Gut microbiota, bacterial metabolites and metabolite sensing GPCRs protect against food allergy

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5th European Immunology & Innate Immunity
Increased prevalence of inflammatory diseases over the last 50 years

Molodecky et al, Gastroenterology 2012
Increased prevalence of inflammatory diseases in western countries


Causes?

**GENETIC**  **WESTERN LIFESTYLE**  **NUTRITION TRANSITION**

**Western diet**: High carbohydrate, high saturated fat and low in fibre
Diet and gut homeostasis as a basis for certain western lifestyle diseases

From Maslowski and Mackay  Nat. Immunol 2011
Role of diet and gut microbiota in food allergy

Current treatment = Food avoidance
Food allergy

What is it: Inappropriate immune response to innocuous (food) antigen

Symptoms: Swelling, itching, wheezing, diarrhea, difficulty in breathing, anaphylaxis

Prevalence: High in Western countries, up to 1 in 10 affected

Cause?? Hygiene hypothesis
Diet hypothesis

- Intake of fibre
- Fermented foods
- Obesity

Host genetics
- Maternal transfer and early colonisation
- Antibiotics and medications
- Infection
- Inflammation
- Stress
- Hygiene
- Age

Extension of the hygiene hypothesis

Symbiosis
- SCFA
- PSA
- PTGN
- and so on

Dysbiosis
- Virulence factors

Immune regulation
- Homeostasis

Immune dysregulation
- Inflammation
Key steps in allergic reaction

SENSITISATION
1. Uptake of allergen by dendritic cells
2. Migration to the mesenteric lymph node
3. Activation of specific T cells-Th2
4. IgE release
5. Pool of memory T cells

ALLERGIC REACTION
= 2\textsuperscript{nd} encounter with the allergen
Anaphylaxis/inflammation/tissue damage
High fibre diet and peanut allergy

Diet deprived in fibre
or
Diet enriched in fibre

**Modified AIN93G Rodent Diet**
20% Cellulose 20% Guar Gum

1\textsuperscript{st} contact
with allergen

Allergic reaction

![Graph showing dietary fibre and allergic reaction]

Dietary fibre is associated with decreased allergic reaction
What controls allergy?

High fibre feeding is associated with increased Treg number in mesenteric LN
CD103+ DCs are key inducer of Treg in the gut
High fibre feeding and CD103$^+$ DCs

% CD103$^+$ dendritic cells under high fibre feeding conditions
High fibre feeding and CD103$^+$ DCs

- Cells are incubated with a special ALDH-substrate
- ALDH-substrate becomes fluorescent upon the action of RALDH enzymes

High fibre feeding = more RALDH activity
Dietary fibre modulate CD103\(^+\) DCs proportion and activity
Mechanisms

Sodium Acetate

Gut microbiota

SCFA

GPR43

Unweighted UNIFRAC

HF microbiota

ZF microbiota

Germ free

HFd

HFr

ZFd

ZFr

phyla

Anaphylaxis Score

%CD25+Foxp3+ of CD4+
Mechanism of action of fibre: Short-chain fatty acids (SCFAs)?

- SCFAs are major metabolites produced by the microbiota

<table>
<thead>
<tr>
<th>SCFAs</th>
<th>GPCR activation</th>
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<tbody>
<tr>
<td>Acetate</td>
<td>GPR43</td>
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<tr>
<td>Propionate</td>
<td>GPR41</td>
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<tr>
<td>Butyrate</td>
<td>GPR109a</td>
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</table>
Role of SCFA in food allergy development

- 200mM acetate
  Or
- 100mM butyrate
  Or
- 100mM propionate
  Or
- water
SCFAs effects in peanut allergy

200mM acetate, 100mM butyrate, 100mM propionate for 3 weeks in drinking water

Acetate and Butyrate have beneficial effects:
- Anaphylaxis
- IgE

Acetate and Butyrate have beneficial effects:
- CD103+ DC
- Treg
Mechanism of action of fibre: Short-chain fatty acids (SCFAs)?

- SCFAs are major metabolites produced by the microbiota
Acetate → GPR43

Butyrate → GPR109a

GPCR activation

GPR43 and GPR109A are implicated in beneficial effects of fibre

Anaphylaxis

IgE

CD103+ DC

Treg

Wildtype  Gpr43−/−  Gpr109a−/−
Anaphylaxis Score

Wildtype  Gpr43−/−  Gpr109a−/−
IgE (ng/mL)

Wildtype  Gpr43−/−  Gpr109a−/−
% MHCIi^CD11c^CD103+

Wildtype  Gpr43−/−  Gpr109a−/−
% CD4^CD25^FoxP3^
Which compartment?

- **Vav-CRExGpr43^flox/flox**: deletion in the hematopoietic compartment
- **Villin-CRExGpr43^flox/flox**: deletion in the gut epithelium

GPR43 in the gut epithelium is important

HF fed mice
Which compartment?

- Study of GPR109A using the model of bone marrow chimera mice

GPR109 is critical in the hematopoietic compartment
Conclusion

Tan et al., 2016, Cell Reports 15, 2809–2824

What’s next?
1. Is it true in human?
2. Bacterial candidate?
3. Targeting GPCR?

Highlights
- Dietary fiber with vitamin A increases the potency of tolerogenic CD103⁺ DCs
- High-fiber diet protects mice against peanut allergy via gut microbiota and SCFA
- High-fiber effects rely on epithelial GPR43 and immune cell GPR109a
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