nature medicine

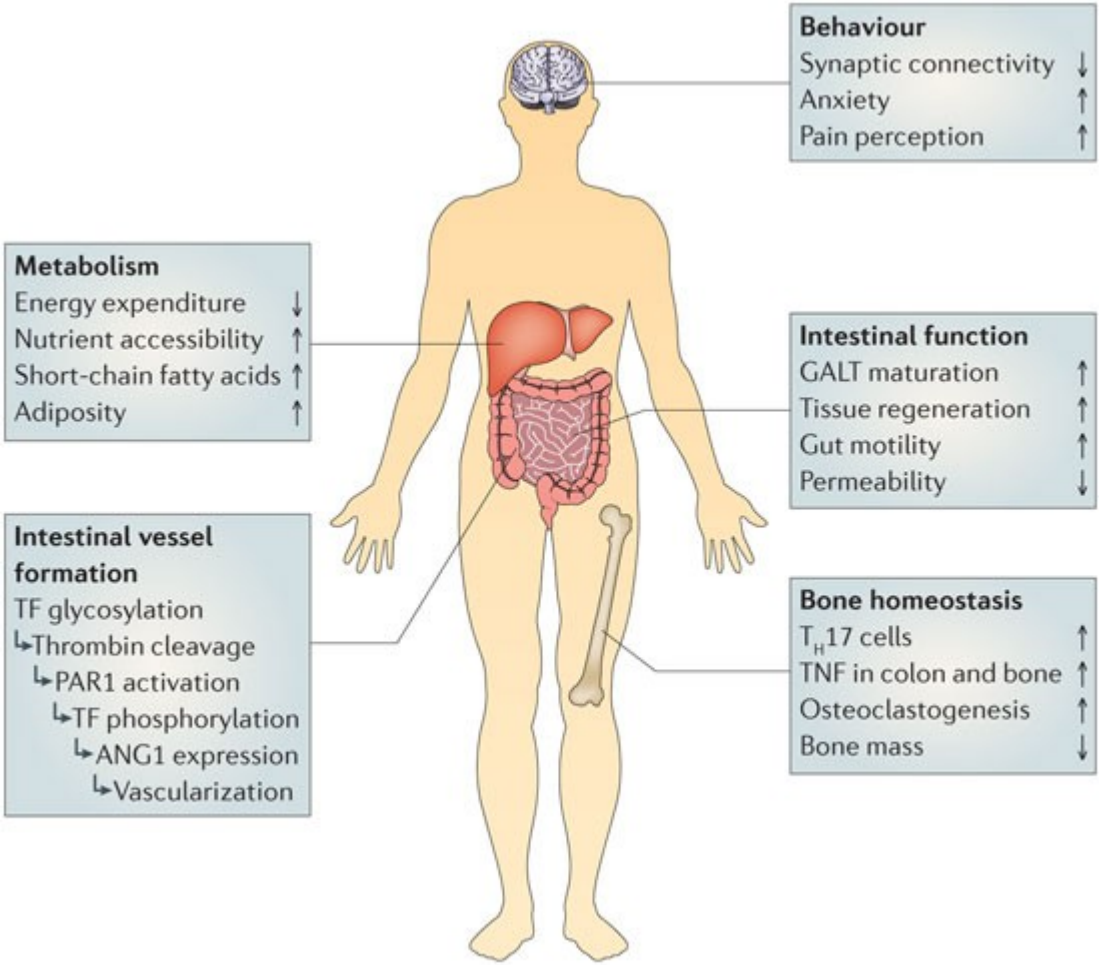
Gut Microbiota Metabolism of Dietary Fiber Influences Allergic Airway Disease and Hematopoiesis

Jenn Hou

Burke Group Literature Seminar

3.21.15

Impact of Host-Microbe Mutualism on Human Physiology



- Home to 100 trillion microbes
- 10X more intestinal bacterial cells than human cells
- "Forgotten organ" on par with functional capacity of the liver
- Protection against pathogenic bacteria
- Affect organ development, health of immune system, and metabolism
- Anaerobic digestion of cellulose and hemicellulose
- **Degradation of polysaccharides into short chain fatty acids (SCFA).**
- Generation of vitamin K, biotin, thiamine, etc.
- Affected by lifestyle, hygiene, and diet

Backhed F *et al.* (2005) Host-bacterial mutualism in the human intestine. *Science.* 307: 1915-1920.
LeBlanc JG *et al.* (2013) Bacteria as vitamin supplies to their host: a gut microbe perspective. *Current Opinion Biotechnology.* 24: 160-168.
Sommer F and Backhed F (2013) The gut microbiota- masters of host development and physiology. *Nature Reviews*. 11: 227-238.

EDITORIAL

GUT MICROBIOTA

Married to our gut microbiota

The gut microbiota — masters of host development and physiology

Felix Sommer[1,2] and Fredrik Bäckhed[1,2,3]

The Impact of the Gut Microbiota on Human Health: An Integrative View

Jose C. Clemente,[1] Luke K. Ursell,[1] Laura Wegener Parfrey,[1] and Rob Knight[1,2,*]

The role of the gut microbiota in nutrition and health

Harry J. Flint, Karen P. Scott, Petra Louis and Sylvia H. Duncan

Shifting the balance: antibiotic effects on host–microbiota mutualism

Benjamin P. Willing[§], Shannon L. Russell*[‡§] and B. Brett Finlay*[‡]*

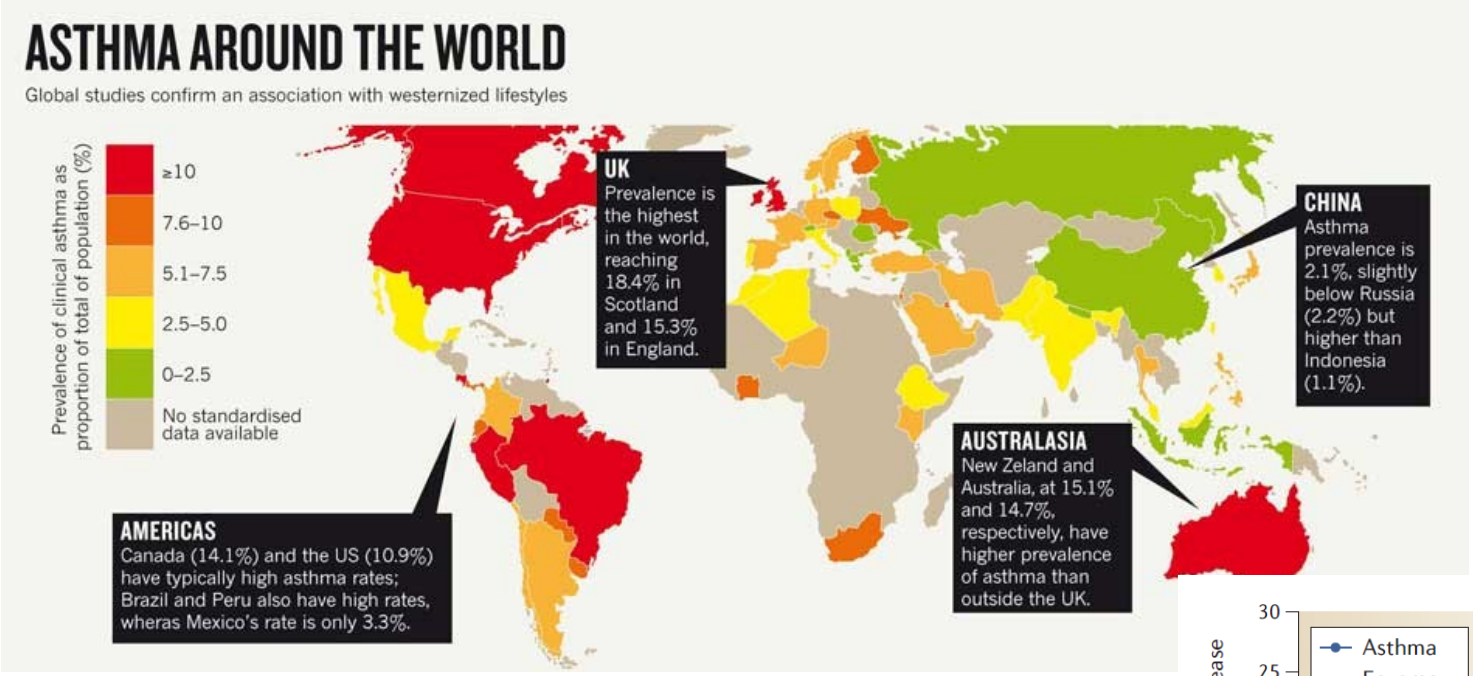
REVIEW

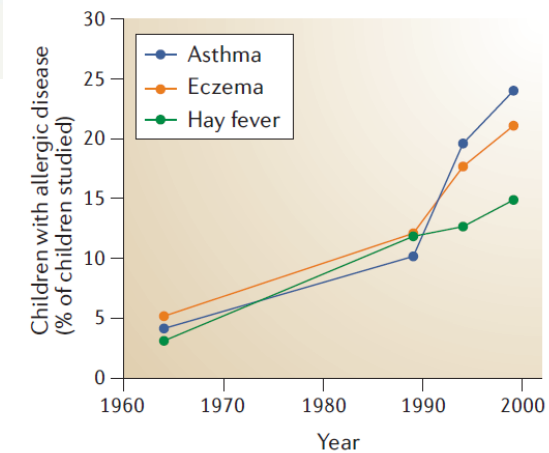
Host-Bacterial Mutualism in the Human Intestine

Fredrik Bäckhed,* Ruth E. Ley,* Justin L. Sonnenburg, Daniel A. Peterson, Jeffrey I. Gordon†

How does the gut microbiota and the metabolites it generates impact the health of peripheral organs?

Developed Countries Show Increased Prevalence of Allergic Asthma

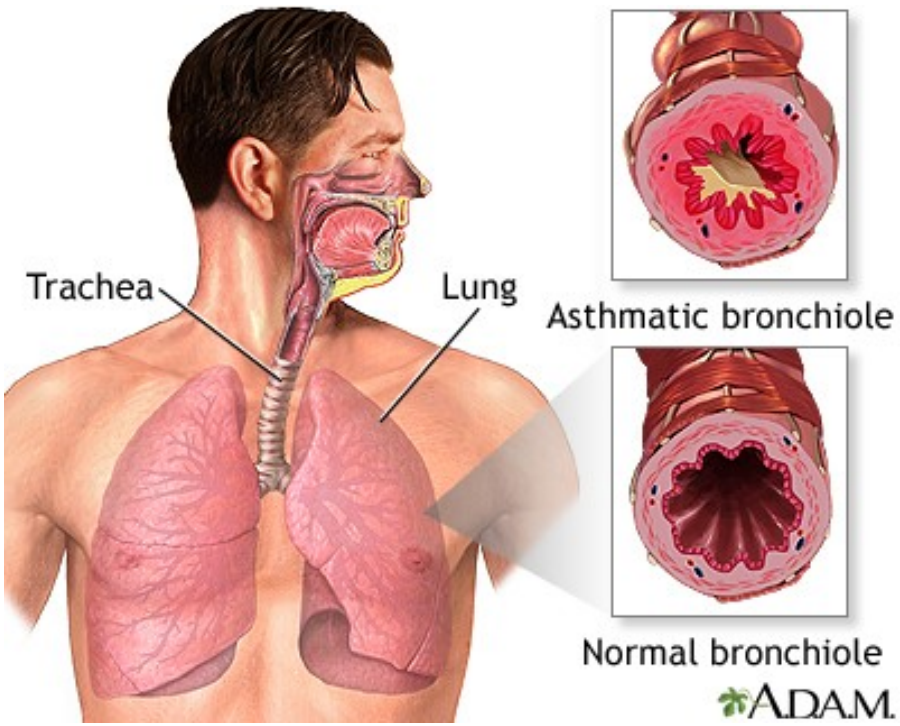




- Rise in allergic and asthma disease since the 1960s
- Hypothesized causes for increased allergy and asthma cases
  - House dust mite (HDM)
  - Less contact with microbes (increased hygiene)
  - Less physical activity
  - **Changes in Western diet (highly processed)**

Devereux G (2006) The increase in the prevalence of asthma and allergy: food for thought. *Nature Reviews Immunology.* 6: 869-870.
Graham-Rowe D (2011) When allergies go west. *Nature*. 479: S2-S4.

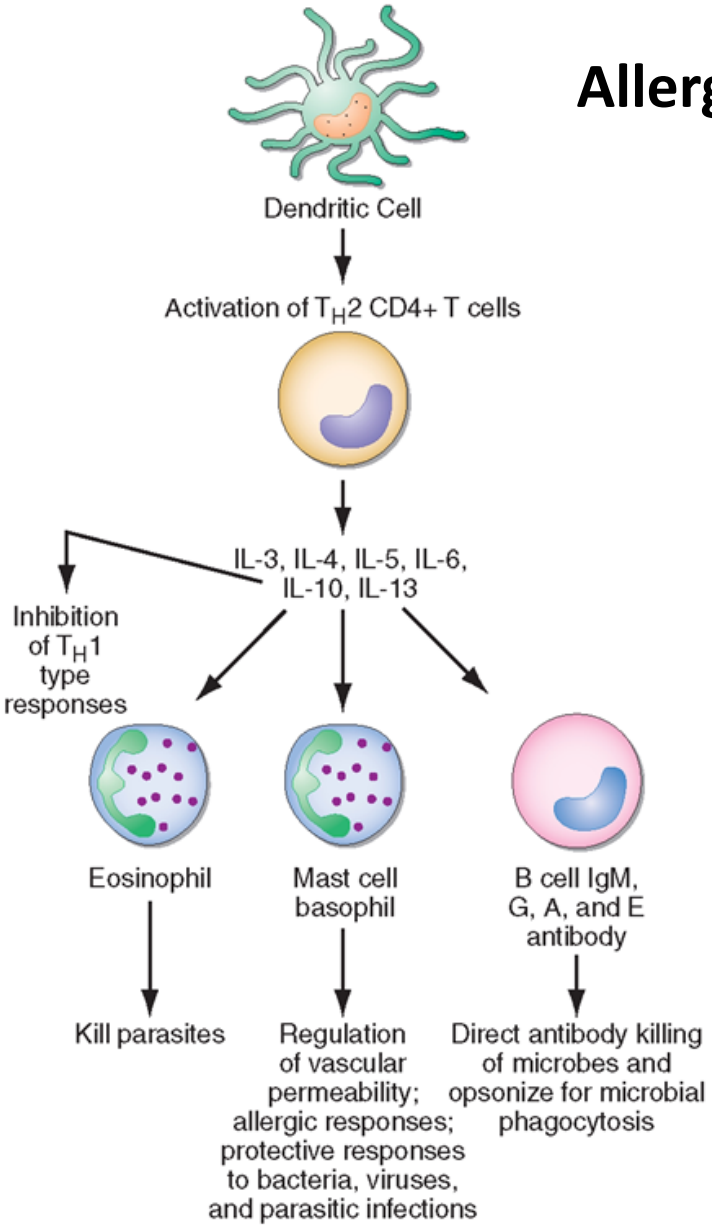
Prevalence and Pathophysiology of Asthma

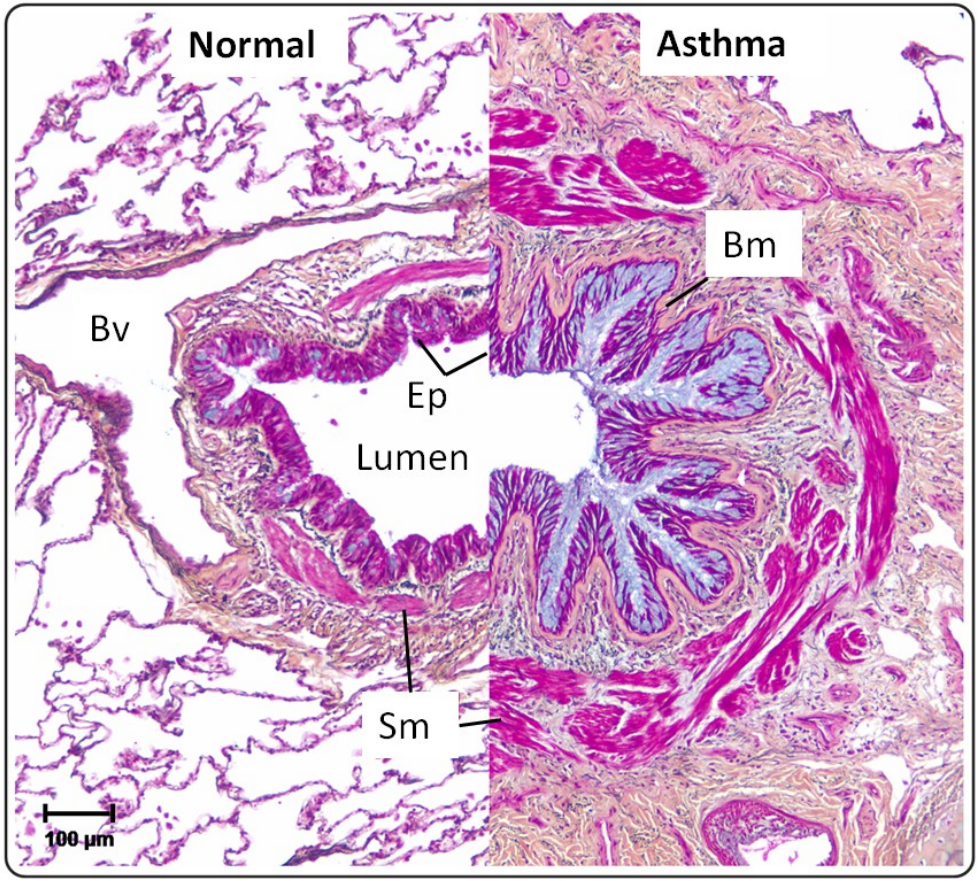


- 300 million people world wide
- Allergic asthma
- Chronic inflammation
    - Breathlessness, coughing, wheezing, tightness of chest
- Mediated by T helper type 2 immune response
    - Cytokines (IL-4, IL-5, IL-9, IL-13)
- Current therapeutic options:
    - Adrenergic bronchodialator
    - Anti-inflammatory drugs

Management of Noncommunicable Diseases Department (2002) Prevention of allergy and allergic asthma. *World Health Organization.* 1-14.
Torgerson DG *et al.* Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nature Genetics.* 43: 887-892.
http://www.newcastle-hospitals.org.uk/services/cardiothoracic_wards-and-clinics_lung-function-department-freeman-hospital.aspx
https://www.aafa.org/display.cfm?id=8&sub=16
http://www.aaaai.org/about-the-aaaai/newsroom/asthma-statistics.aspx

Allergic Hypersensitivity: Pathophysiology of Asthma





Histology of Airway: BV= Blood vessel, **Ep=** Epithelium, **Bm=** Basement membrane, **Sm=** Smooth muscle

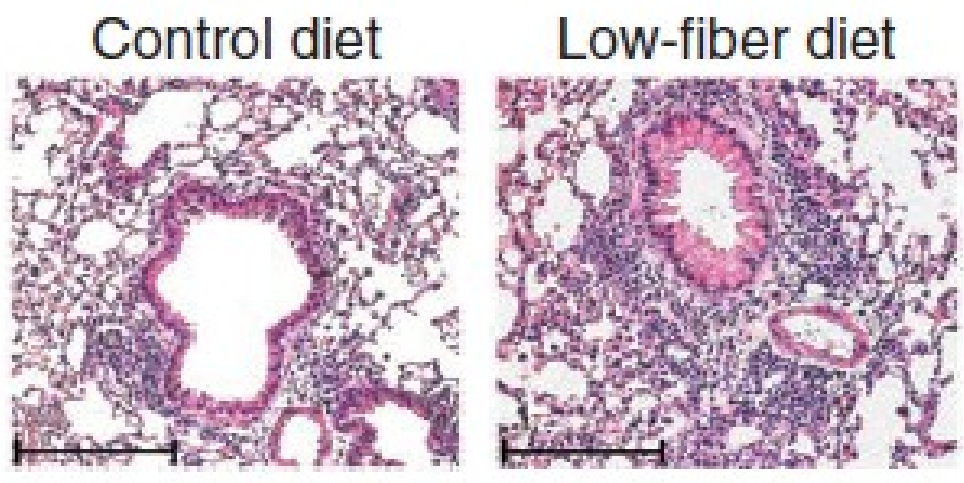
http://what-when-how.com/rheumatology/introduction-to-the-immune-system-the-immune-system-in-health-and-disease-rheumatology-part-3/
http://www.intechopen.com/books/carbohydrates-comprehensive-studies-on-glycobiology-and-glycotechnology/il-13-asthma-and-glycosylation-in-airway-epithelial-repair

Key Questions and Central Hypothesis

- How does dietary fiber affect the health of the gut microbiota and of the human host?
- Could dietary fiber have a beneficial role in other tissues including the lungs?
- **Hypothesis: Increased dietary fiber impacts the composition of gut microbiota; generation of byproducts diminishes the immune response and ameliorates allergic airway inflammation.**

http://www.nytimes.com/2013/07/23/science/allergies-in-the-time-of-research.html?_r=0
http://www.medicalnewstoday.com/articles/270827.php

Mice Fed on Low Fiber Diet Showed Increased Allergic Airway Inflammation

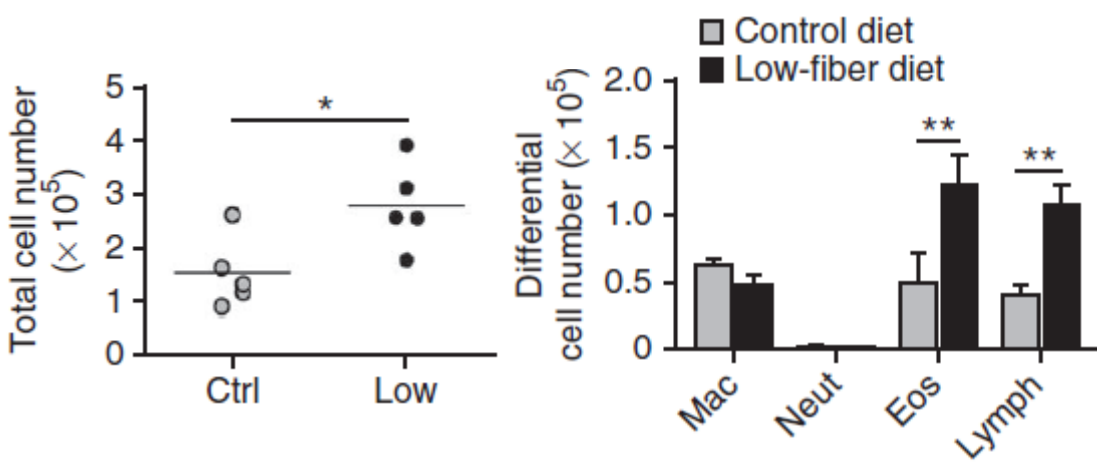


Method: Adult Mice Fed

- Control diet (4% fiber)
- Low fiber (<0.3%)
- Internasal administration of house dust mite

Result:

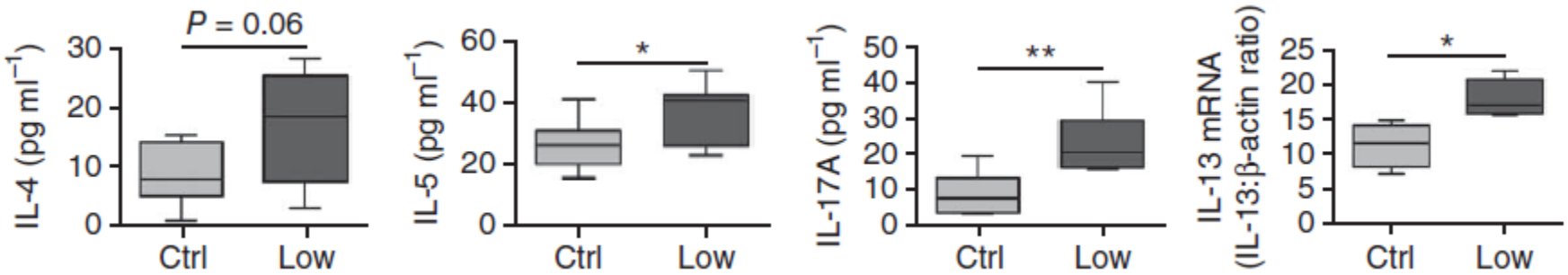
- **Observed infiltration of inflammatory cells in low-fiber diet mice**



Results:

- **Quantified increase in inflammatory cells**
- **Mostly eosinophils and lymphocytes**

Mice Fed on Low Fiber Diet Showed Increased Allergic Airway Inflammation



- **IL 4:** Induces B cells to class switch from making IgM to IgE antibody
- IgE triggers mast cell degranulation (histamine and leukotrienes)

- **IL-5 :** turns on eosinophils

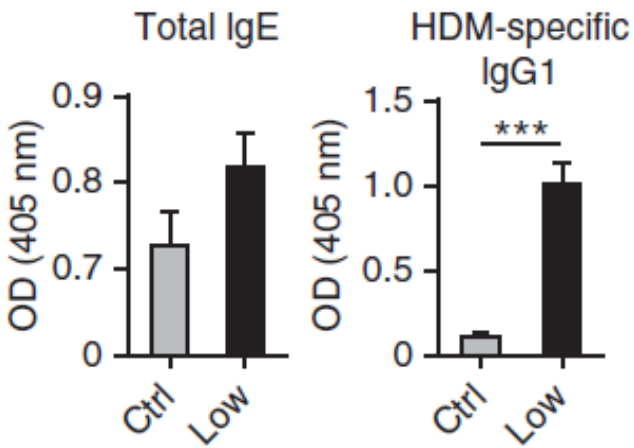
- **IL-17A :** promotes neutrophil migration, part of mucosal immunity

- **IL-13 :** promotes IgE release from B cells

Result:
- **Observed increased release of cytokines: IL-4, IL-5, IL-17A, IL-13**

Mice Fed on Low Fiber Diet Showed Increased Allergic Airway Inflammation

Serum Levels

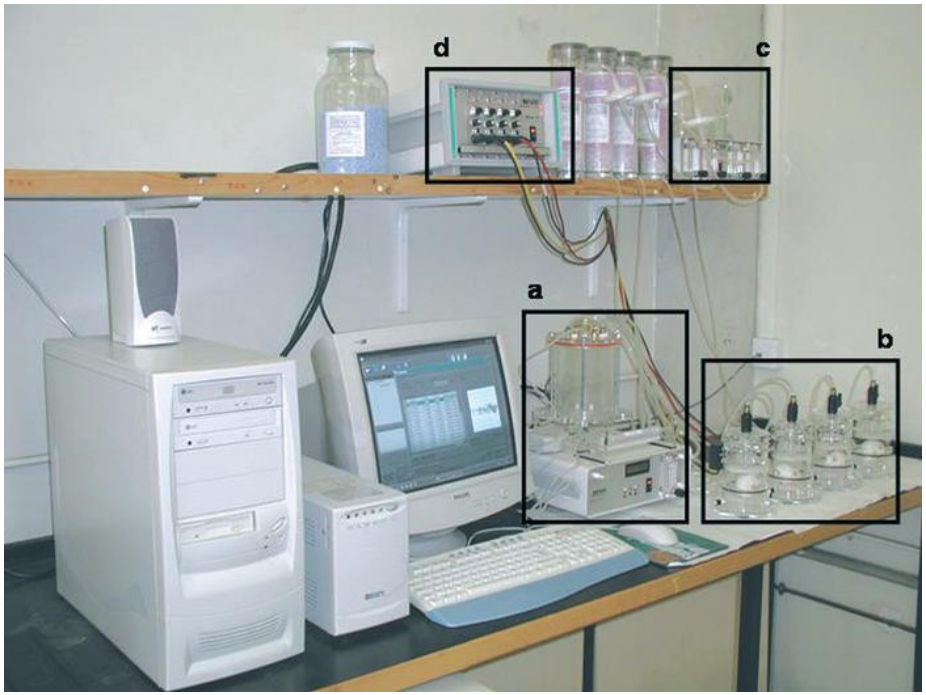


Result:
- **Quantified increased titers of IgE and House Dust Mite IgG1 in serum**

Additional Diagnostic Testing for Asthma

Methacholine Lung Function Test

Methacholine Lung Function Test in Mice

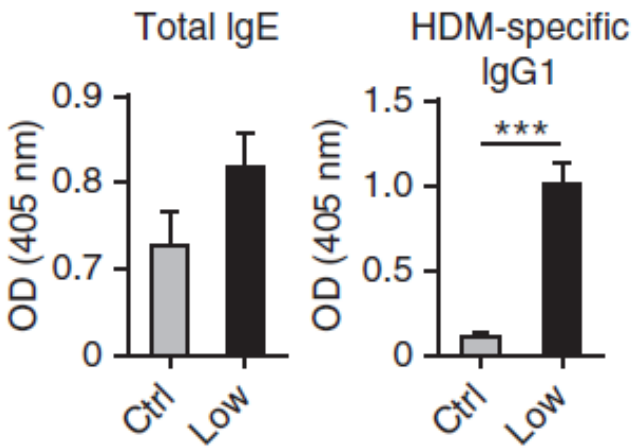


- Patient breathes aerosolized brachioconstrictor methacholine.
- Monitor forced expiratory volume.
- "High negative predictive value."

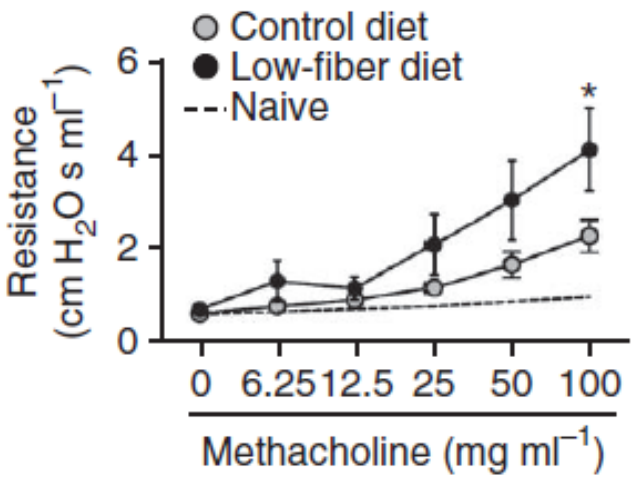
Swartz E and Lang D (2008) When should a methacholine challenge be ordered for a patient with suspected asthma? *One-Minute Consult*. (75)1: 37-40.
http://www.newcastle-hospitals.org.uk/services/cardiothoracic_wards-and-clinics_lung-function-department-freeman-hospital.aspx
http://www.archbronconeumol.org/en/use-of-the-mouse-to/articulo/13072689/

Mice Fed on Low Fiber Diet Showed Increased Allergic Airway Inflammation

Serum Levels



Rise in Airway Hyper-Reactivity

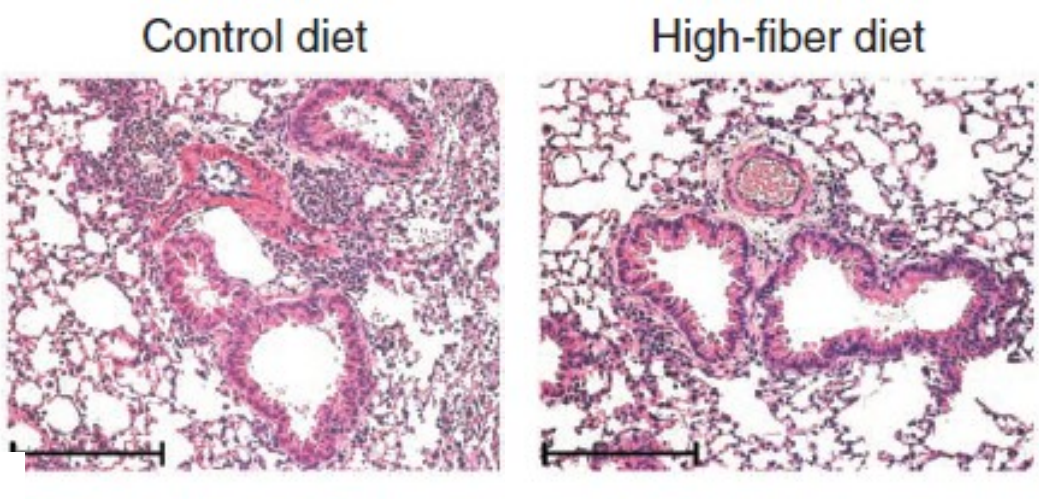


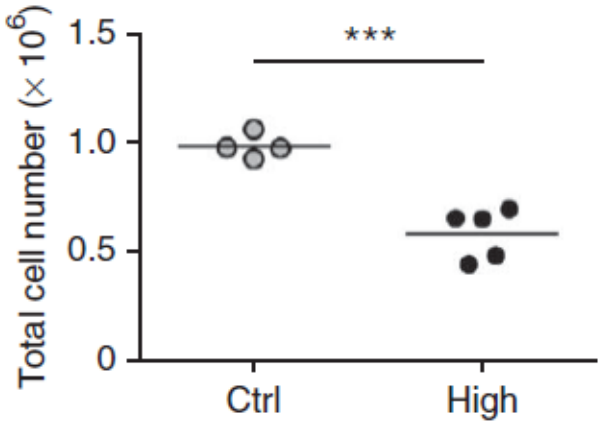
Result:
- **Quantified increased titers of IgE and House Dust Mite IgG1 in serum**

Result:
- **Greater airway resistance**

Question: What happens when mice are fed on a high-fiber diet?

Mice Fed on High Fiber Diet Showed Decreased Airway Hyper-reactivity





Method: Adult Mice Fed

- Control diet (cellulose)
- High-fiber (pectin)
- Internasal administration of house dust mite

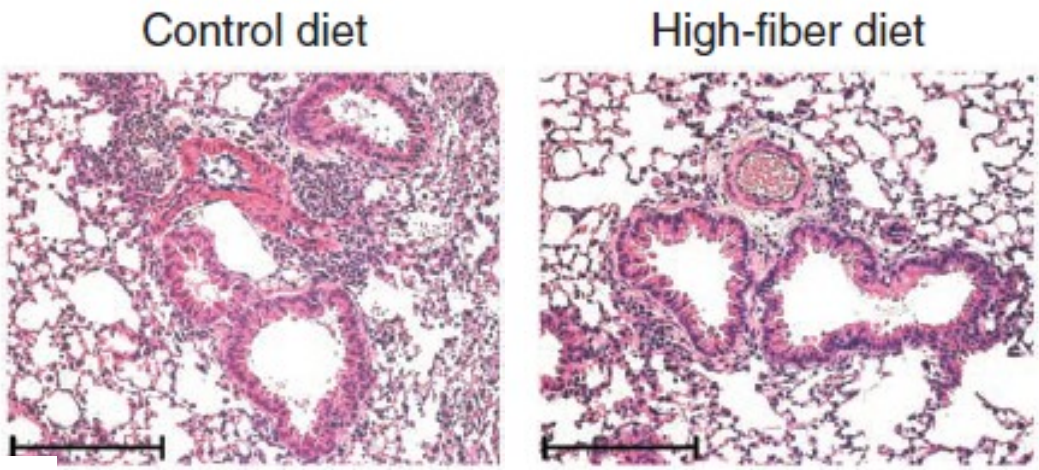
Result:

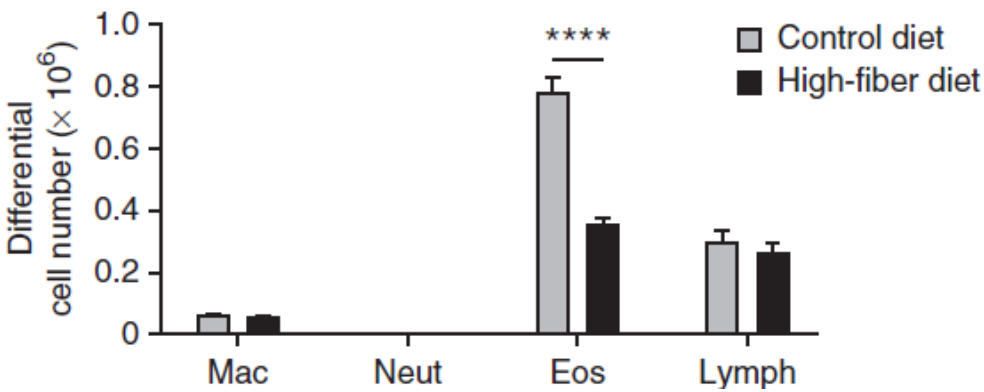
- **Observed decreased infiltration of inflammatory cells in pectin fed mice**

Result:

- **Quantified decrease in inflammatory cells**

Mice Fed on High Fiber Diet Showed Decreased Airway Hyper-reactivity





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- Control diet (cellulose)
- High-fiber (pectin)
- Internasal administration of house dust mite

Result:

- **Observed decreased infiltration of inflammatory cells in pectin fed mice**

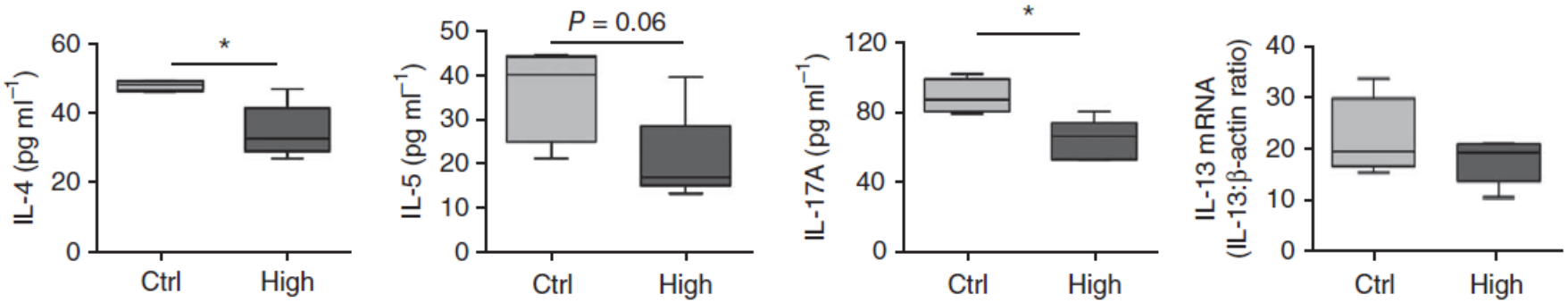
Result:

- **Quantified decrease in inflammatory cells**

Result:

- **Quantified decrease in eosinophils**

Mice Fed on High Fiber Diet Showed Decreased Airway Hyper-reactivity



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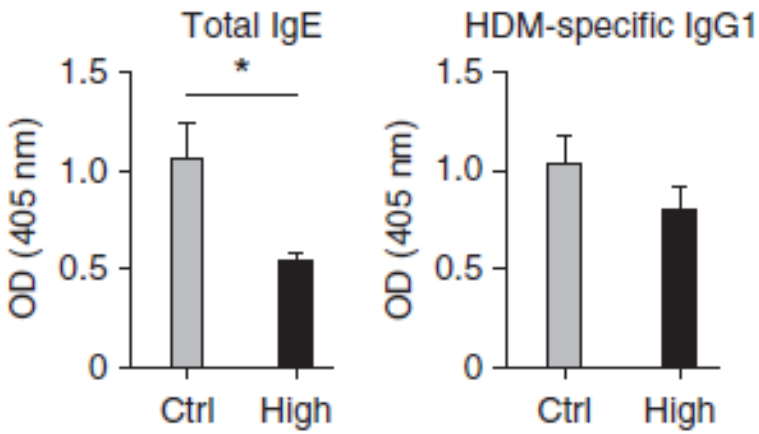
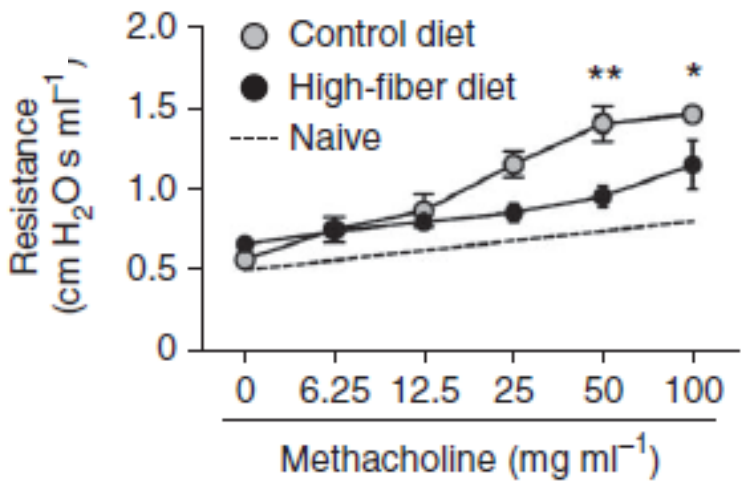
Result:
- **Observed decreased release of cytokines: IL-4, IL-5, IL-17A, IL-13**

Mice Fed on High Fiber Diet Showed Decreased Airway Hyper-reactivity

Serum Levels



Decrease in Airway Hyper-Reactivity



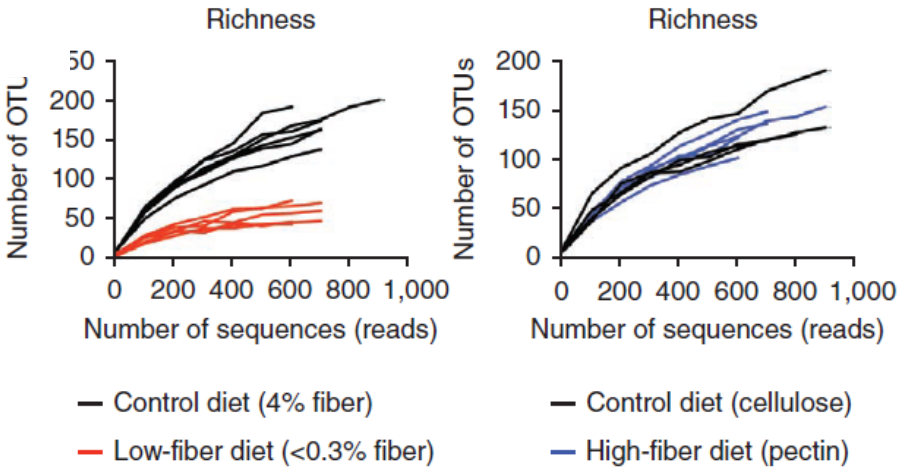
Result:
- **Quantified decreased titers of IgE and House Dust Mite IgG1 in serum**

Result:
- **Decreased airway resistance**

Question: How does the increase in dietary fiber affect the composition of the gut microbiota?

Increased Dietary Fiber Affects the Composition of the Gut and Lung Microbiota

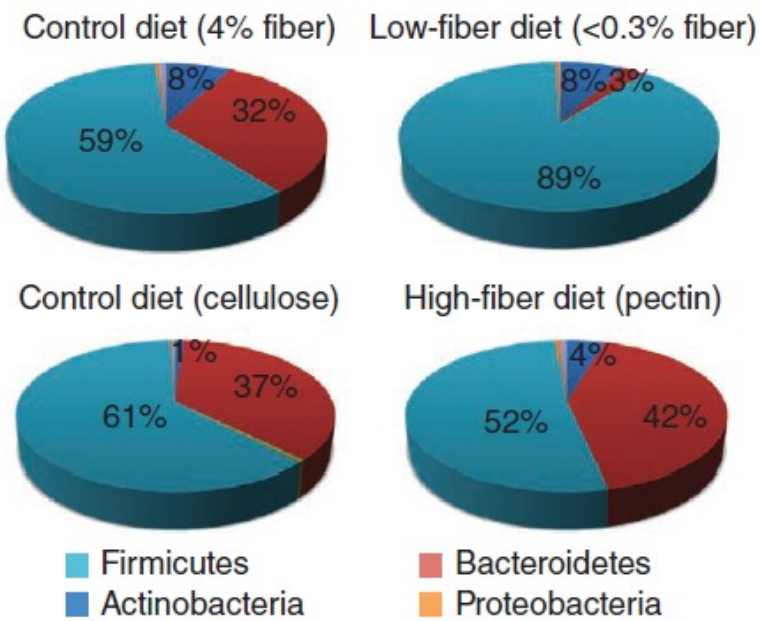
Effect of Diet on Gut Microbiota Diversity



- Isolated mouse fecal samples
- Sequence analysis of 16S ribosomal DNA
- Determined microbial variance
- (OTU= Operational Taxonomic Units)

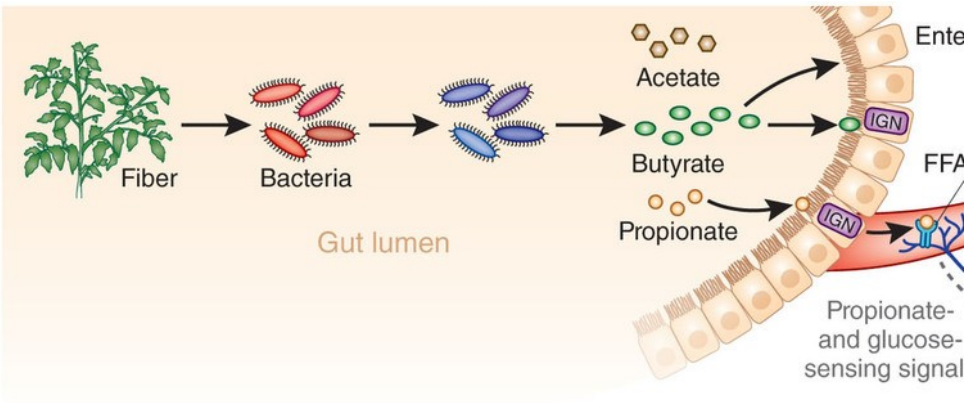
Results:
- **Loss of diversity in low-fiber fed mice**
- **Similar diversity for high-fiber fed mice**

Microbiota Composition in Mouse Fecal Samples



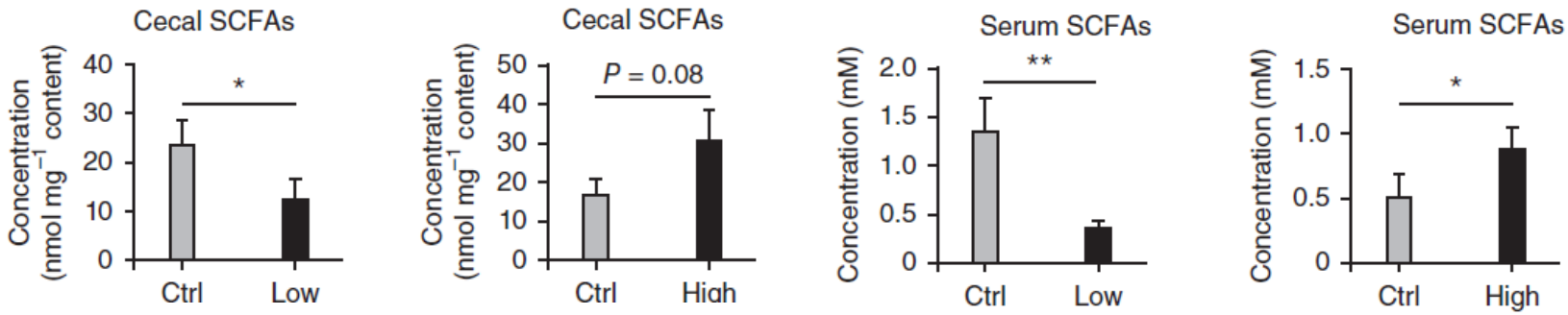
Results:
- **Increased percentage of bacteroidetes upon increased dietary fiber intake**
- **Increased percentage of firmicutes upon decreased dietary fiber intake**

Increased Dietary Fiber Affects the Composition of the Gut and Lung Microbiota



- Bacteroidetes converts fiber into SCFA
    - Acetate
    - Propionate

Increased Dietary Fiber Affects the Composition of the Gut and Lung Microbiota

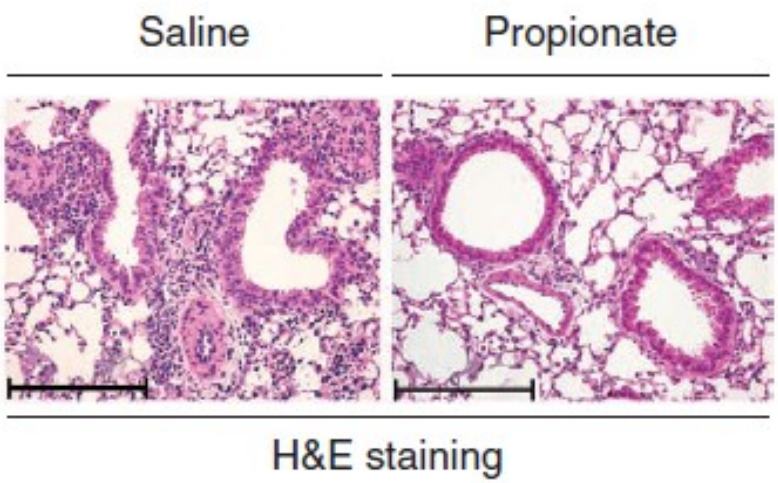


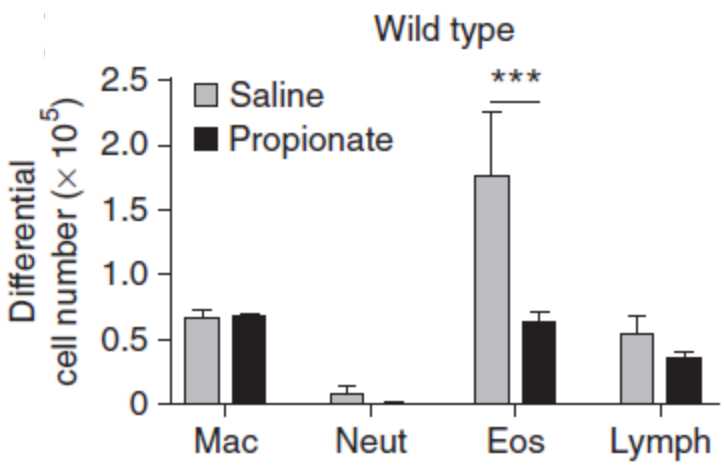
Results Quantified by HPLC:
- **Lower cecal SCFA in low-fiber fed mice**
- **Higher cecal SCFA in high-fiber fed mice**

Results Quantified by HPLC:
- **Lower serum SCFA in low-fiber fed mice**
- **Higher serum SCFA in high-fiber fed mice**

Question: Does direct supplementation of propionate improve allergic airway inflammation?

Propionate Ameliorates Allergic Airway Inflammation





Method: Adult Mice

- Added saline or propionate to drinking water
- Internasal administration of house dust mite

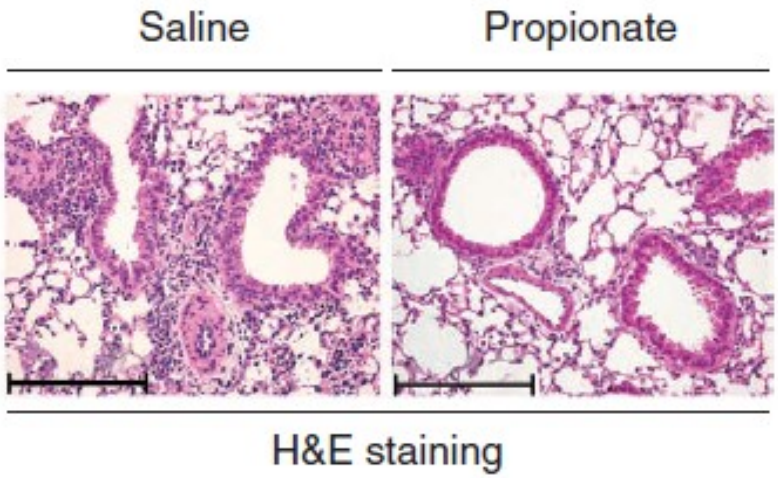
Result:

- **Observed decreased infiltration of inflammatory cells**

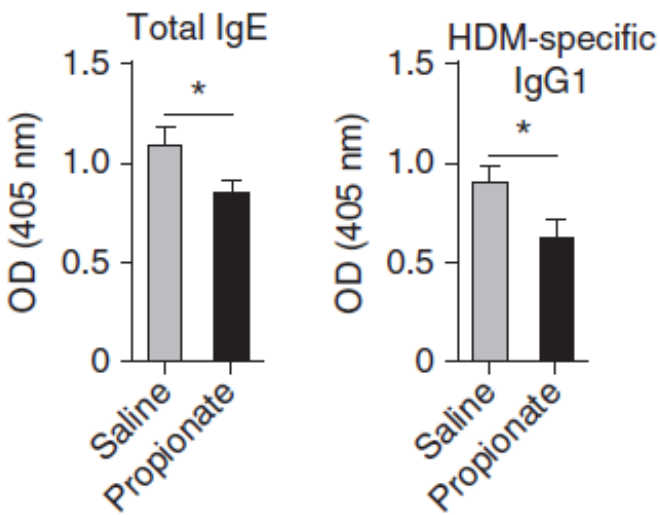
Result:

- **Observed decreased eosinophils in propionate treated mice**

Propionate Ameliorates Allergic Airway Inflammation



Serum Levels



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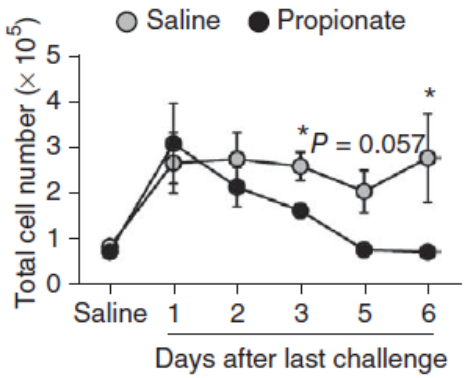
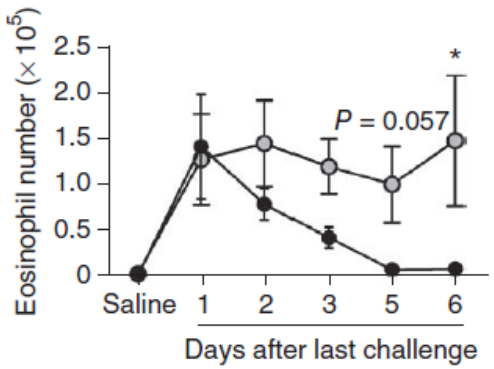
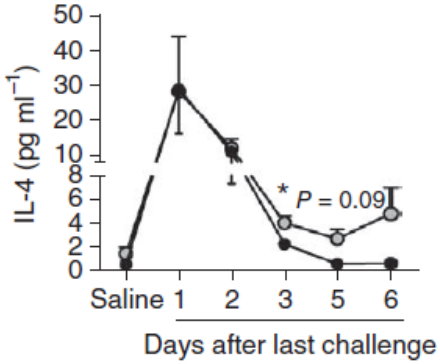
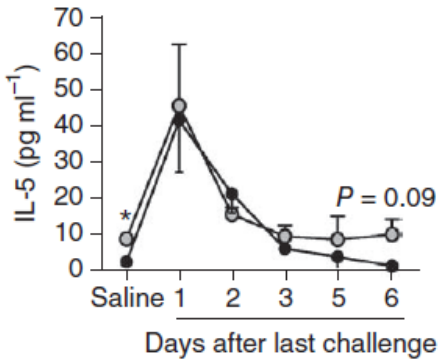
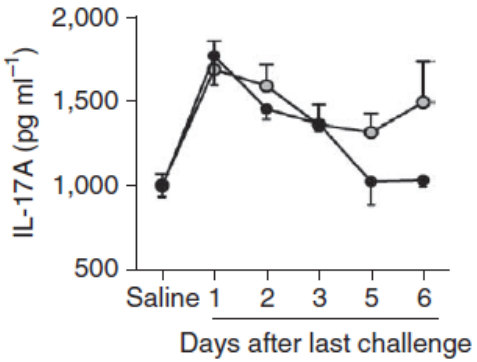




Result:
- **Observed faster remediation of inflammatory cell infiltration upon propionate treatment, specifically of eosinophils**







Result:
- **Observed faster denouement of cytokine levels in propionate treated mice**

Conclusions

- Mice fed on **low** fiber diet showed **increased** allergic airway inflammation.
- Mice fed on **high** fiber diet showed **decreased** airway hyper-reactivity.
- Increased dietary fiber affects the composition of the gut and lung microbiota.
- Propionate ameliorates allergic airway inflammation.