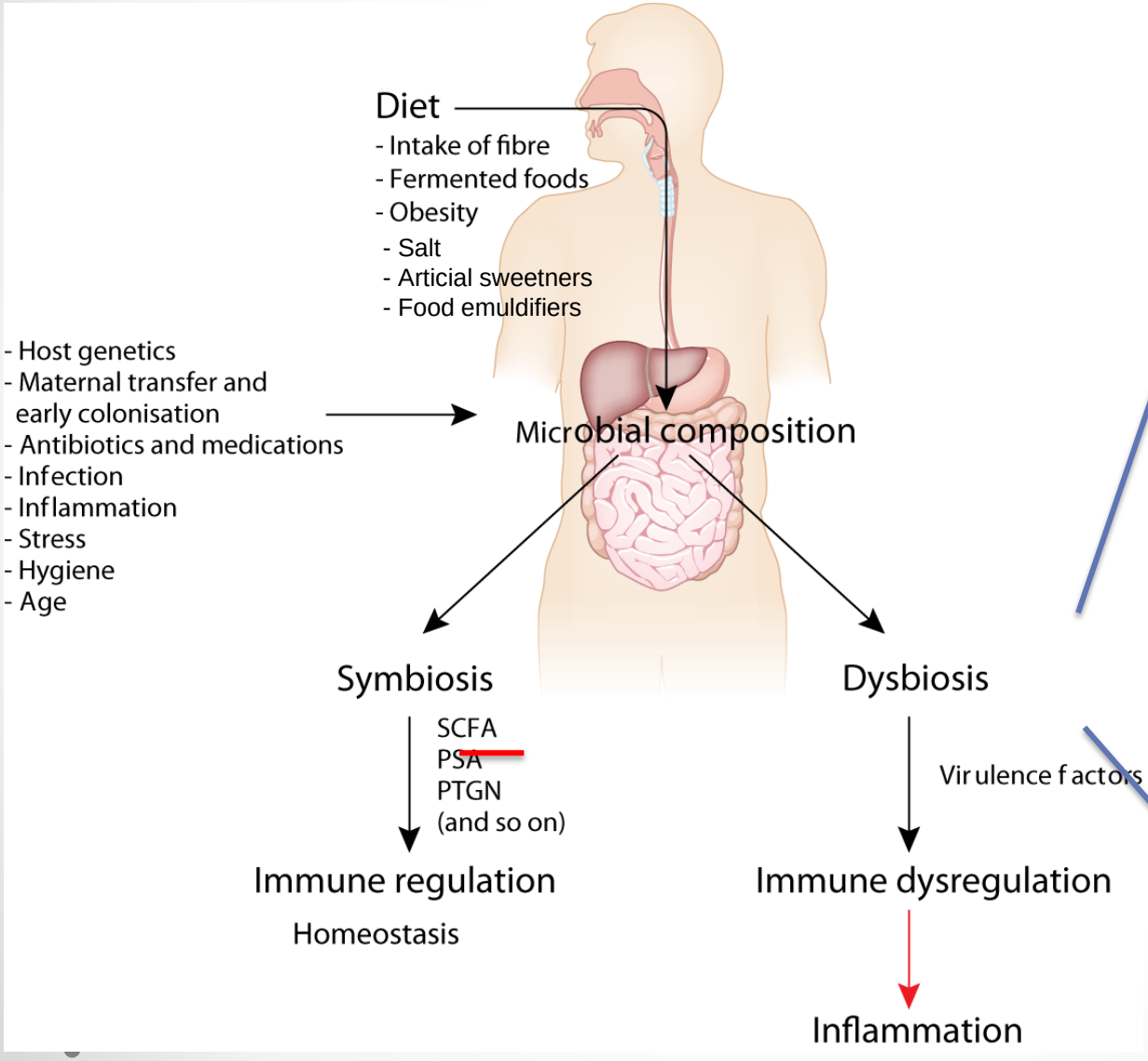
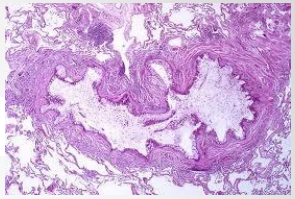
Diet, microbiota and the immune system: A gut feeling about type 1 diabetes

Dr. Eliana Mariño
Monash University
Melbourne, Australia

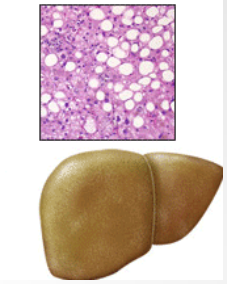
Diet, gut microbiota and Western lifestyle diseases



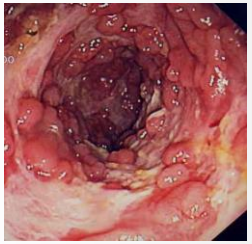
Asthma



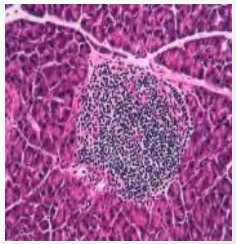
Fatty liver



IBD



Type 1 diabetes



Food allergies

From Maslowski and Mackay Nat. Immunol 2011

The role of dietary metabolites in inflammatory diseases

nature COMMUNICATIONS

ARTICLE

Received 5 Mar 2015 | Accepted 27 Apr 2015 | Published xx xxx 2015

DOI: 10.1038/ncomms8320

Evidence tha
disease influ
metabolites

Alison N. Thorburn[1], Craig
Laura E. Roberts[1], Connie H
Eliana Mariño[1], Rob J. Moc
Vanessa E. Murphy[9], Joerg

OPEN

Cell Reports
Article

OPEN ACCES
CellPres

Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways

Clinical & Translational Immunology (2016) 5, e82; doi:10.1038/cti.2016.29

www.nature.com/cti

E. Mebius,[3]

doi:10.1038/nature13398

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vitalla[1], Begüm Aydin[2], Paul K. Ziegler[3,4,5],
dreas Böck[6], Carl Alpert[7]†, Michael Blaut[8],
V. Polson[10] & Melek C. Arkan[1]

,* Angela Castoldi,*

REVIEW

nature COMMUNICATIONS

Dietary metabolites and the gut microbiota: an alternative approach to control inflammatory and autoimmune diseases

James L Richards, Yu Anne Yap, Keiran H McLeod, Charles R Mackay and Eliana Mariño

ey

ARTICLE

Received 11 Sep 2014 | Accepted 24 F

Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome

Laurence Macia[1], Jian Tan[1], Angelica T. Vieira[1,2], Katie Leach[3], Dragana Stanley[4,5], Suzanne Luong[1], Mikako Maruya[6], Craig Ian McKenzie[1], Atsushi Hijikata[6], Connie Wong[1], Lauren Binge[1], Alison N. Thorburn[1], Nina Chevalier[1], Caroline Ang[1], Eliana Marino[1], Remy Robert[1], Stefan Offermanns[7], Mauro M. Teixeira[2], Robert J. Moore[4,8], Richard A. Flavell[9,10], Sidonia Fagarasan[6] & Charles R. Mackay[1]

Diet, Metabolites, and "Western-Lifestyle" Inflammatory Diseases

Alison N. Thorburn,[1,2] Laurence Macia,[1,2] and Charles R. Mackay[1,*]
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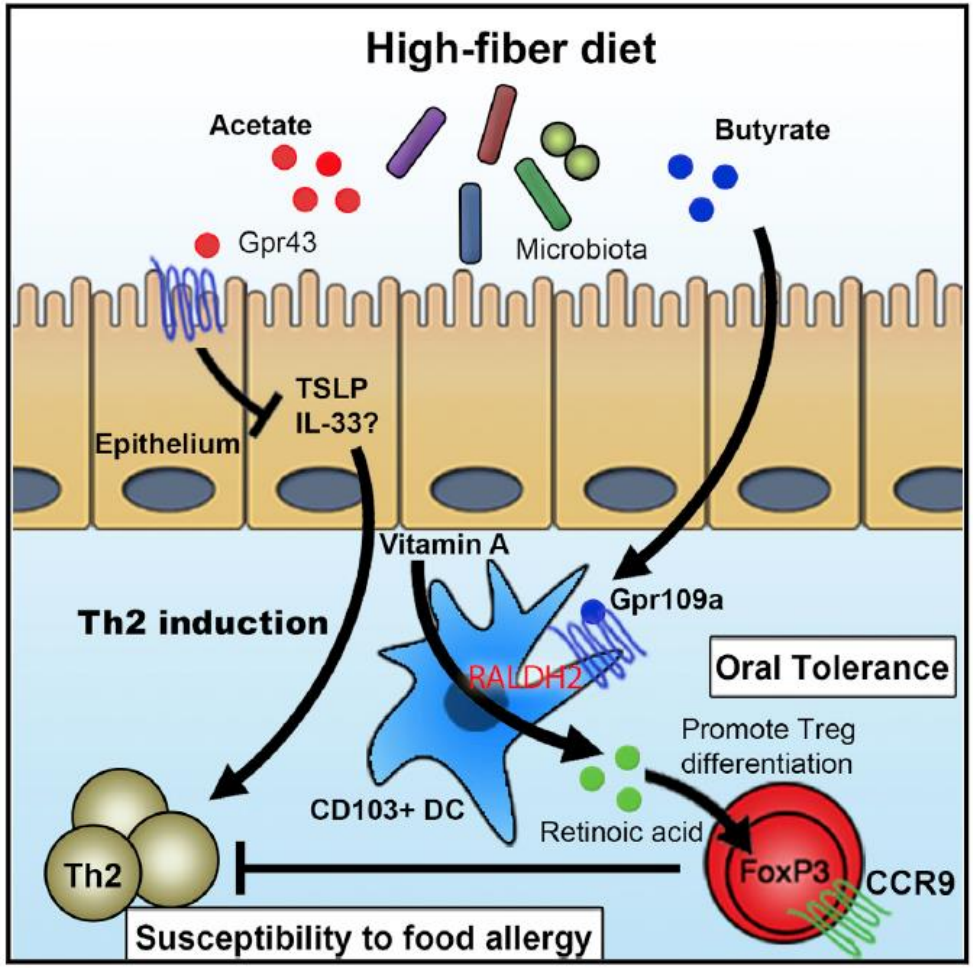
http://dx.doi.org/10.1016/j.immuni.2014.05.014

Cell Reports

Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways

Graphical Abstract



Authors

Jian Tan, Craig McKenzie, Peter J. Vuillermin, ..., Reina E. Mebius, Laurence Macia, Charles R. Mackay

Correspondence

laurence.macia@sydney.edu.au (L.M.), charles.mackay@monash.edu (C.R.M.)

In Brief

Tan et al. examine the beneficial roles of dietary fiber in peanut allergy using mice. The authors find that this effect involves reshaping of the gut microbiota as well as increased levels of short-chain fatty acids and activity of their receptors GPR43 and GPR109a. High-fiber feeding also increased tolerogenic CD103^{+} DCs activity, leading to increased Treg cell differentiation.

ARTICLES

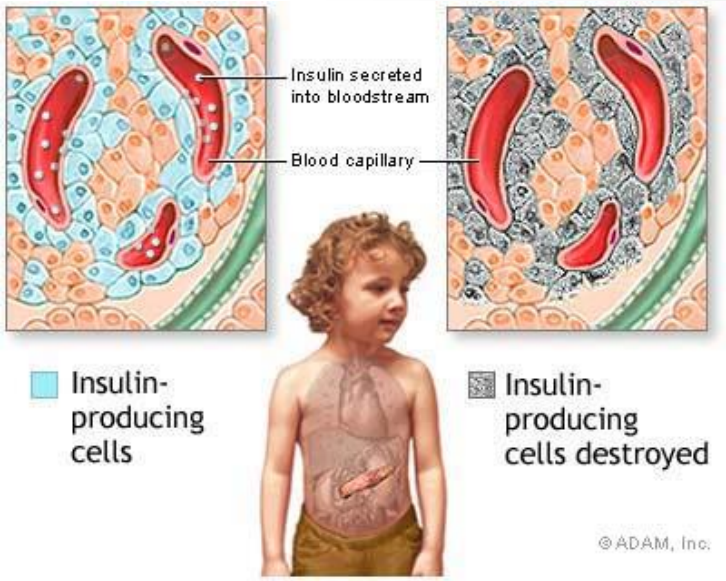
nature immunology

Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes

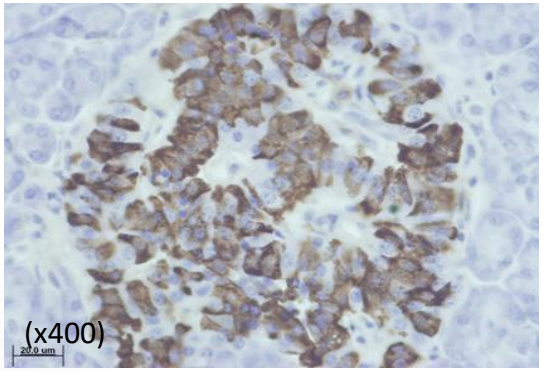
Eliana Mariño[1], James L Richards[1], Keiran H McLeod[1], Dragana Stanley[2], Yu Anne Yap[1], Jacinta Knight[1], Craig McKenzie[1], Jan Kranich[3], Ana Carolina Oliveira[4], Fernando J Rossello[5–7], Balasubramanian Krishnamurthy[8], Christian M Nefzger[5–7], Laurence Macia[1,9,10], Alison Thorburn[1], Alan G Baxter[11], Grant Morahan[12], Lee H Wong[1], Jose M Polo[5–7], Robert J Moore[13,14], Trevor J Lockett[15], Julie M Clarke[16], David L Topping[16], Leonard C Harrison[17] & Charles R Mackay[1]

Type 1 Diabetes

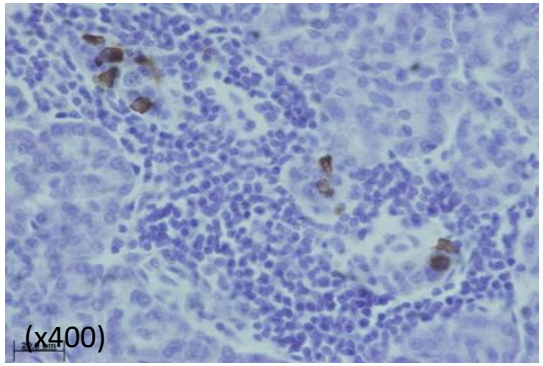
- Blood sugar regulation lost
- Loss of insulin production and Hyperglyceamia
- Insulin producing beta cells destroyed
- Immune attack - *autoimmune disease*
- Controlled with exogenous insulin
- Diabetic complications are a major issue



Insulin labelling



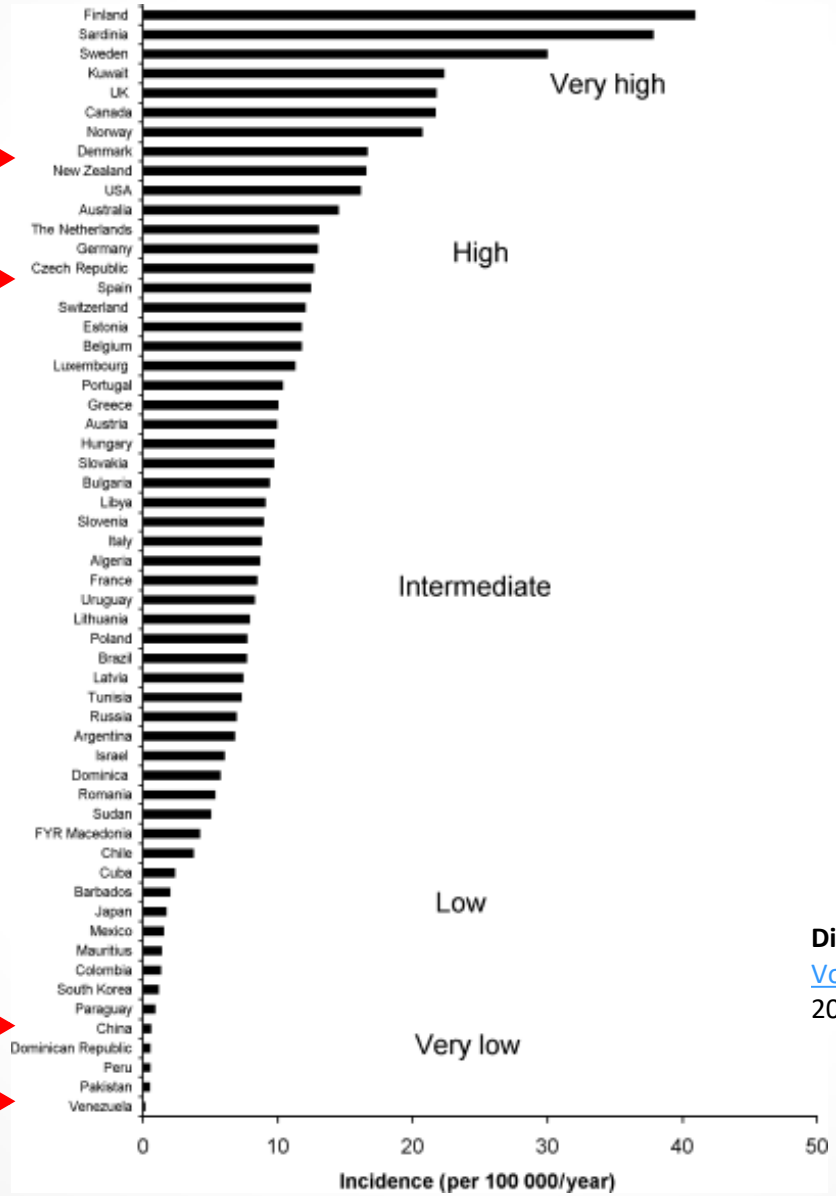
Insulin labelling - pancreas T1D subject



Images: thnx to Pete Campbell & Tom Kay SVI Melbourne

Epidemiology of T1D

Findland
Sweeden
UK
USA
Australia



Mexico

China

Venezuela

Diabetic Medicine
Volume 23, Issue 8, pages 857-866, 26 JUN 2006 DOI: 10.1111/j.1464-5491.2006.01925.x

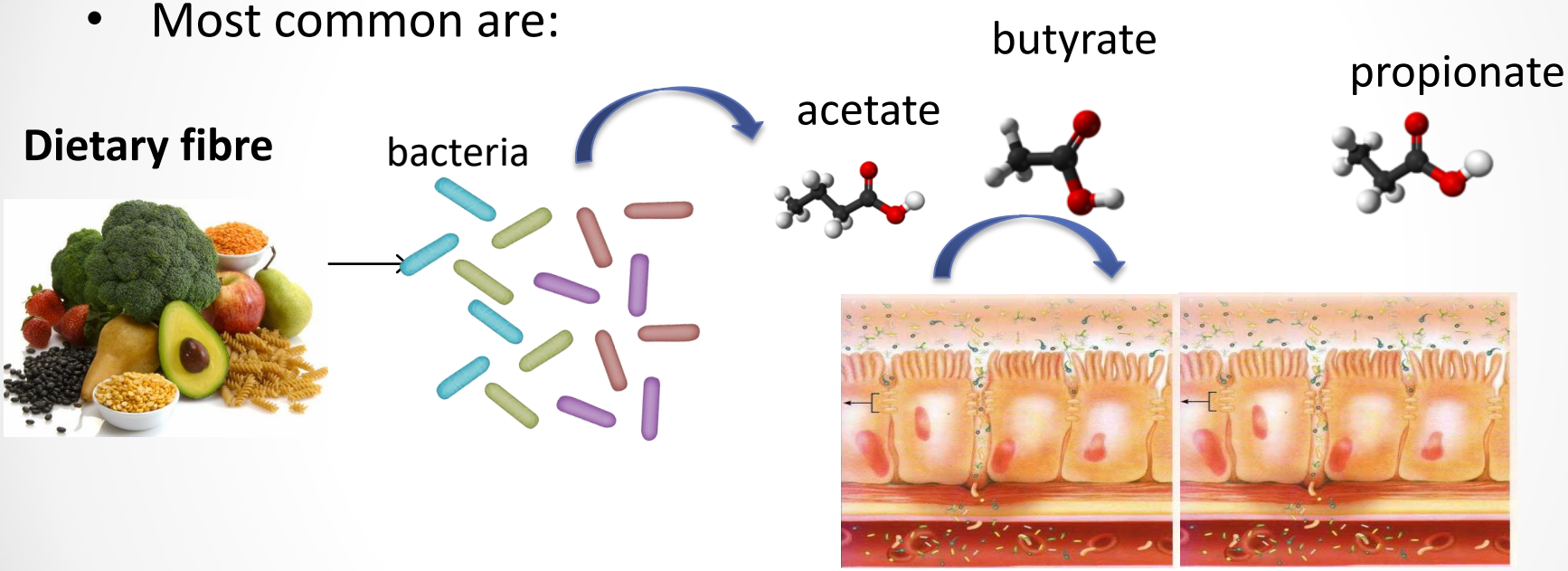
Diet and Inflammatory Disease

- Increase in diabetes and inflammatory diseases = ↑ popularity of Western-style diets
  - Diet (↓ fibre ↑ fat)

- Developing countries diets (↑ fibre) = ↓ inflammatory disease
  - Mediterranean diet = ↓ cardiovascular disease, asthma

Gut microbiota and Short-Chain Fatty Acids (SCFAs)

- SCFAs are produced by the gut microbiota from fermentation of dietary fibre
- Most common are:



- SCFAs are absorbed across the gut epithelium
- They pass through the portal vein to the liver – the primary site of metabolism

Hypothesis

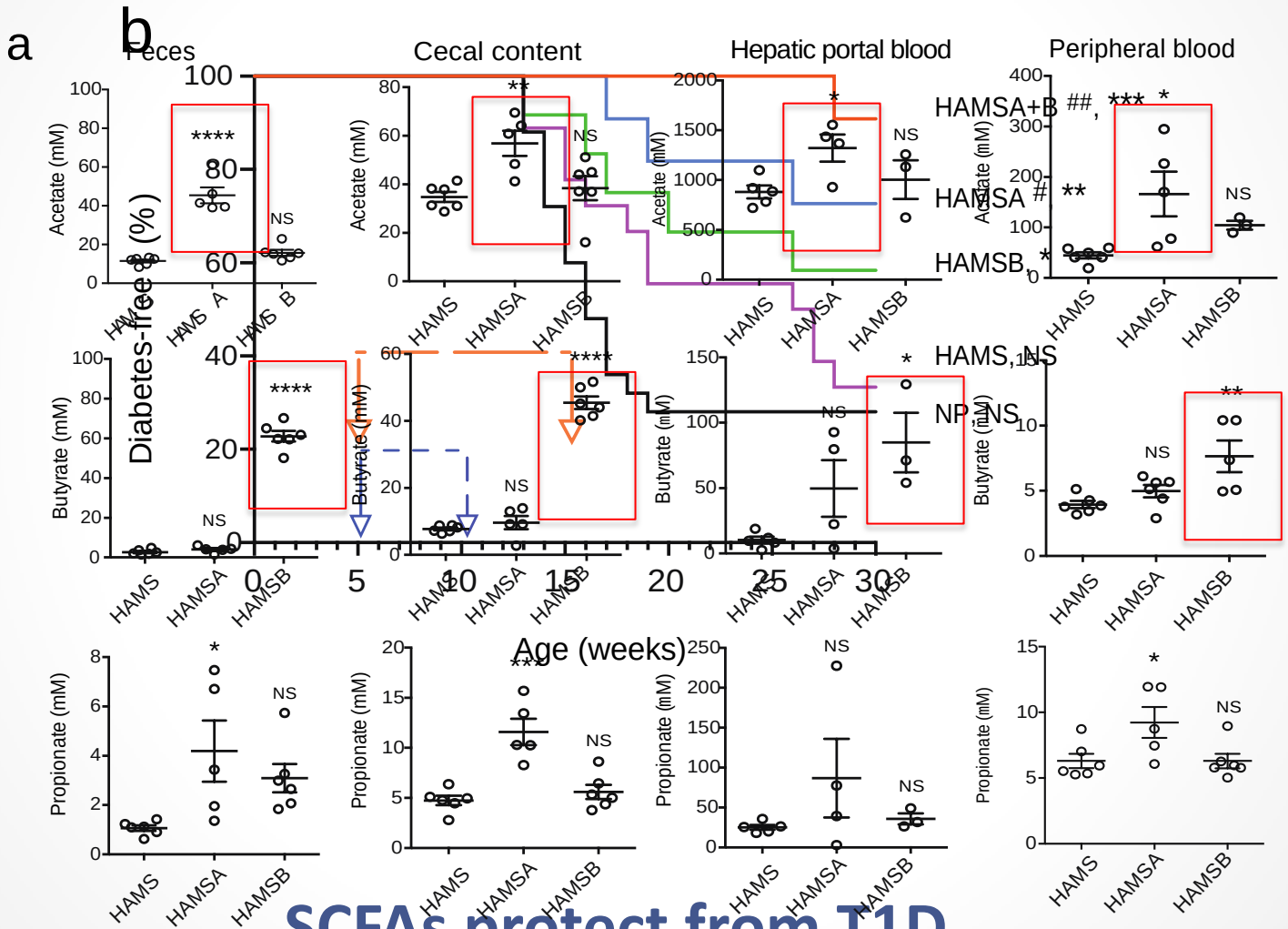
Diet alters gut microbiota and reduced production of microbial SCFAs affect immune tolerance that increase T1D susceptibility

Aim

To study the cellular and molecular mechanisms by which diet and SCFAs influence the course of autoimmune diabetes

HAMSA diet increase levels of acetate In plasma from NOD mice

Marino et al. Fig. 2



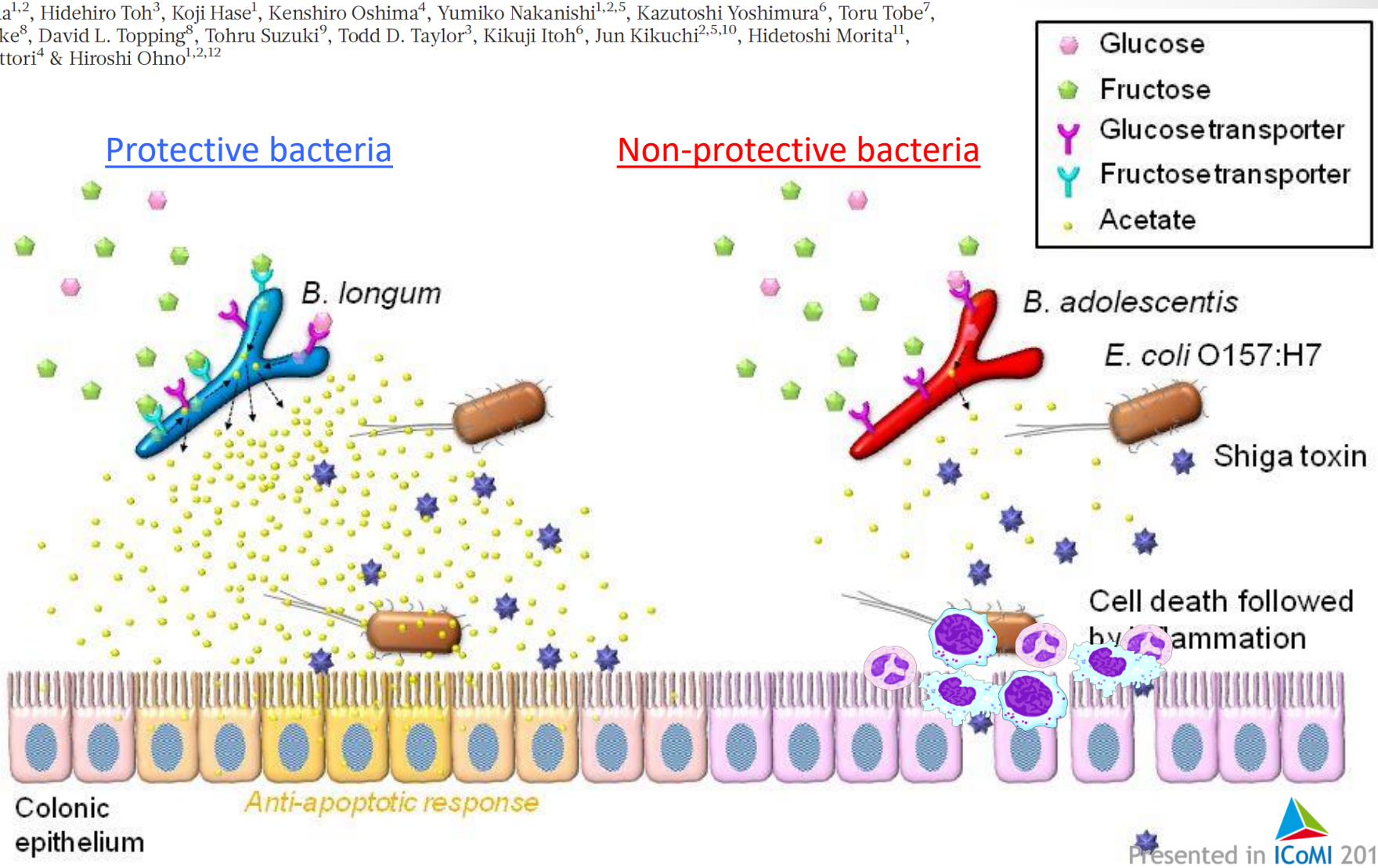
SCFAs protect from T1D

LETTER

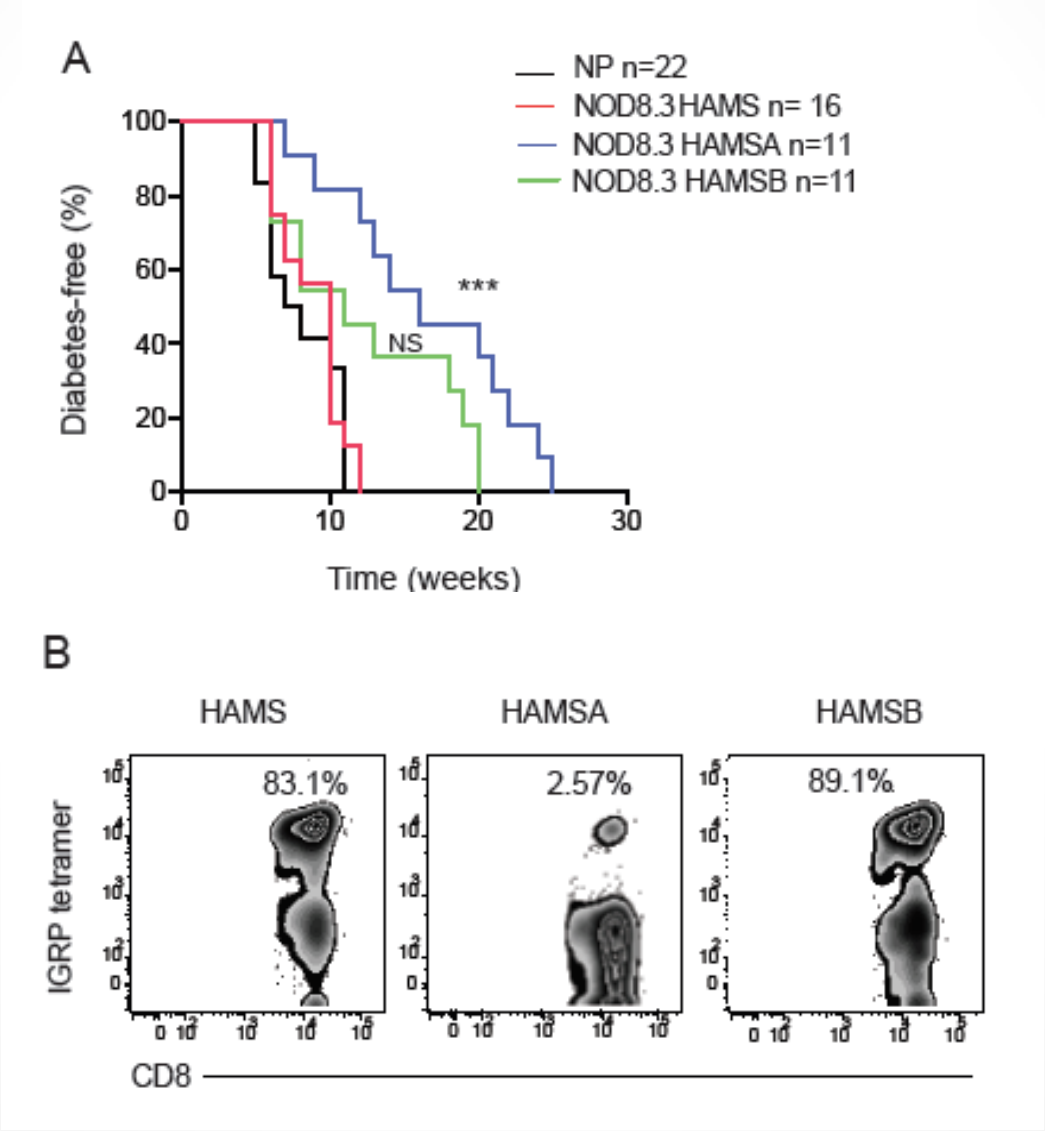
doi:10.1038/nature09646

Bifidobacteria can protect from enteropathogenic infection through production of acetate

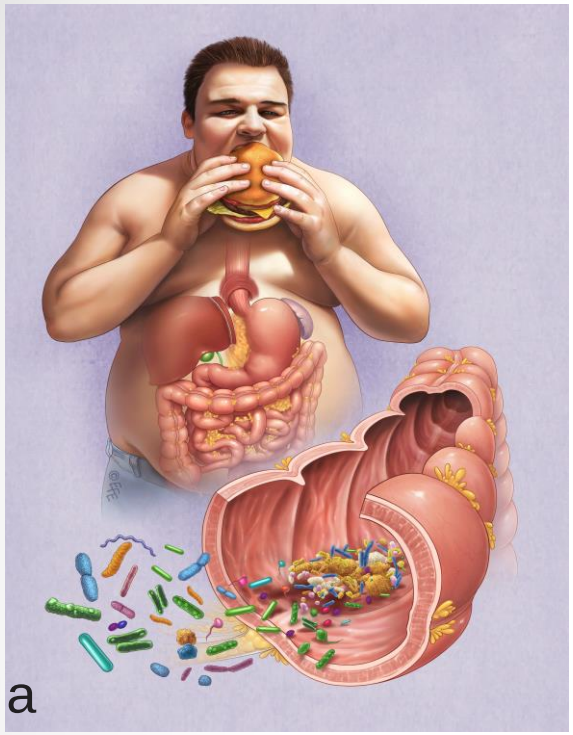
Shinji Fukuda[1,2], Hidehiro Toh[3], Koji Hase[1], Kenshiro Oshima[4], Yumiko Nakanishi[1,2,5], Kazutoshi Yoshimura[6], Toru Tobe[7], Julie M. Clarke[8], David L. Topping[8], Tohru Suzuki[9], Todd D. Taylor[3], Kikuji Itoh[6], Jun Kikuchi[2,5,10], Hidetoshi Morita[11], Masahira Hattori[4] & Hiroshi Ohno[1,2,12]

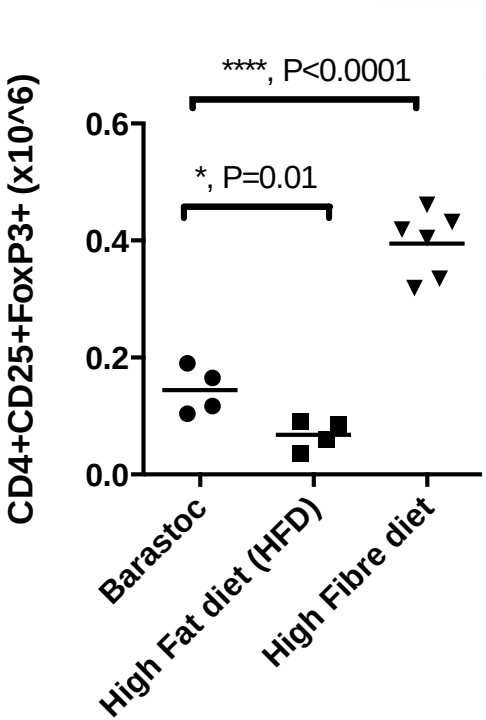


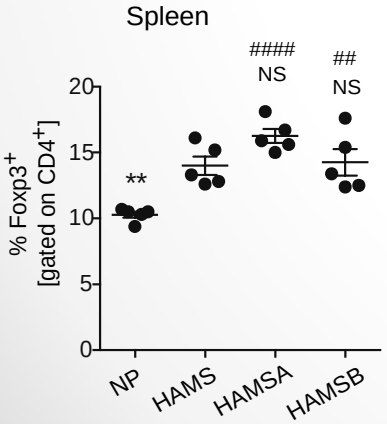
Acetate markedly reduces auto-reactive effector T cell numbers in NOD8.3 mice

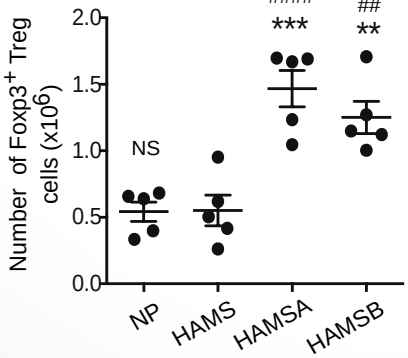


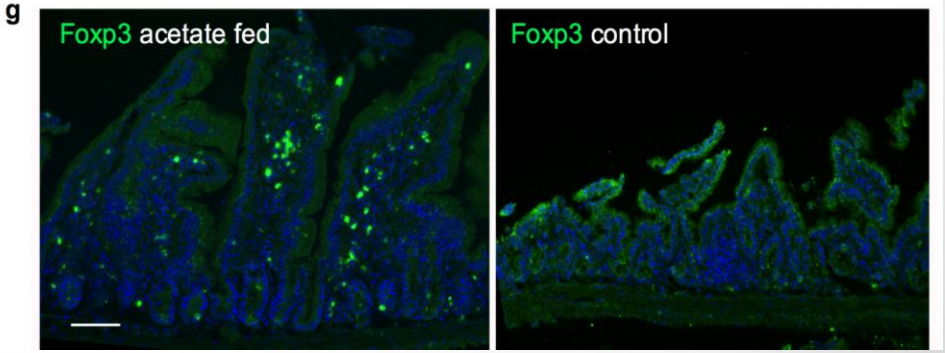
Diet controls peripheral Treg numbers



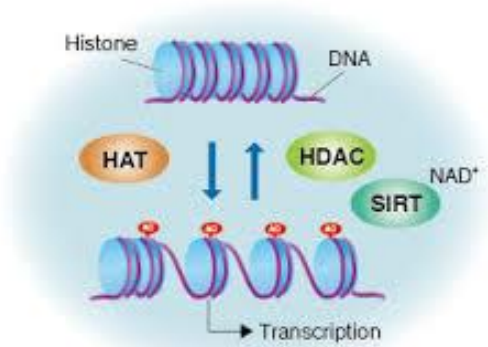




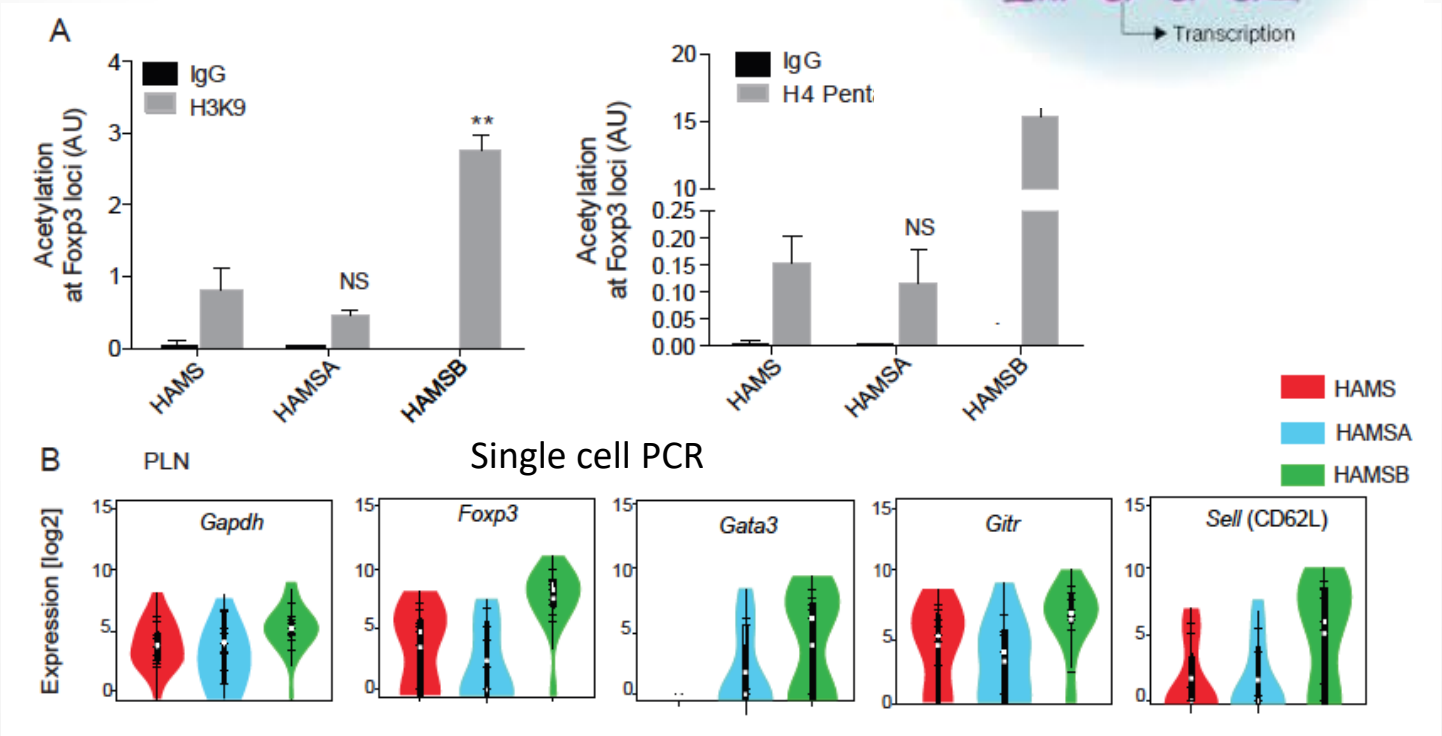




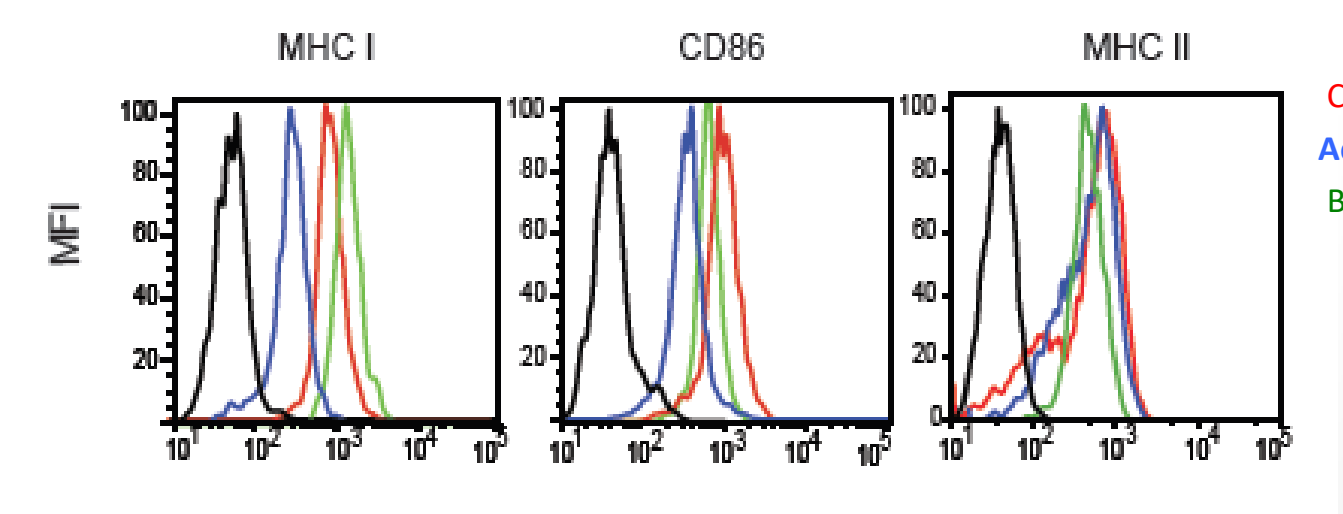
HDAC inhibition/ epigenetic mechanisms



Foxp3



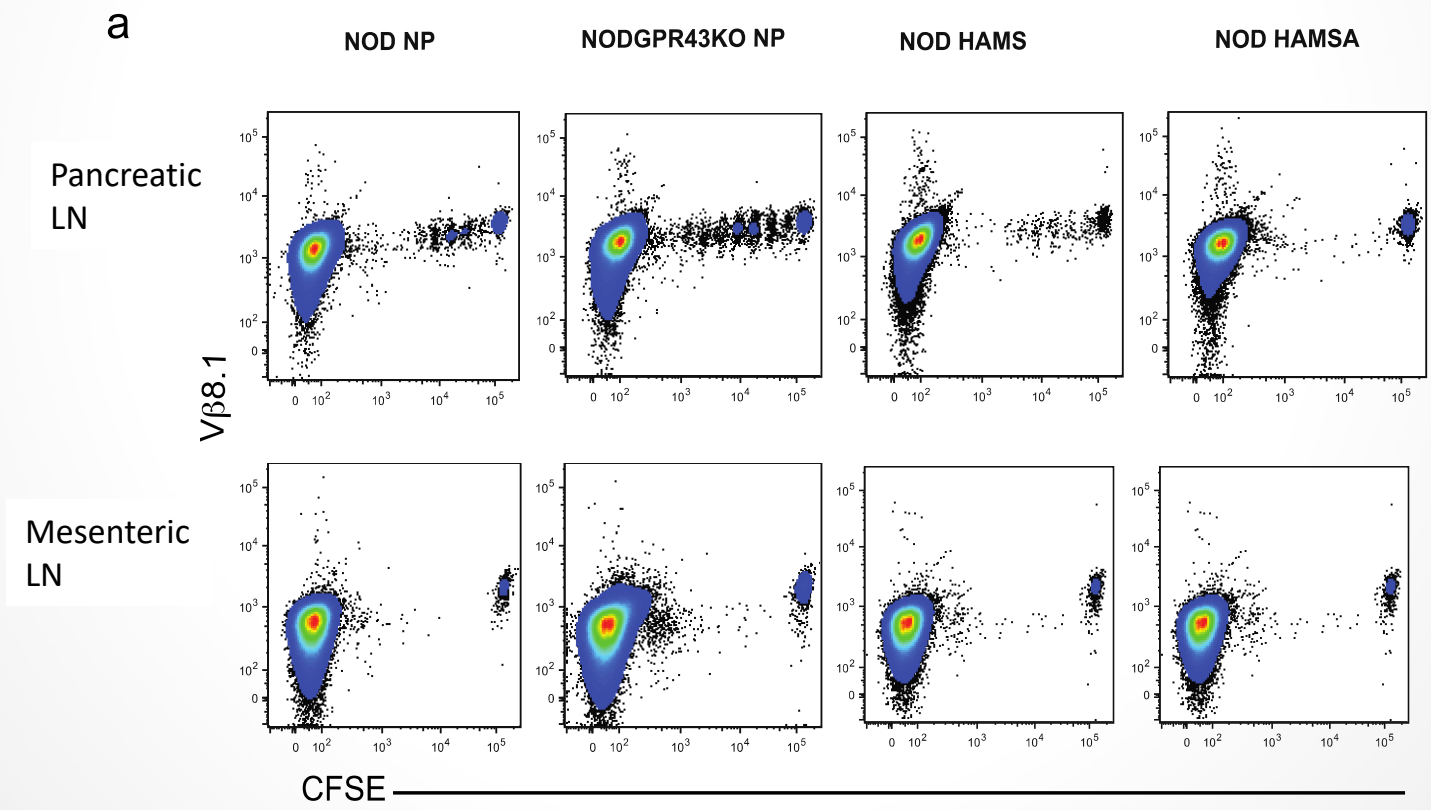
Diet (particularly acetate) changes MHC I and co-stimulatory molecules on B cells (and DCs)



Effector T cells don't proliferate when transferred to HAMSA fed mice

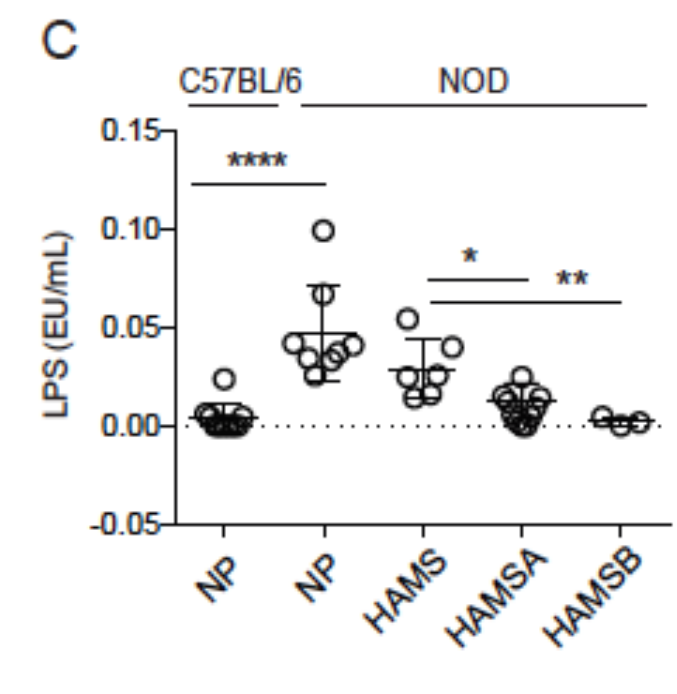
NOD8.3 TCR Tg CD8+ cells transferred to NOD on different diets

autoantigen (IGRP) recognised by transgenic TCR

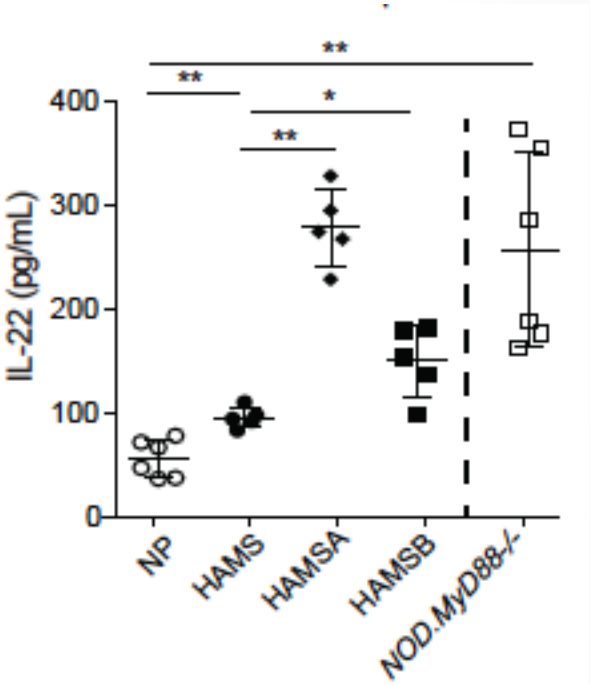


SCFAs improve barrier function

LPS in serum

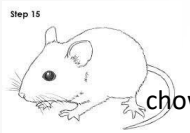


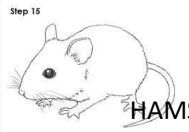
IL-22 (gut homeostasis) in serum

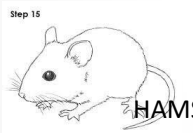


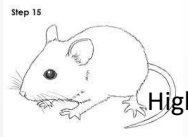
Microbiota shaped by different diets differs markedly contributes to disease susceptibility/protection

Mice on different diets

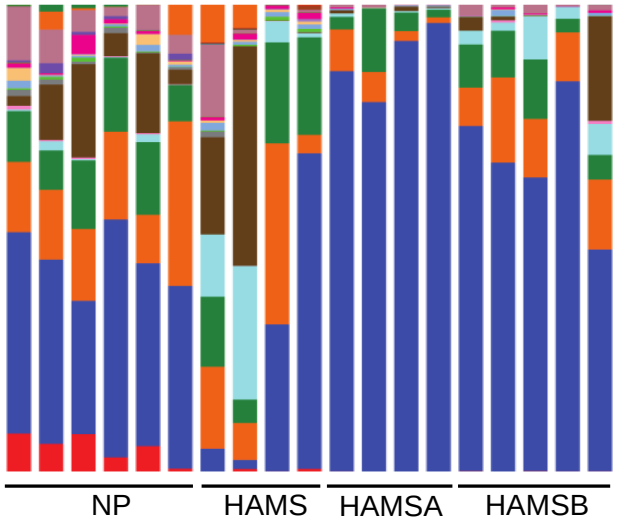


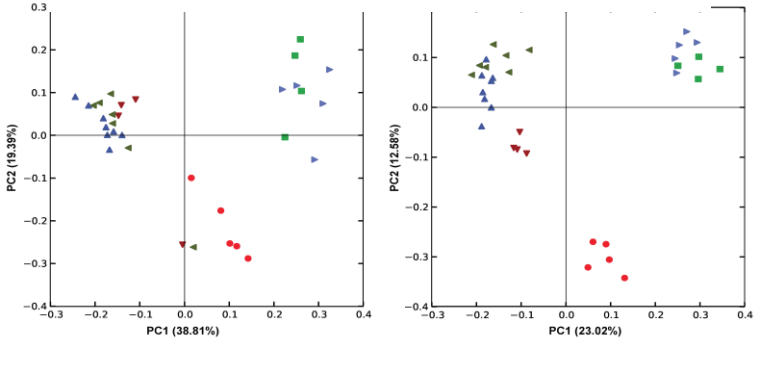




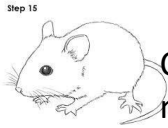


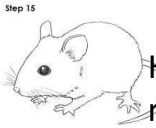
Dramtic changes in microbiota composition

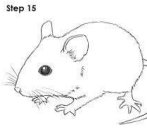


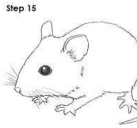


Germ free Mice on the same chow diet

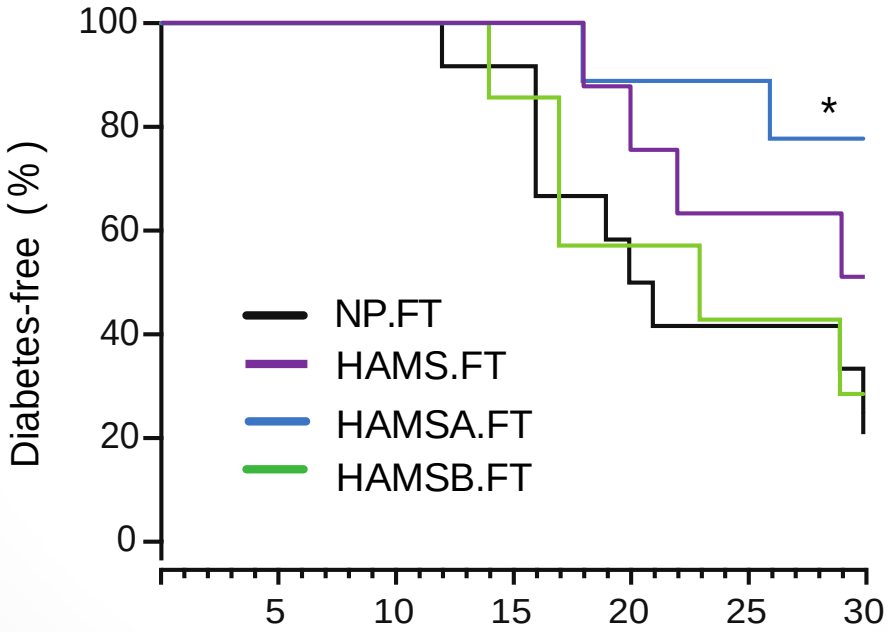








SCFA acetate change abundance of Bacteroidetes phyla in NOD mice associated with T1D protection



Summary

nature immunology

Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes

Eliana Mariño[1], James L Richards[1], Keiran H McLeod[1], Dragana Stanley[2], Yu Anne Yap[1], Jacinta Knight[1], Craig McKenzie[1], Jan Kranich[3], Ana Carolina Oliveira[4], Fernando J Rossello[5–7], Balasubramanian Krishnamurthy[8], Christian M Nefzger[5–7], Laurence Macia[1,9,10], Alison Thorburn[1], Alan G Baxter[11], Grant Morahan[12], Lee H Wong[1], Jose M Polo[5–7], Robert J Moore[13,14], Trevor J Lockett[15], Julie M Clarke[16], David L Topping[16], Leonard C Harrison[17] & Charles R Mackay[1]

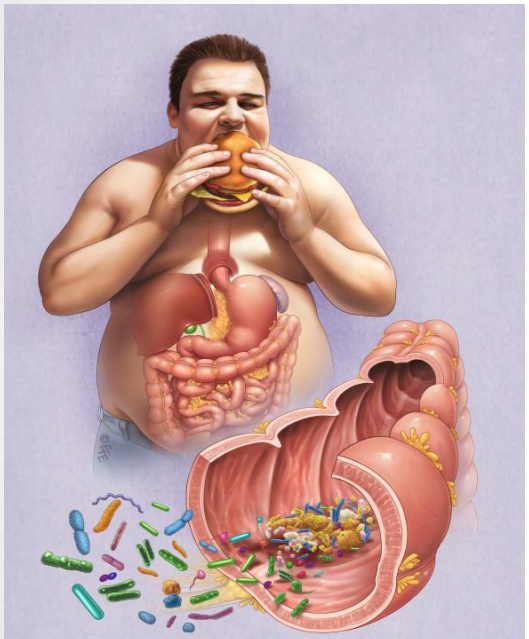
Received 7 October 2016; accepted 21 February 2017; published online 27 March 2017; doi:10.1038/ni.3713

Summary of mechanisms

- Improvements to gut homeostasis/integrity
- Effects on Treg biology
- Effects on co-stimulatory molecules on B cells/DCs
- Decreased autoimmune T effector numbers
- Changes in gut microbiota composition

Metabolites and disease

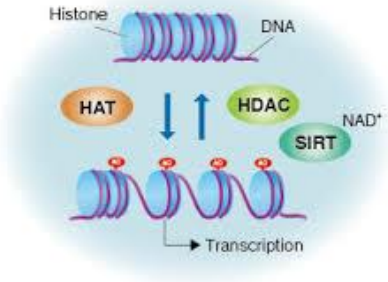
Western lifestyle diet
Hygiene? Antibiotic use?
Microbiota composition

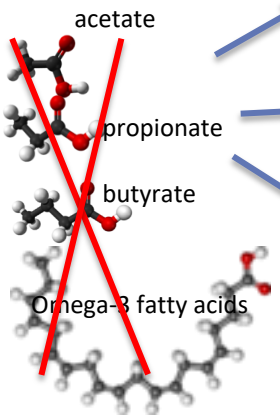


Tan et al Annual Review Immunol 2017

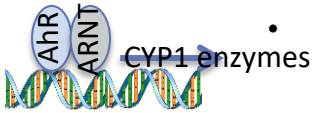
Dysbiosis
Leaky gut
LPS distribution

HDAC inhibition



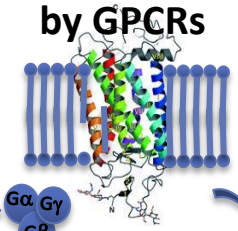


Transcription factors



- IL-22

Metabolite sensing by GPCRs



Cell shape/ motility

PI3K

MAP kinases

PKC

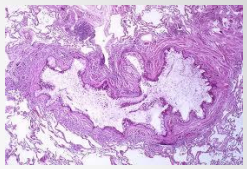
mTOR

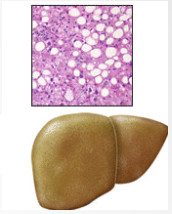
Inflammasome activation

β-arrestin2

TAK
NF-κB
Inhibition of inflammatory cytokines

Asthma

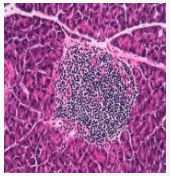




Fatty liver

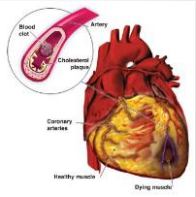
IBD

Type 1 diabetes



Food allergies

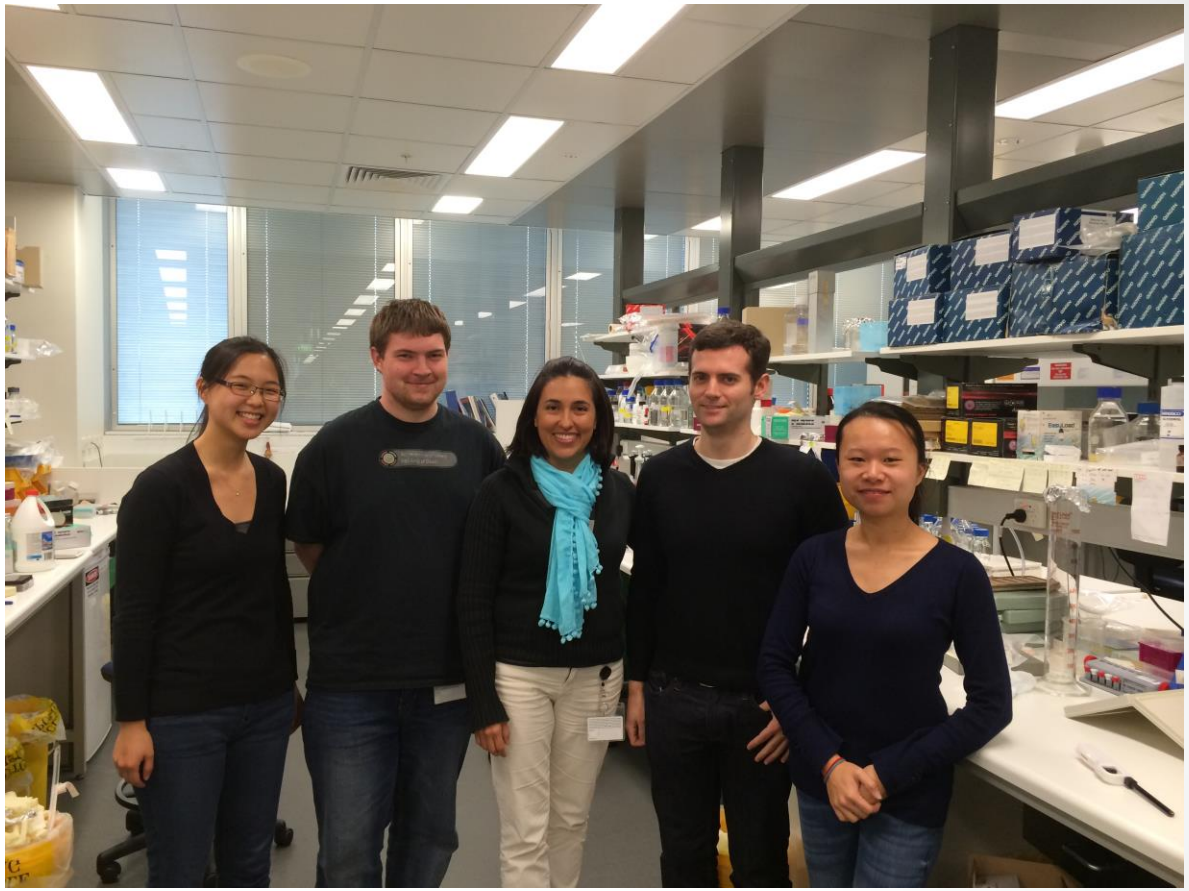
Cardiovascular



Neural conditions

Acknowledgements

- Prof Charles Mackay
- James Richards
- Keiran McLeod
- Yu Anne Yap



JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

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