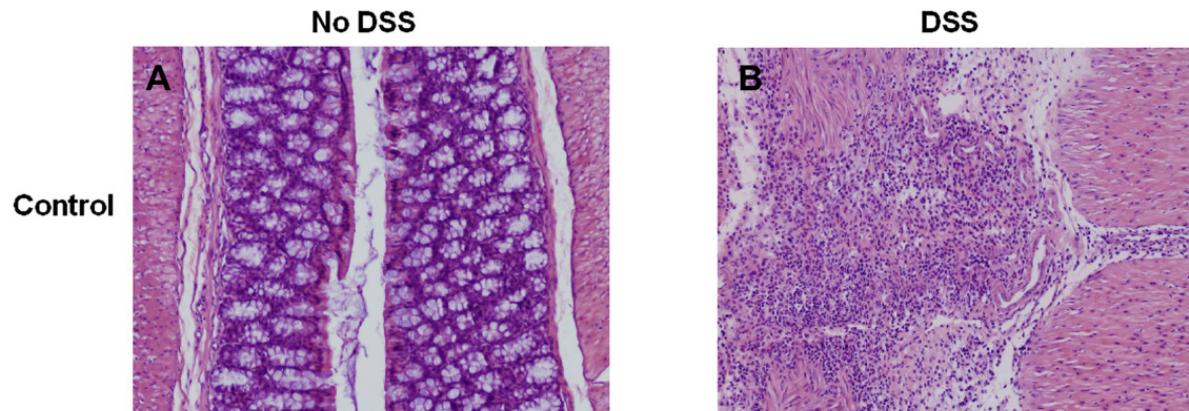
Regulation of Mucosal Treg cells by ABA
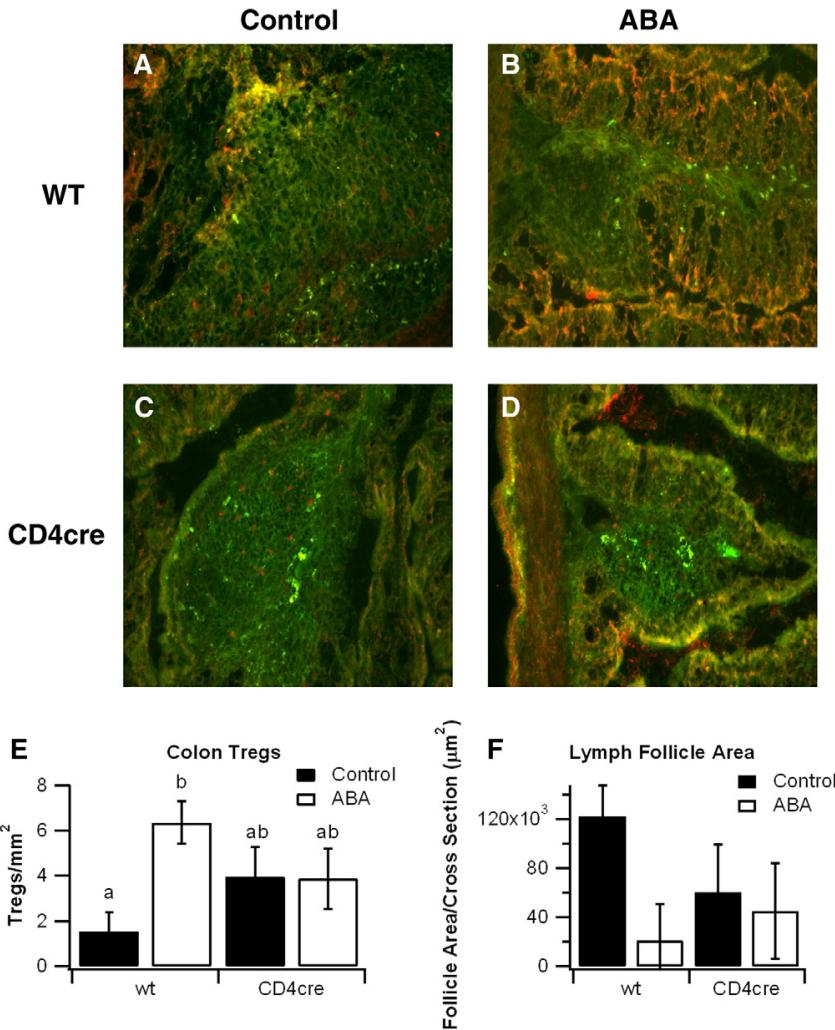
- Ameliorated experimental IBD by enhancing regulatory T cell accumulation in the colonic lamina propria through a PPARγ-dependent mechanism

Colonic Adhesion Molecule Expression
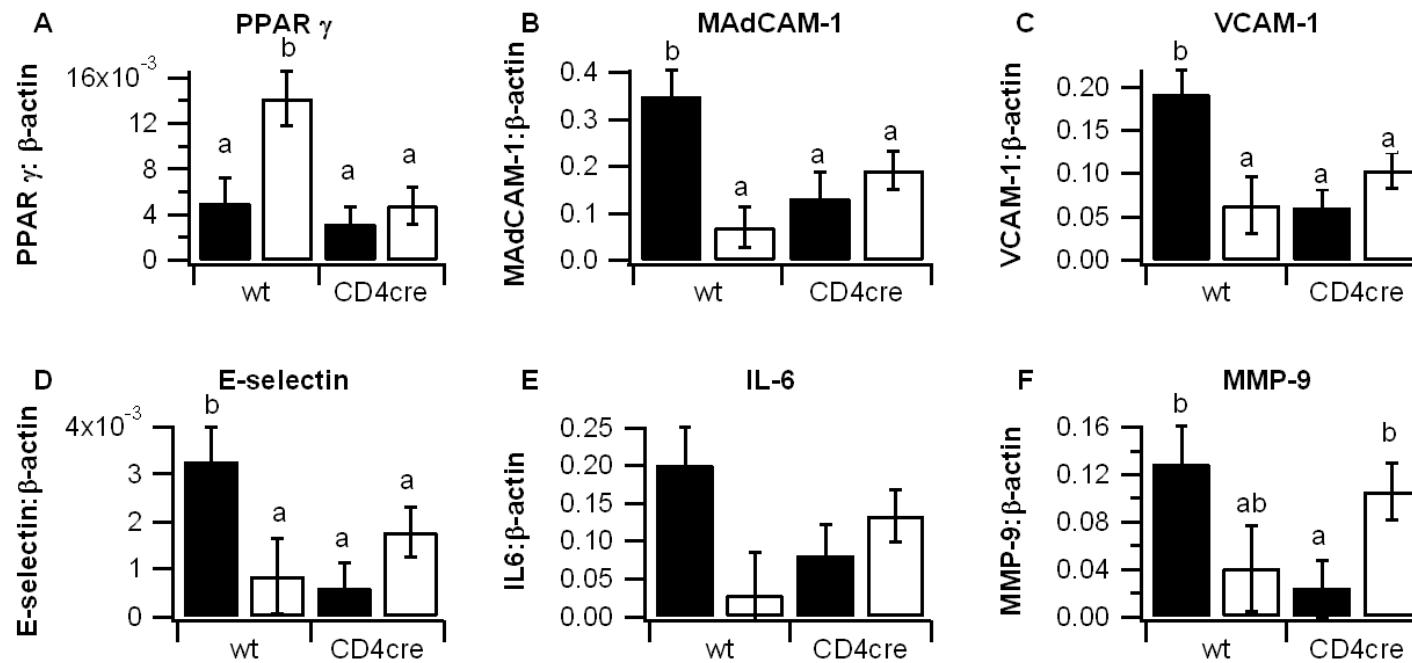
Modulation of Colitis by ABA

- ABA ameliorated gut inflammation by modulating T cell distribution and adhesion molecule expression
  - Decreased colonic inflammatory lesions
  - Increased Treg cells at the mucosal sites
 - Downregulated adhesion molecules and inflammatory cytokine expression
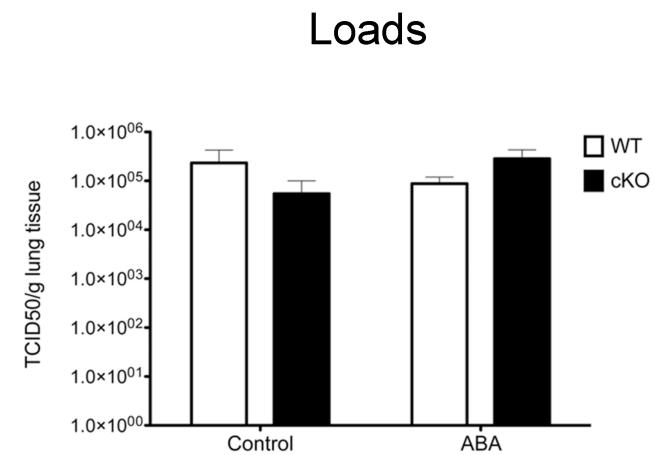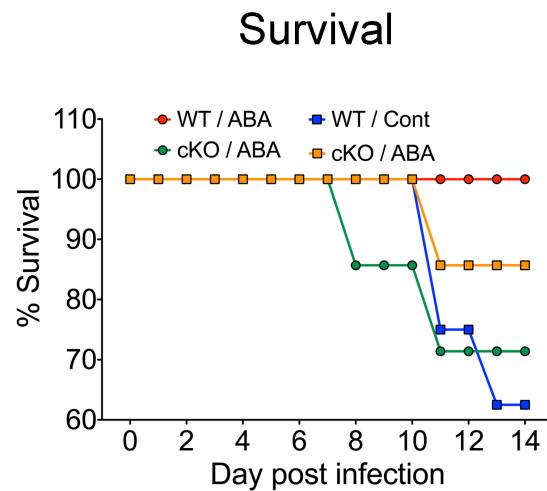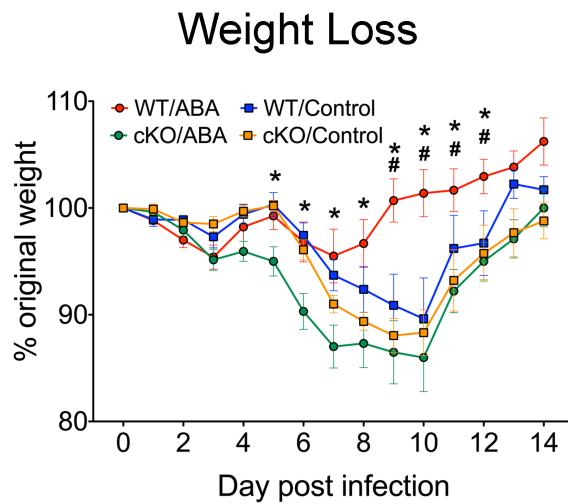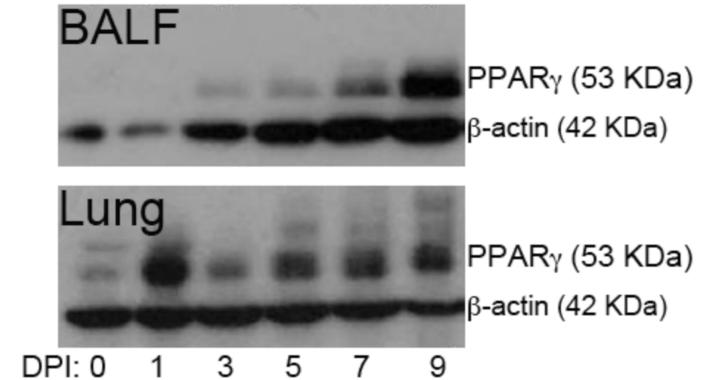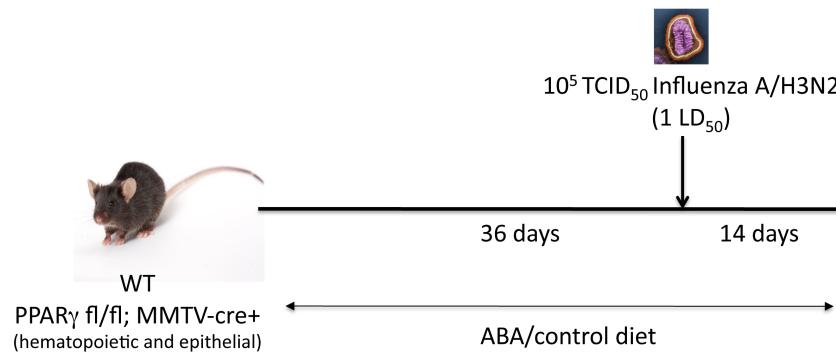
Modulation Influenza by ABA

Modulation Influenza by ABA

Clinical Immunology Volume 144, Issue 1 2012 57 - 69
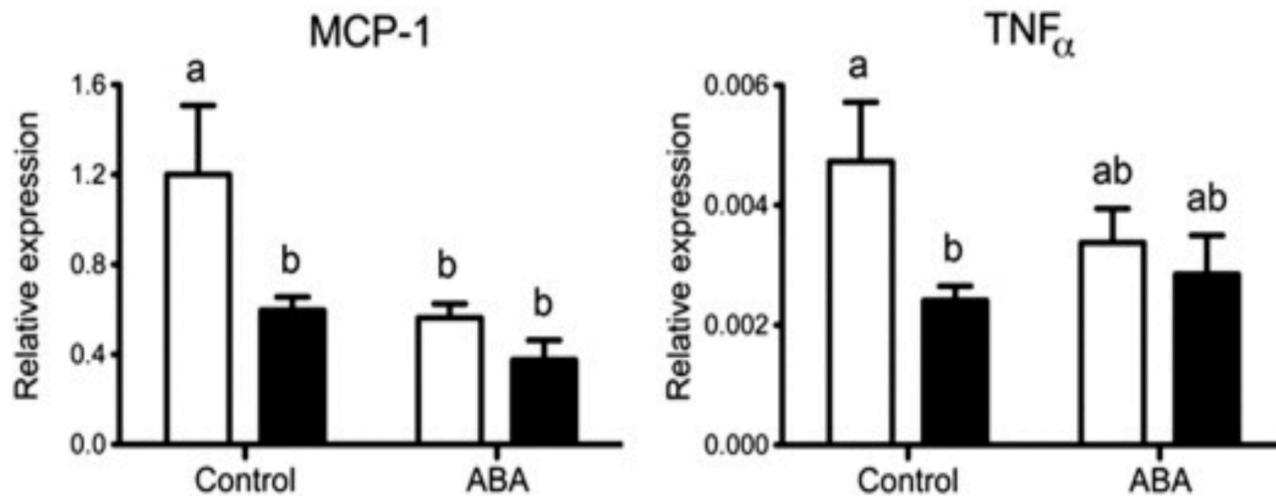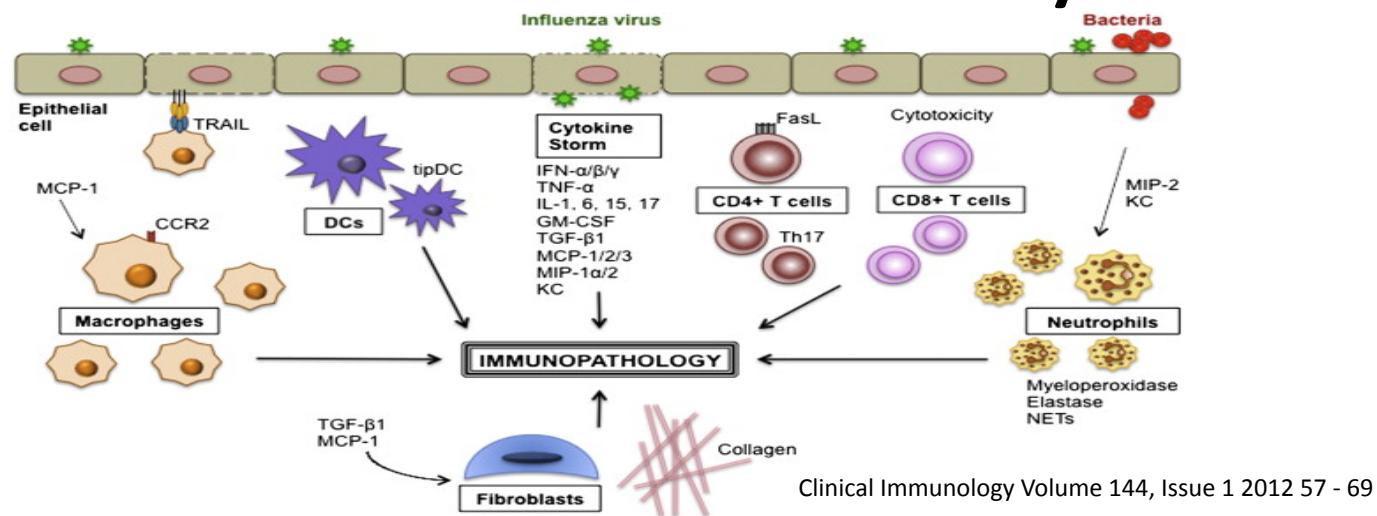
Modulation Influenza by ABA
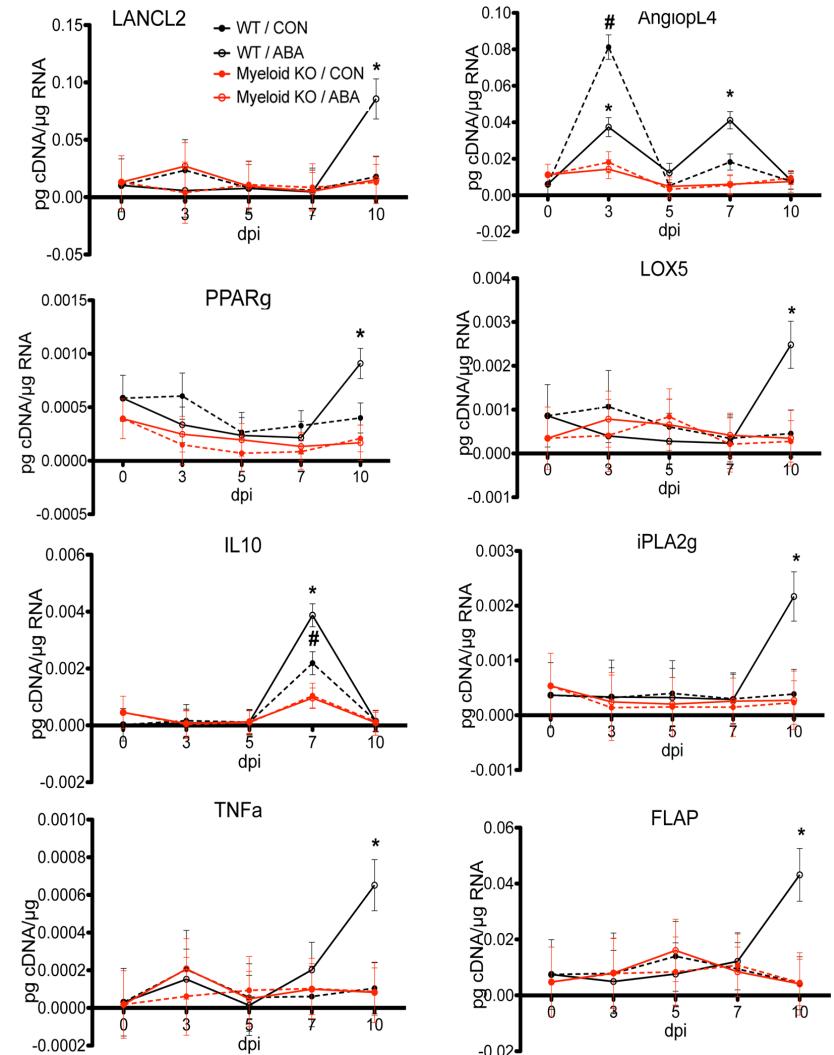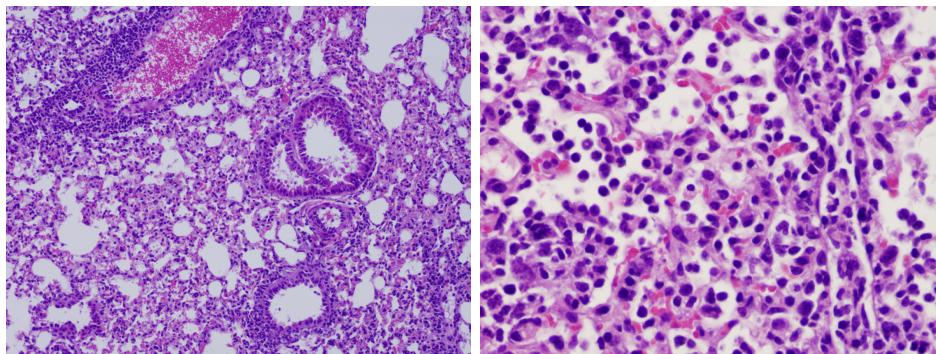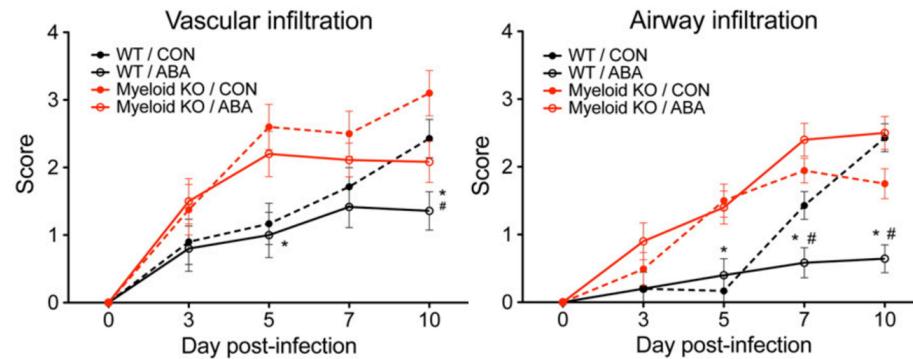
ABA ameliorated influenza-virus-induced pathology by activating PPARγ in pulmonary immune cells, suppressing initial proinflammatory responses and promoting resolution

Molecular Mechanisms of Action

- ABA activates PPARγ in preadipocytes and macrophages
- ABA upregulates PPARγ in WAT, colon and lungs
- PPARγ mediates ABA's immune modulatory effects
- Does ABA bind to PPARγ?
- Are there other molecular targets for ABA in mice and humans?

In vitro effects of ABA isomers
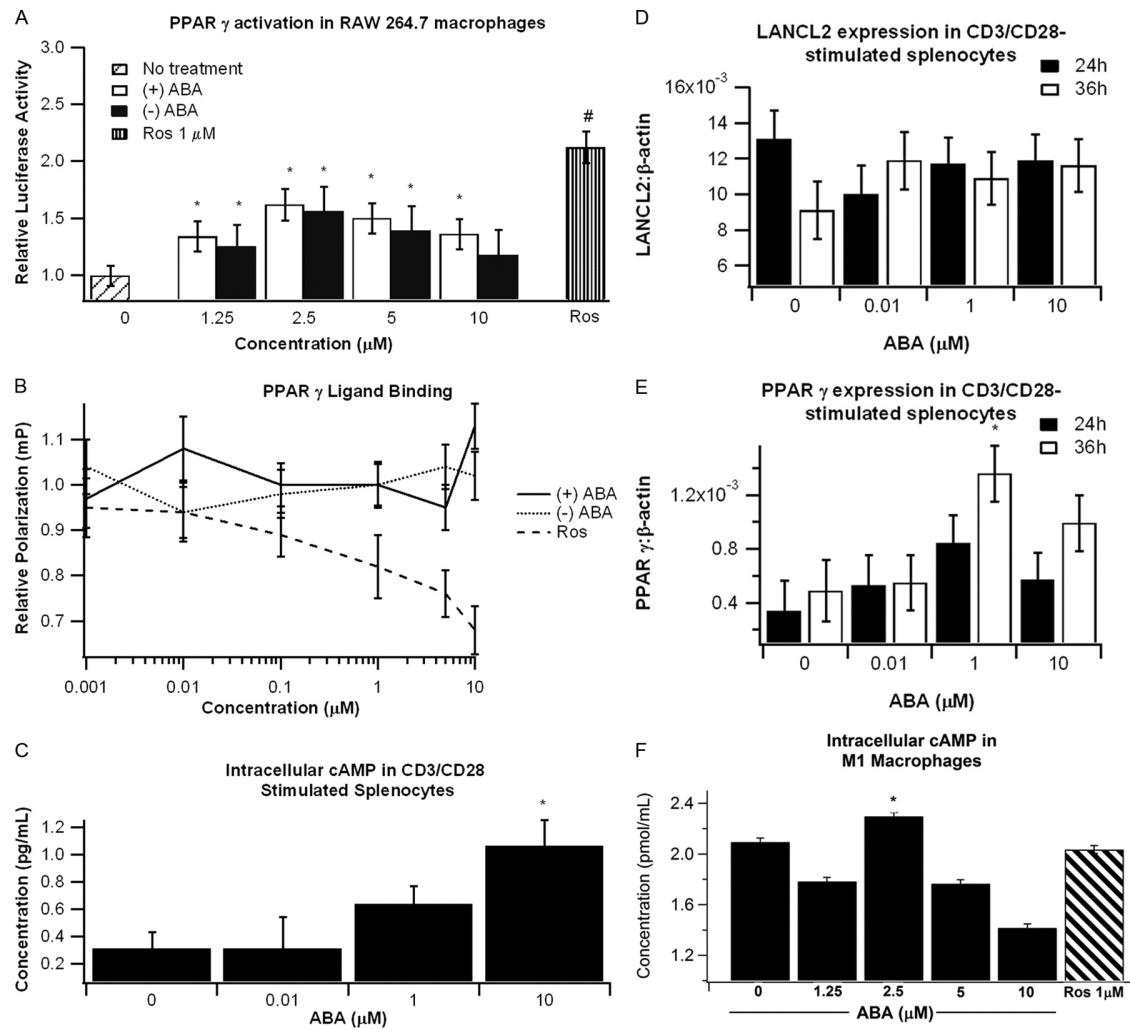
Lanthionine synthetase component C-like protein 2

- First identified in human brain and testis

- Increased cellular sensitivity to adriamycin

- Associated with the plasma membrane

- Structure predicted by homology modeling

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LANCL2 disruption on PPAR γ activation
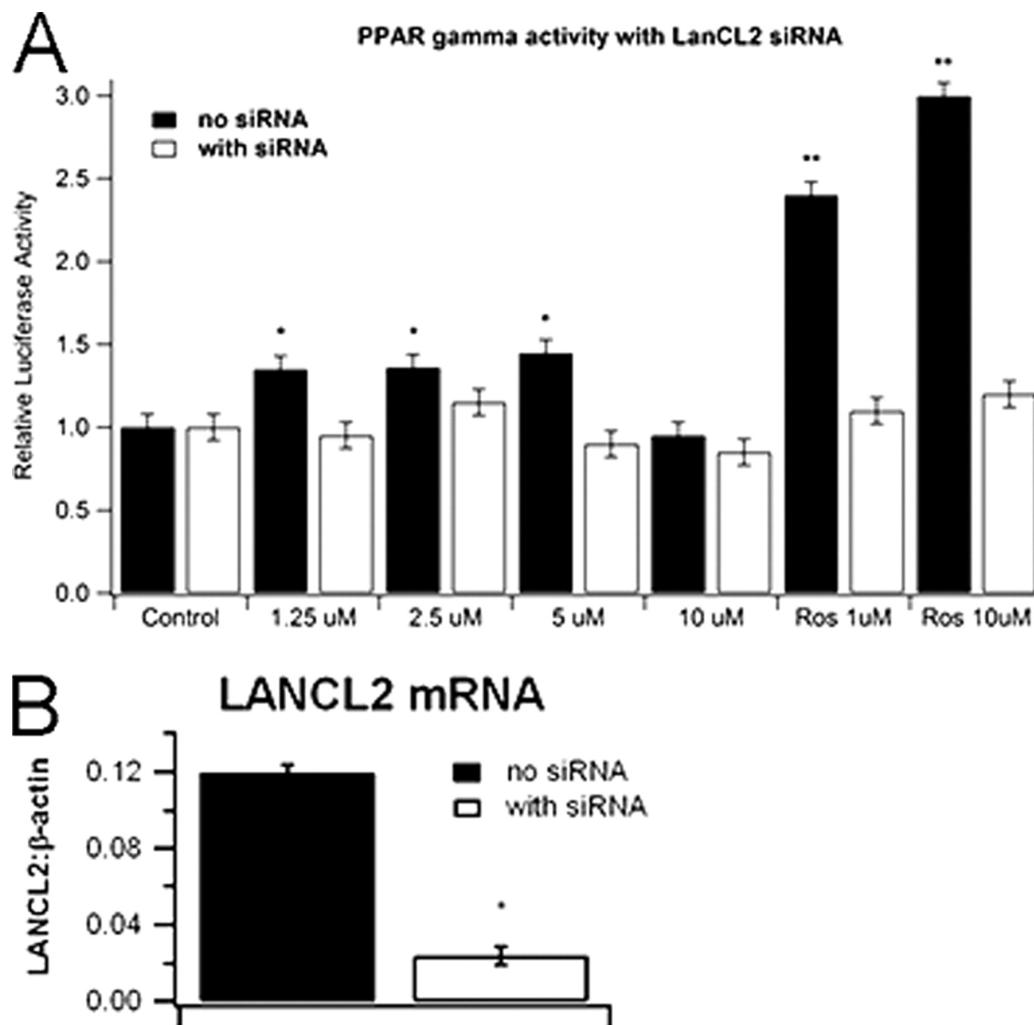
Molecular Mechanisms of Action

- Increased PPARγ reporter activity in RAW 264.7 macrophages, adipocytes and mouse tissues

- ABA does not bind to PPARγ

- Predicted binding of ABA to LANCL2 in silico

- Activation of PPARγ by ABA requires LANCL2 expression

- Activation of cAMP accumulation in lymphocytes

LANCL2 Pathway

Acknowledgements

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