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

Laurence Macia, PhD

5th European Immunology & Innate Immunity

THE UNIVERSITY OF SYDNEY

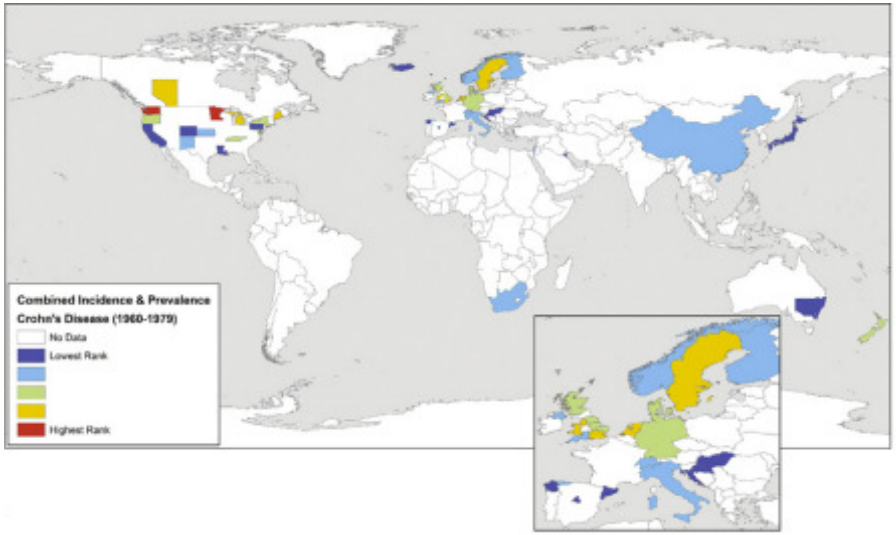
MONASH University

Increased prevalence of inflammatory diseases over the last 50 years

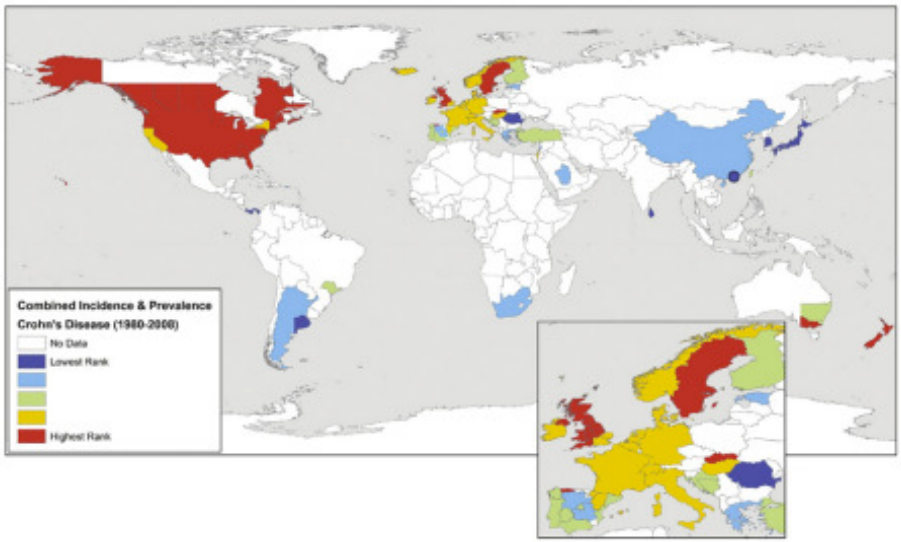
Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review

NATALIE A. MOLODECKY,[*,‡] ING SHIAN SOON,[‡,§] DOREEN M. RABI,[*,‡] WILLIAM A. GHALI,[*,‡] MOLLIE FERRIS,[*] GREG CHERNOFF,[‖] ERIC I. BENCHIMOL,[¶,#] REMO PANACCIONE,[*] SUBRATA GHOSH,[*] HERMAN W. BARKEMA,[‡,**] and GILAAD G. KAPLAN[*,‡]

1960-1979



After 1980

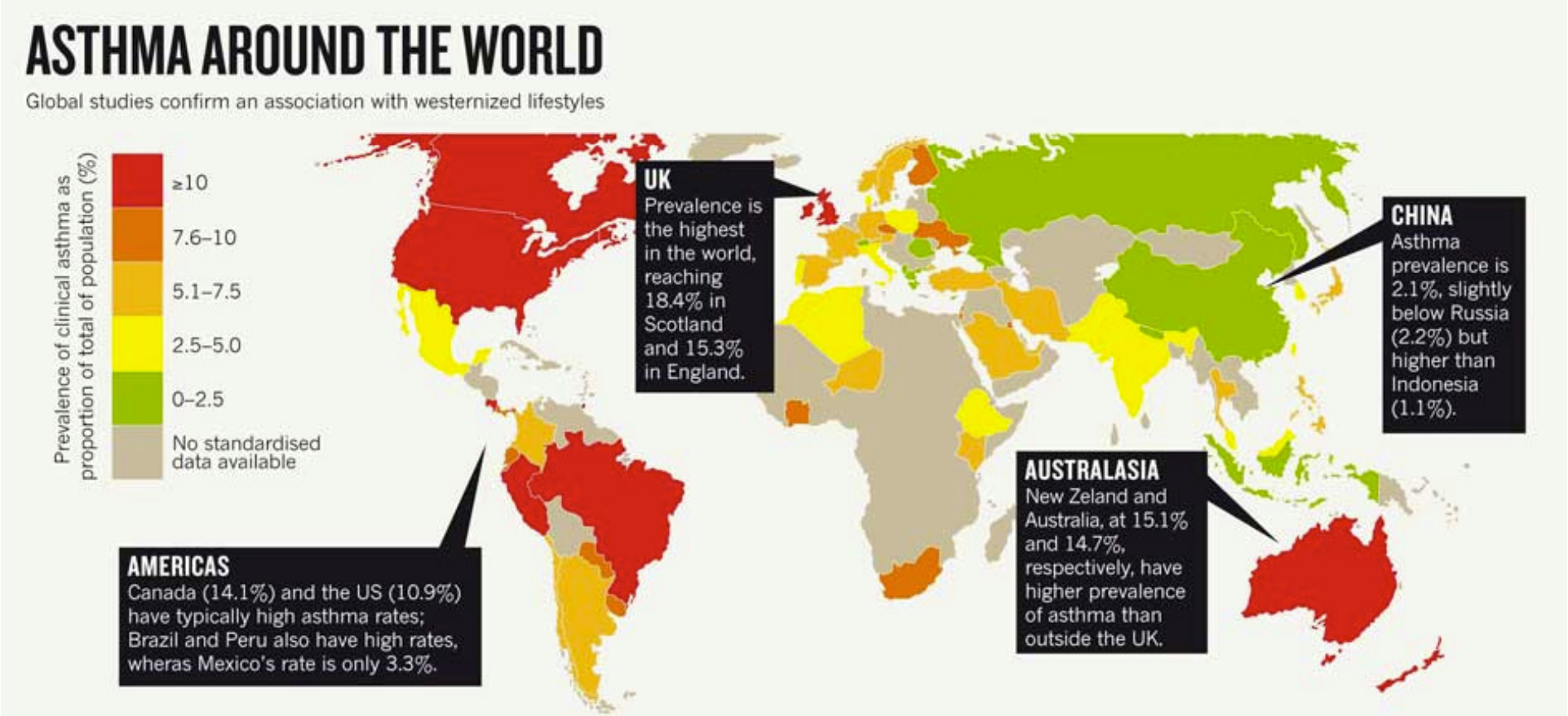


Molodecky et al, Gastroenterology 2012

Increased prevalence of inflammatory diseases in western countries

MASOLI, M. ET AL, Nature, 2011, 479, S2–S4

THE GLOBAL BURDEN OF ASTHMA (2004)



Causes?

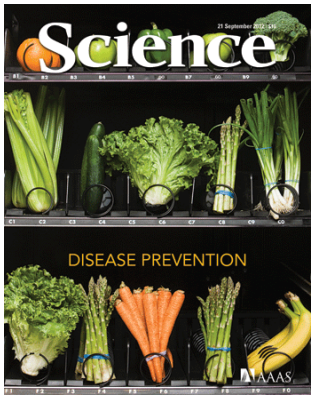
GENETIC

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



Diet
- Intake of fibre
- Fermented foods
- Obesity

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

Microbial composition

Symbiosis

SCFA
PSA
PTGN
(and so on)

Immune regulation

Homeostasis

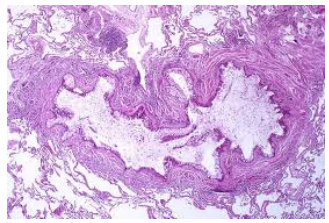
Dysbiosis

Virulence factors

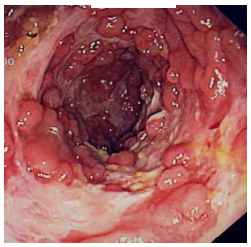
Immune dysregulation

Inflammation

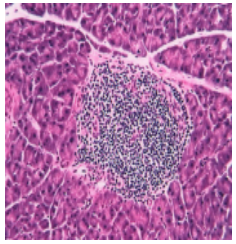
Asthma



IBD



Type 1 diabetes



Food allergies

From Maslowski and Mackay Nat. Immunol 2011

Role of diet and gut microbiota in food allergy

Current treatment=

Food avoidance

Food allergy

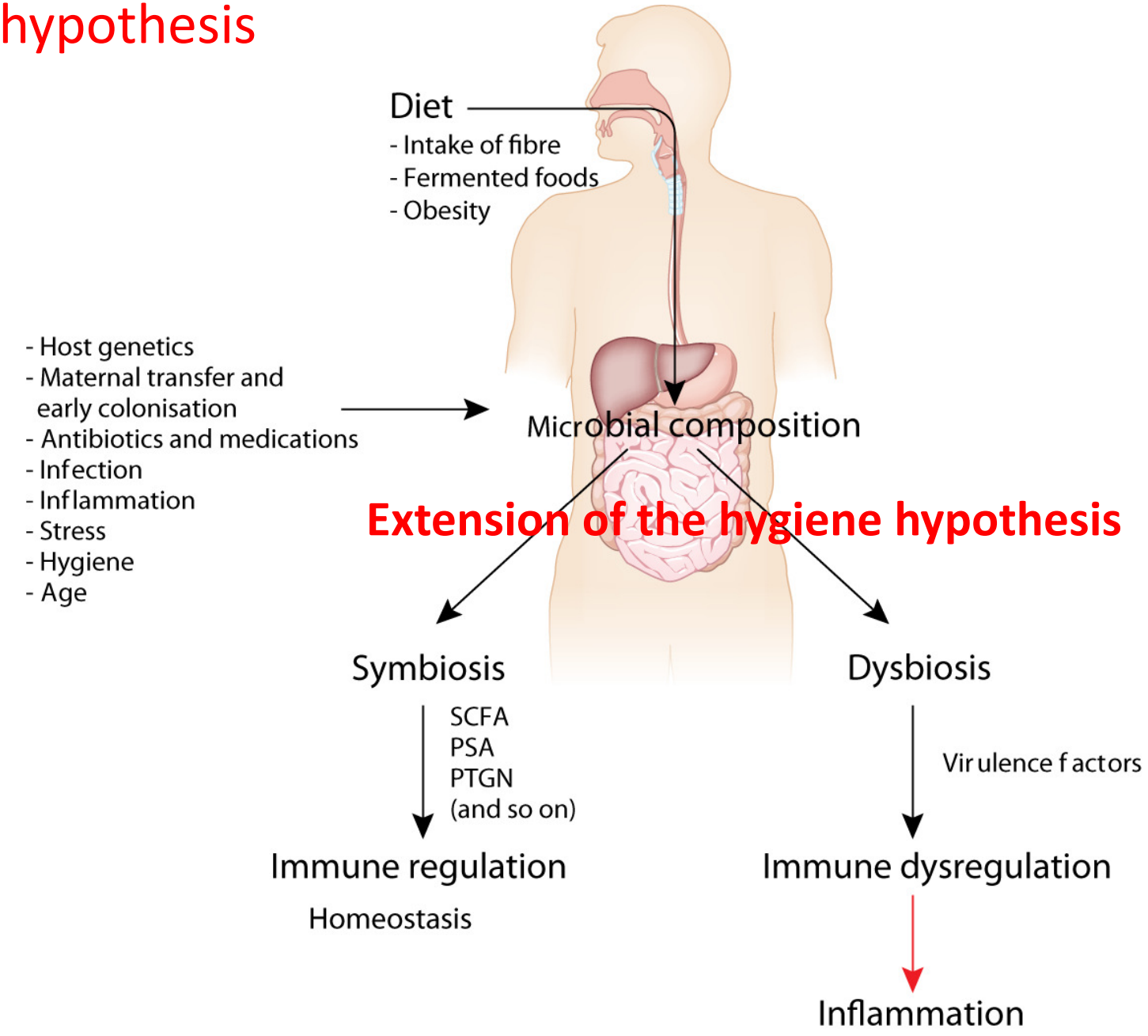
What is it: Inappropriate immune response to innocuous (food) antigen

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

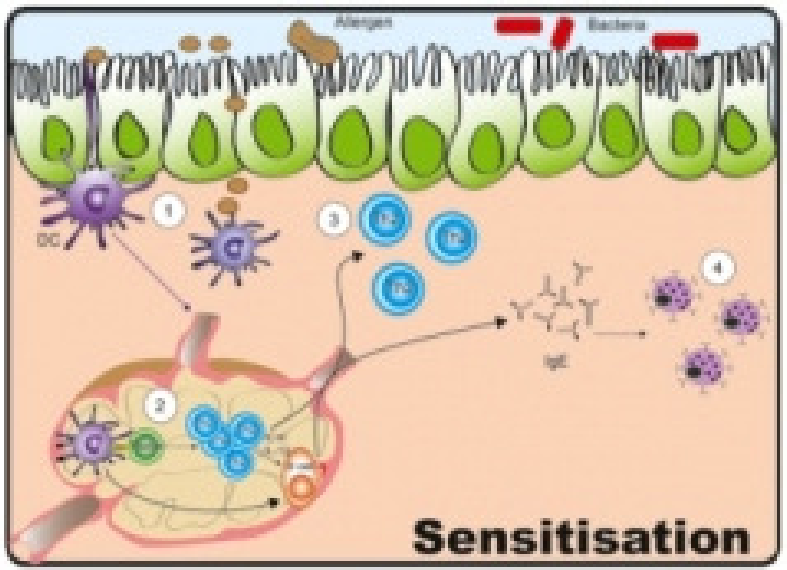
Prevalence: High in Western countries, up to 1 in 10 affected

Cause?? Hygiene hypothesis

Diet hypothesis

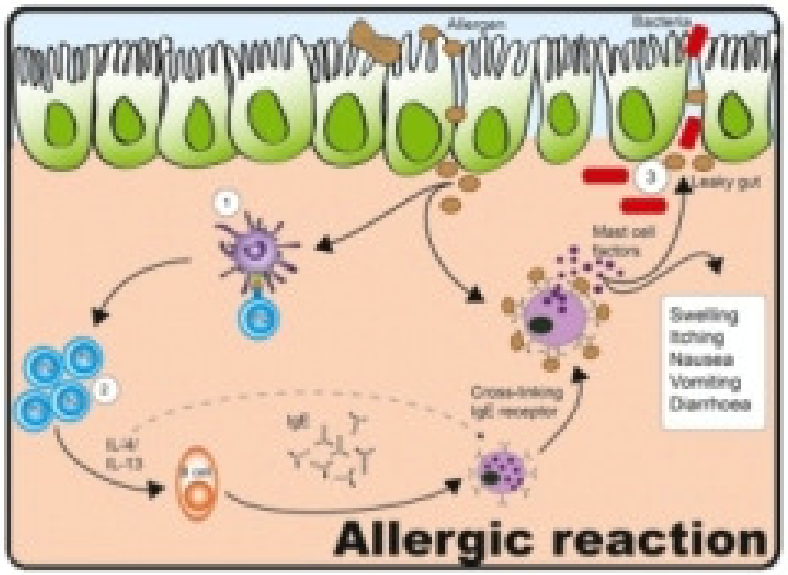


Key steps in allergic reaction



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

= 2nd encounter with the allergen

Anaphylaxis/inflammation/tissue damage

High fibre diet and peanut allergy

Diet deprived in fibre

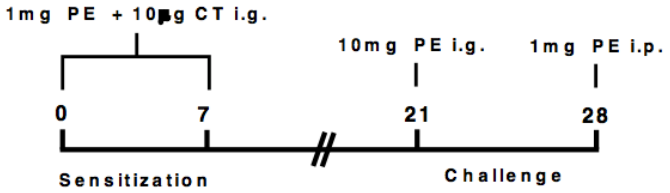
or

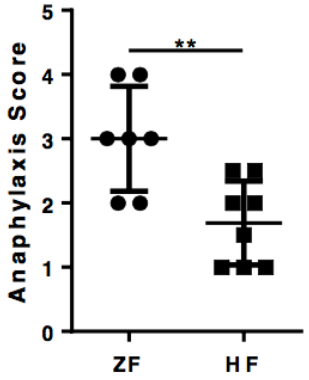
Diet enriched in fibre

Modified AIN93G Rodent Diet
20% Cellulose 20% Guar Gum

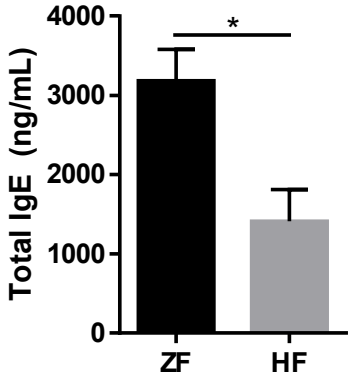
1st contact with allergen

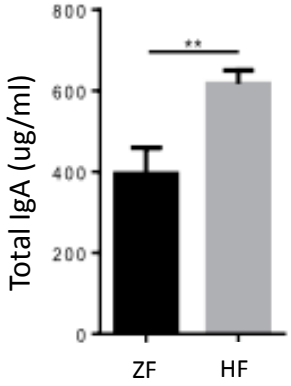
Allergic reaction





0	no symptoms
1	repetitive mouth/ear scratching and ear canal digging with hind legs
2	decreased activity, self-isolation, puffiness around eyes and/or mouth
3	Periods of motionless for more than 1min, lying prone on stomach
4	No response to whisker stimuli, reduced or no response to prodding
5	tremor, convulsion, death

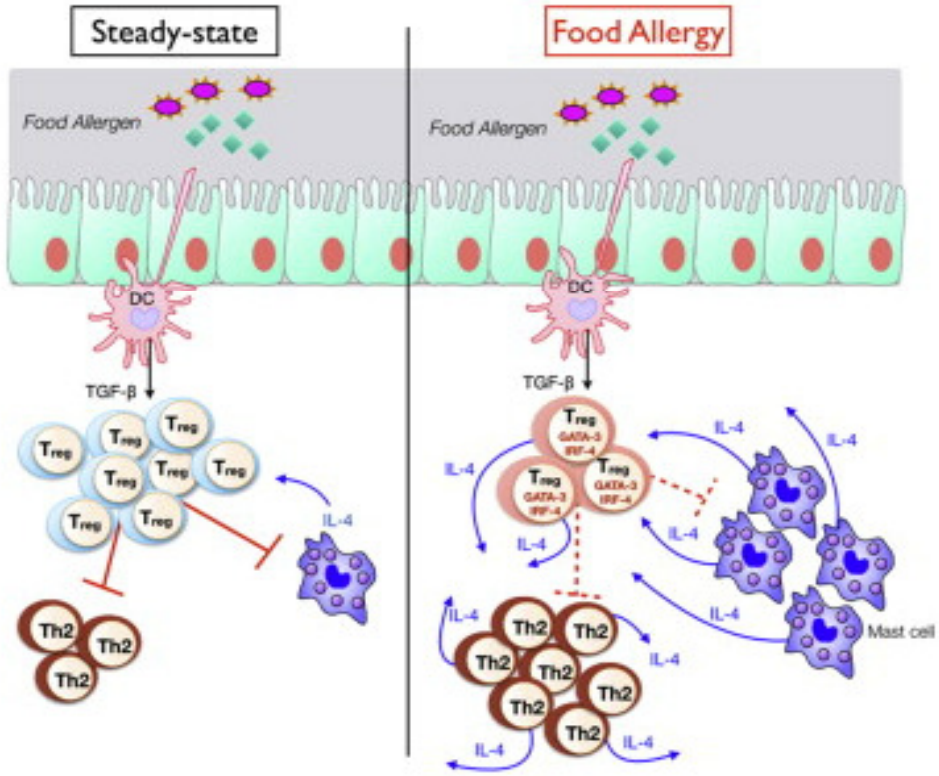


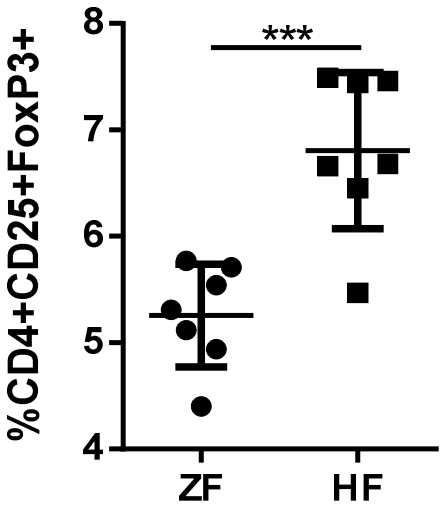


Dietary fibre is associated with decreased allergic reaction

What controls allergy?

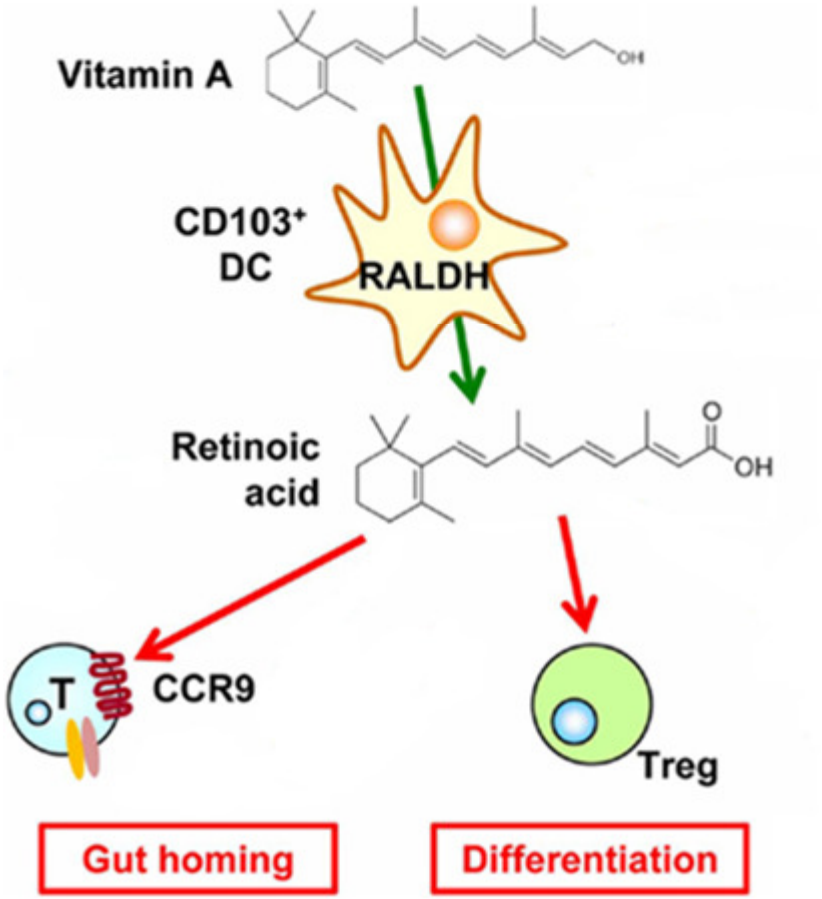
Treg



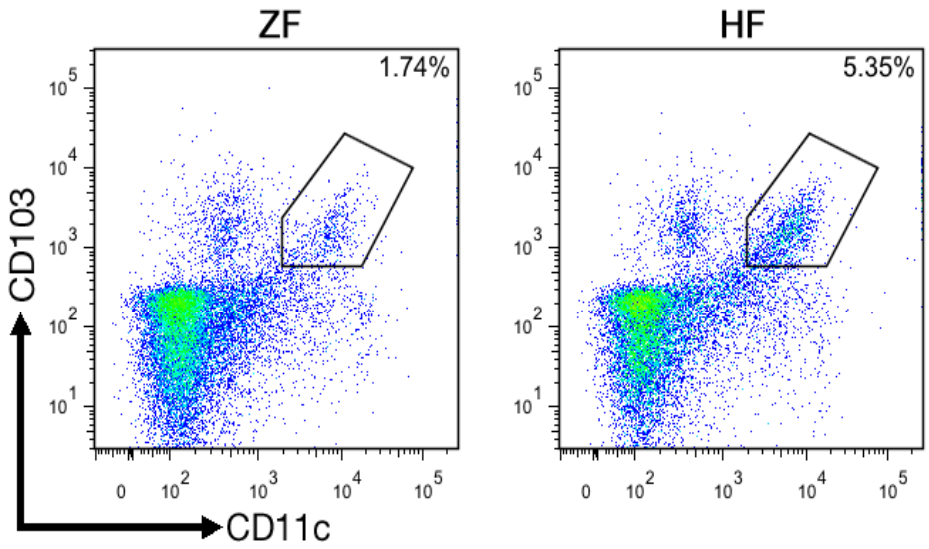


High fibre feeding is associated with increased Treg number in mesenteric LN

CD103^{+} DCs are key inducer of Treg in the gut



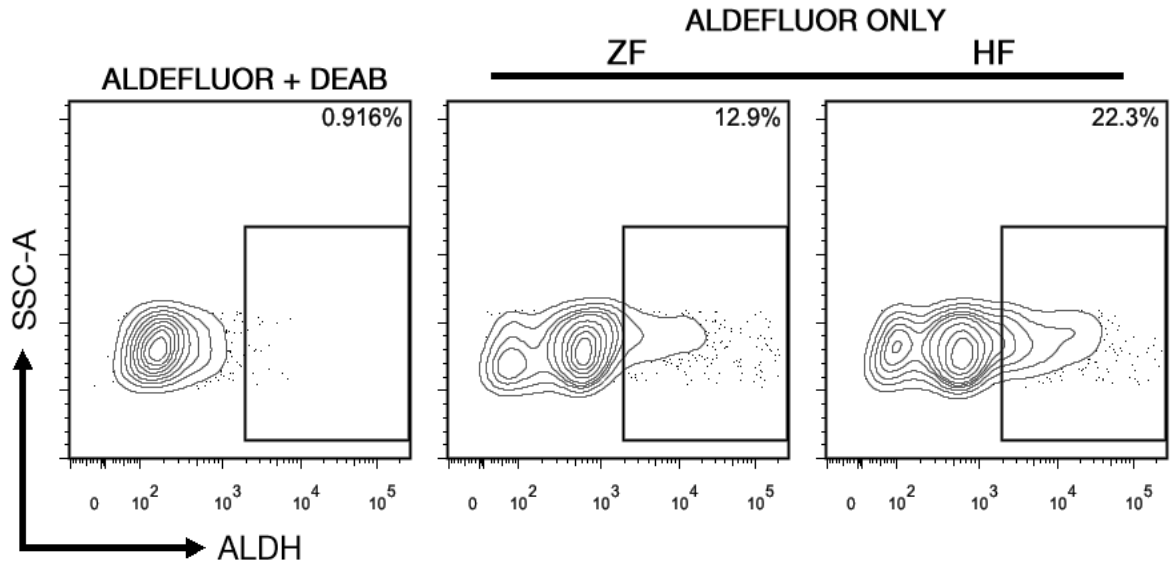
High fibre feeding and CD103^{+} DCs



↑ % CD103^{+} dendritic cells under high fibre feeding conditions

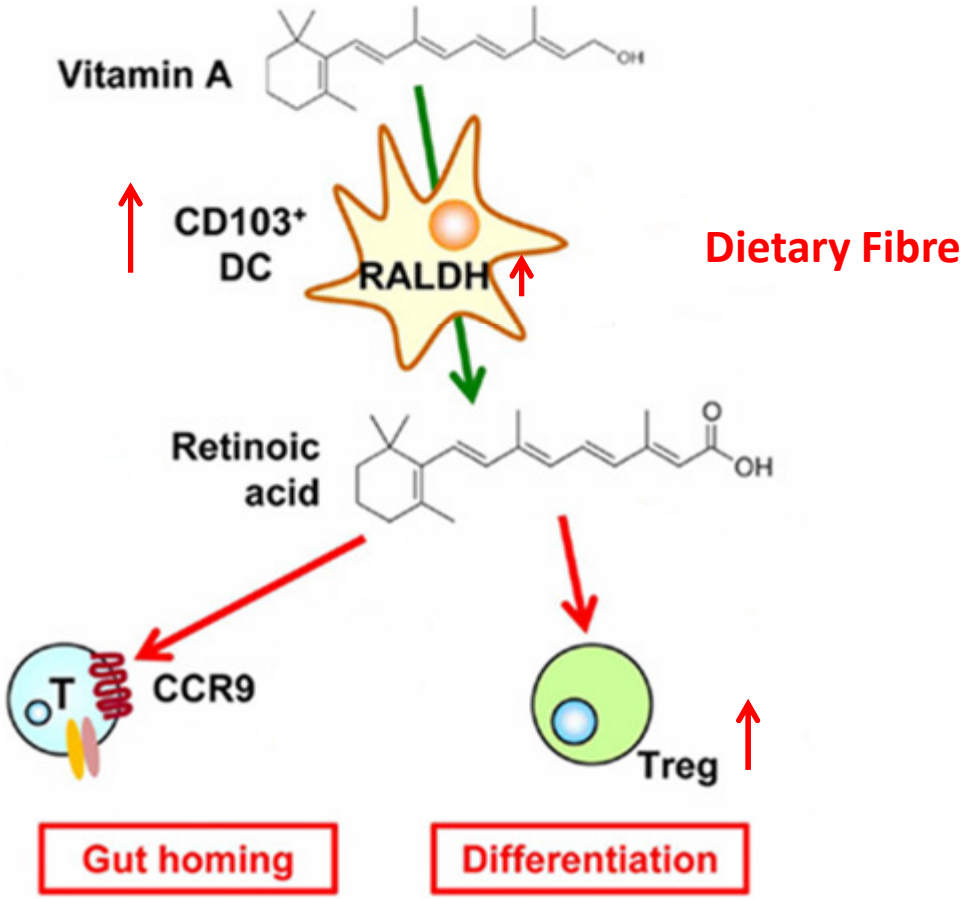
High fibre feeding and CD103^{+} DCs

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



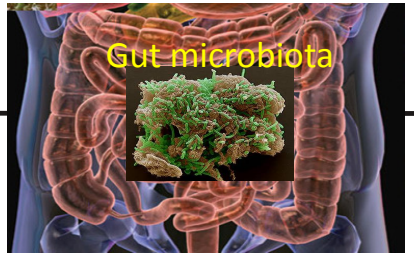
High fibre feeding = more RALDH activity

Dietary fibre modulate CD103^{+} DCs proportion and activity



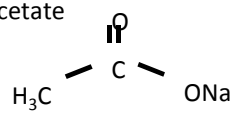
Mechanisms

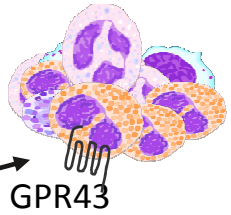
?

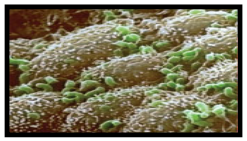


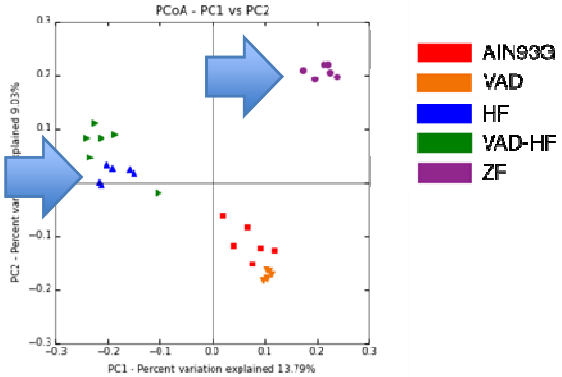
SCFA

Sodium Acetate





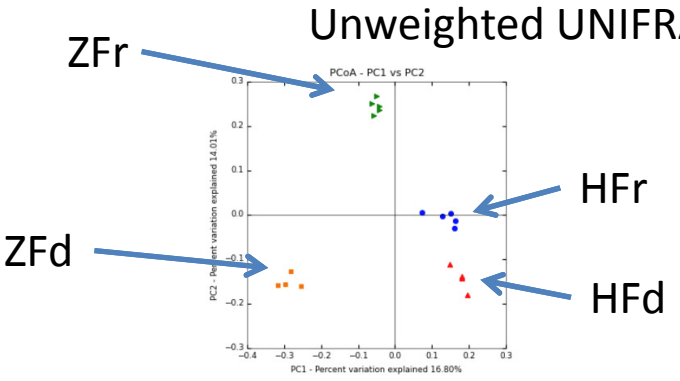


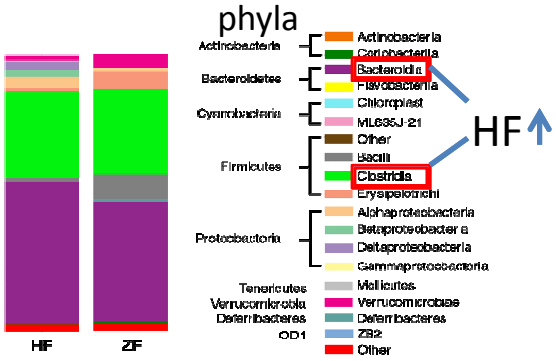


Germ free

HF microbiota

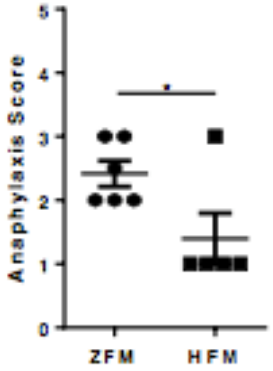
Unweighted UNIFRAC

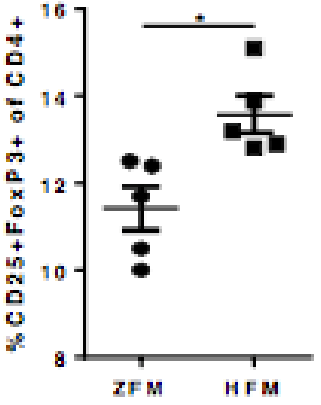




Germ free

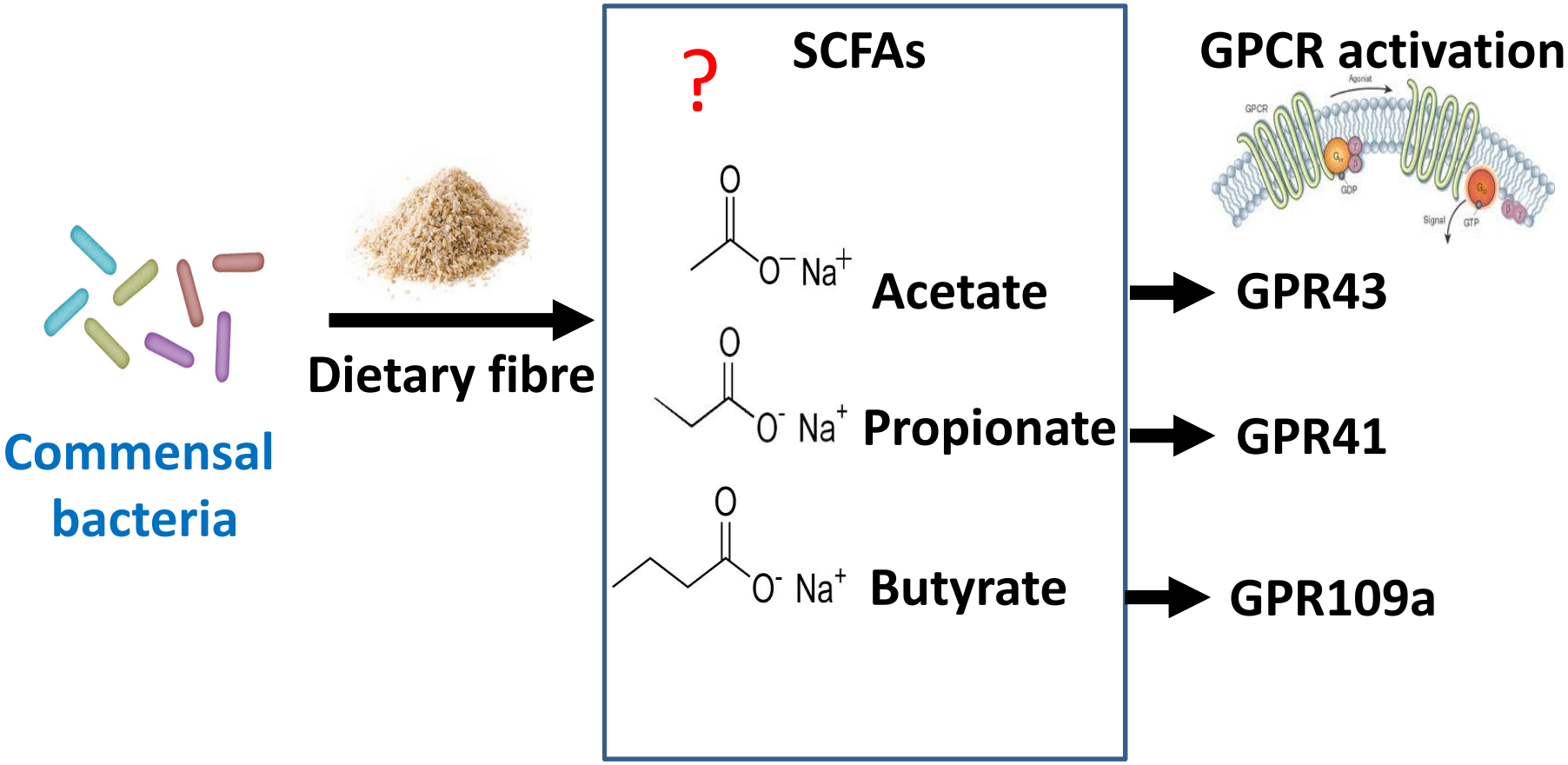
ZF microbiota



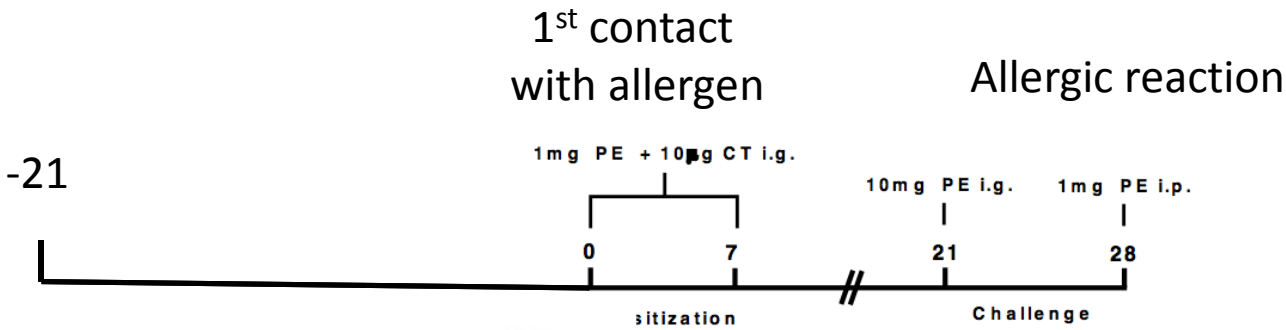


Mechanism of action of fibre: Short-chain fatty acids (SCFAs)?

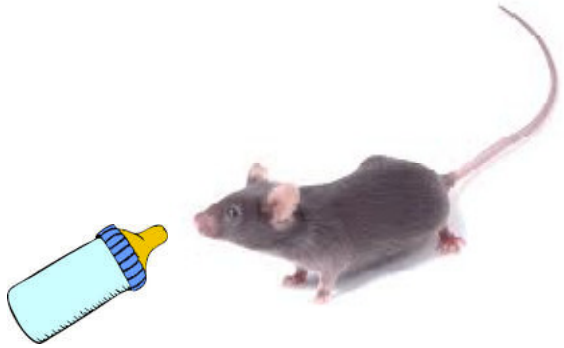
- SCFAs are major metabolites produced by the microbiota



Role of SCFA in food allergy development

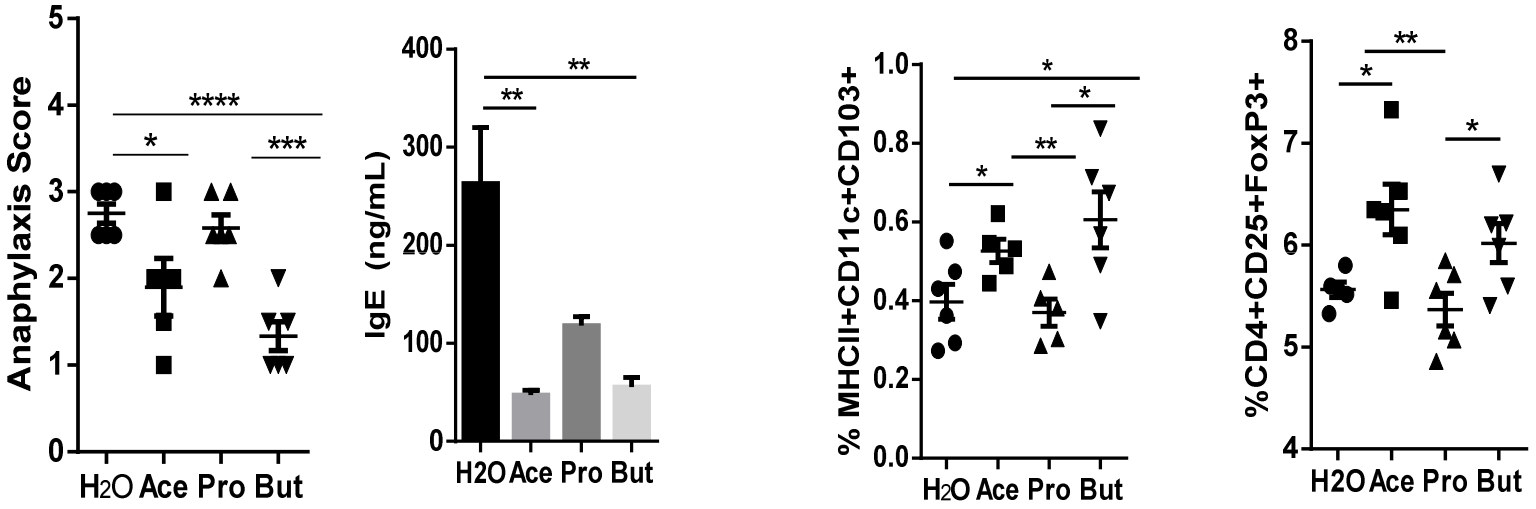


200mM acetate
Or
100mM butyrate
Or
100mM propionate
Or
water



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

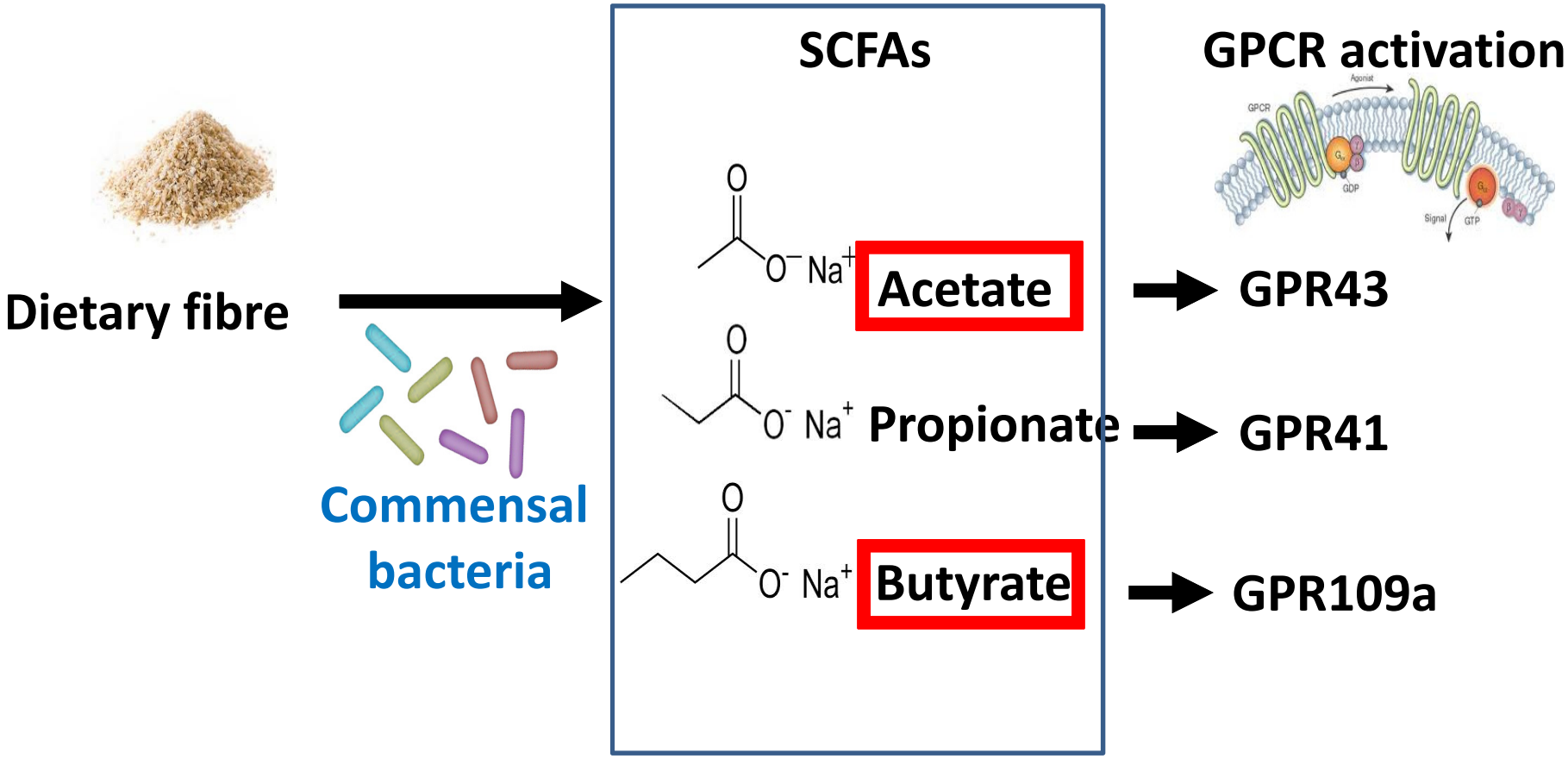
Acetate and Butyrate have beneficial effects:

↑ $CD103^+$ DC

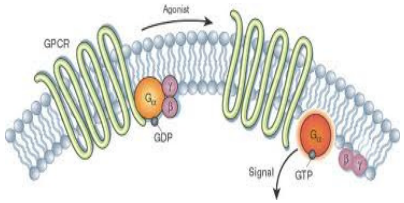
↑ Treg

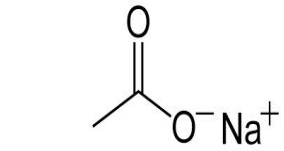
Mechanism of action of fibre: Short-chain fatty acids (SCFAs)?

- SCFAs are major metabolites produced by the microbiota

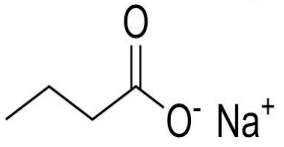


GPCR activation

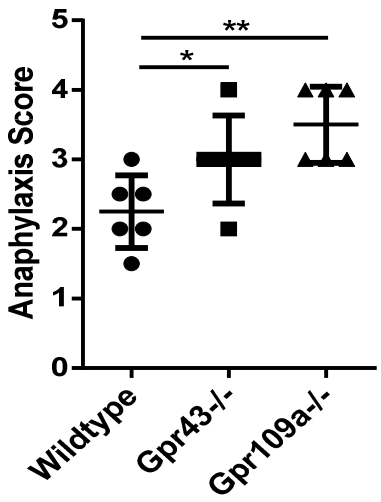


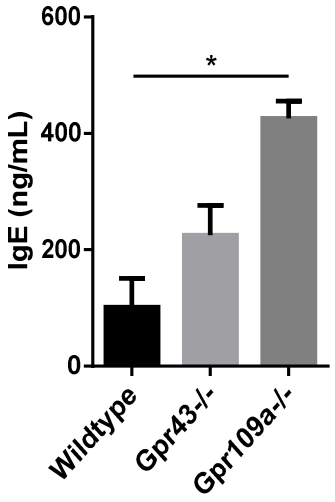


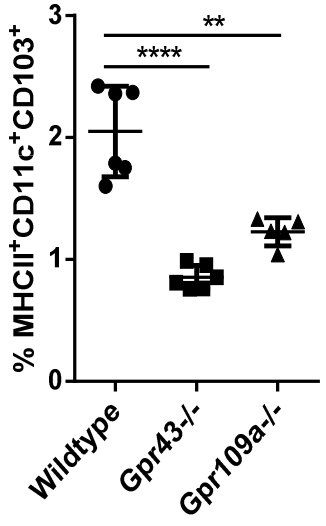
Acetate → GPR43

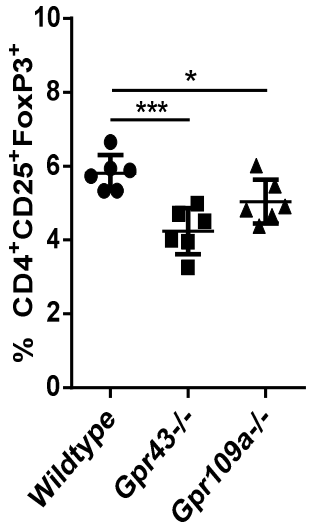


Butyrate → GPR109a









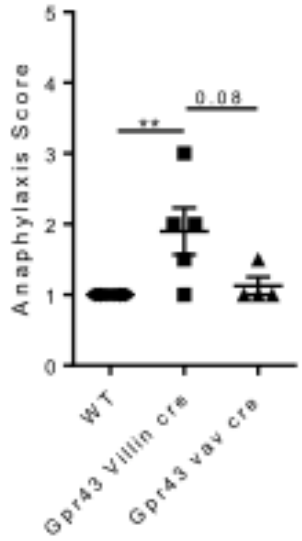
GPR43 and GPR109A are implicated
In beneficial effects of fibre

↑ Anaphylaxis
↑ IgE

↓ $CD103^+$ DC
↓ Treg

Which compartment?

- *Vav-CRExGpr43*$^{flox/flox}$= deletion in the hematopoeitic compartment
- *Villin-CRExGpr43*$^{flox/flox}$: deletion in the gut epithelium

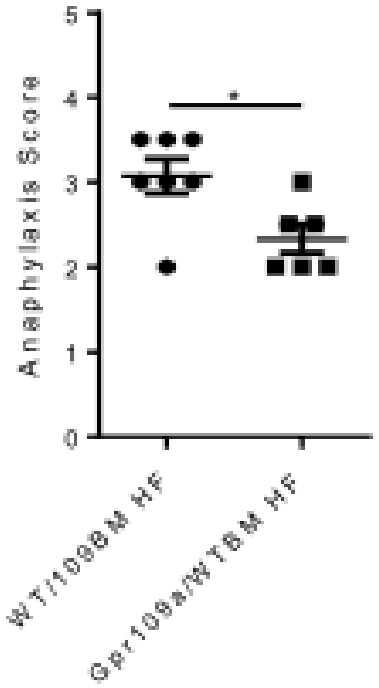


HF fed mice

GPR43 in the gut epithelium is important

Which compartment?

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



GPR109 is critical in the hematopoeitic compartment

Conclusion

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

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

What's next?

1. Is it true in human?
2. Bacterial candidate?
3. Targeting GPCR?

Acknowledgments

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Laurence.macia@sydney.edu.au

THE UNIVERSITY OF SYDNEY

Nutritional Immunometabolism group