PARTIE 2

« LE MICROBIOME »
de découverte en stupéfaction

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Colloque AIPI

16-18 mai 2016

Les maladies inflammatoires

- Maladies inflammatoires de l'intestin (MII)
  - Maladie de Crohn, colite ulcéreuse
  - Risque de SCA augmenté connu depuis 30ans
- Maladie coronarienne = maladie inflammatoire
- Arthrite rhumatoïde, SEP
- Maladies de peau (psoriasis)
- Alzheimer ? Autisme ?
- Troubles anxieux? Dépression ?

Le coup de tonnerre pas vraiment compris en 2008

NIH Public Access
Author Manuscript

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Specific microbiota direct the differentiation of Th17 cells in the mucosa of the small intestine

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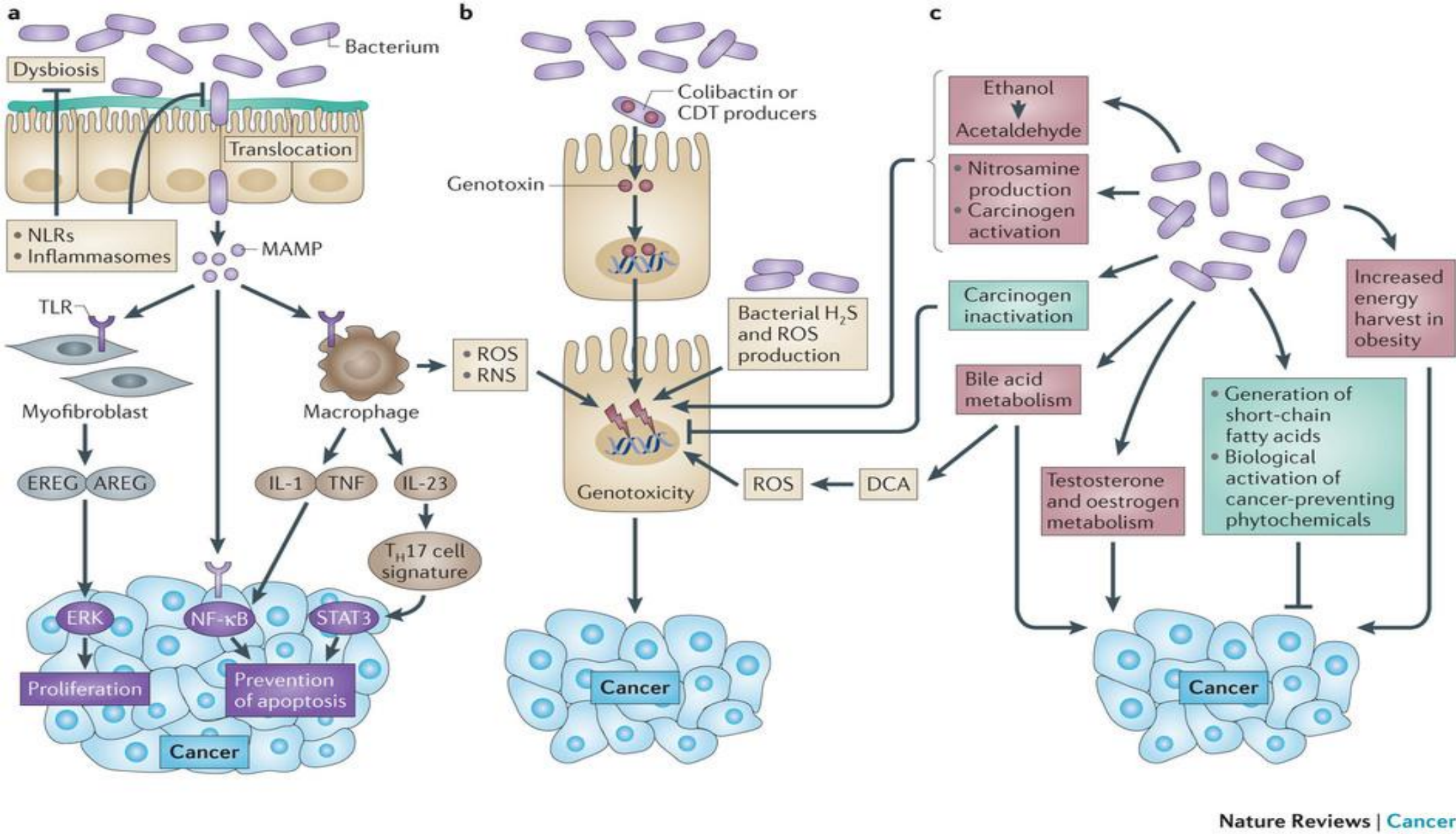


Nature Reviews | Cancer

OMS

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

Diet, nutrition, and the prevention of chronic diseases

Report of a
WHO Study Group

World Health Organization
Technical Report Series
797

World Health Organization, Geneva 1990

Diète et maladies?

- 1940, 1950, 1960 (hexane, DDT, BPC) ?
- 1990 Premier rapport de l'OMS
- 1995 Rôle du fructose, du gluten?
- 1997 Produits laitiers?
- 1998 Rôle de l'acrylamide?
- 2000 Procédés industriels?

Le microbiome et l'inflammation

- Plusieurs études convergent
- Altérations ou différence significatives
  - Santé = grande diversité dans le microbiome
  - Maladie = pauvreté du microbiome
- Quand l'intestin produit des cytokines inflammatoires tous les tissus susceptibles s'enflamment aussi

Depuis 1 an

American College of Cardiology (ACC) 2014 Scientific Sessions
Celiac Disease Linked to Almost Doubled Risk of CAD
Marlene Busko March 29, 2014

TheJournal of Allergy and Clinical Immunology
Administration of a probiotic with peanut oral immunotherapy: A randomized trial
Tang & al, March 2015

Mbio
Evidence of extensive DNA transfer between bacteroidales species within the human gut
Coyne & al., June 2014

Etc. etc. etc.

Liens directs avec les autres maladies inflammatoire ?

- Faits par plusieurs personnes depuis longtemps
  - Food that Fight Pain (Bernard MD)
  - Comment j'ai vaincu la douleur (Lagacé PhD)
- Études en cours pour plusieurs maladies
  - Alzheimer, PAR, Sclérodermie, Psoriasis etc
  - Autisme, syndrome anxiété/métab./diabète
  - Sclérose en plaques

Un mécanisme épigénétique

- < 5% de nos gènes codent pour des substances
- 90 % du matériel génétique sert à « contrôler » le <5% qui code nos composantes
- Les petits ARN ne sont pas du « junk »
- Les petits AN sont stables
- Les petits AN peuvent provenir du tube digestif
- Les bactéries s'échangent et échangent des AN

Études en cours

- Pour trouver la ou les bactéries ou parasites (amibes/vers) impliquées (rôle des oxyures?)
- Les interactions sont complexes
- Combiner aliments et microbiome ??
  - Ex.: Bifidobactéries et inuline (topinambour, artichauts)
- Pour diminuer les coups de santé reliés aux maladies chroniques
  - Ex.: la Chine

La SEP

- On savait depuis assez longtemps que:
  - Certains aliments modifient la fréquence des rechutes
    - » Déficience fréquente en vitamines D
  - Que certaines substances bactériennes déclenchent la maladie dans des modèles animaux
  - Que la transplantation de matière fécales (TMF) peut renverser le cours de la maladie (C. diff et constipation)
  - Que l'utilisation d'antibiotiques ou de probiotiques dans les modèles animaux modifie l'évolution de la maladie

SEP: une maladie auto-immune

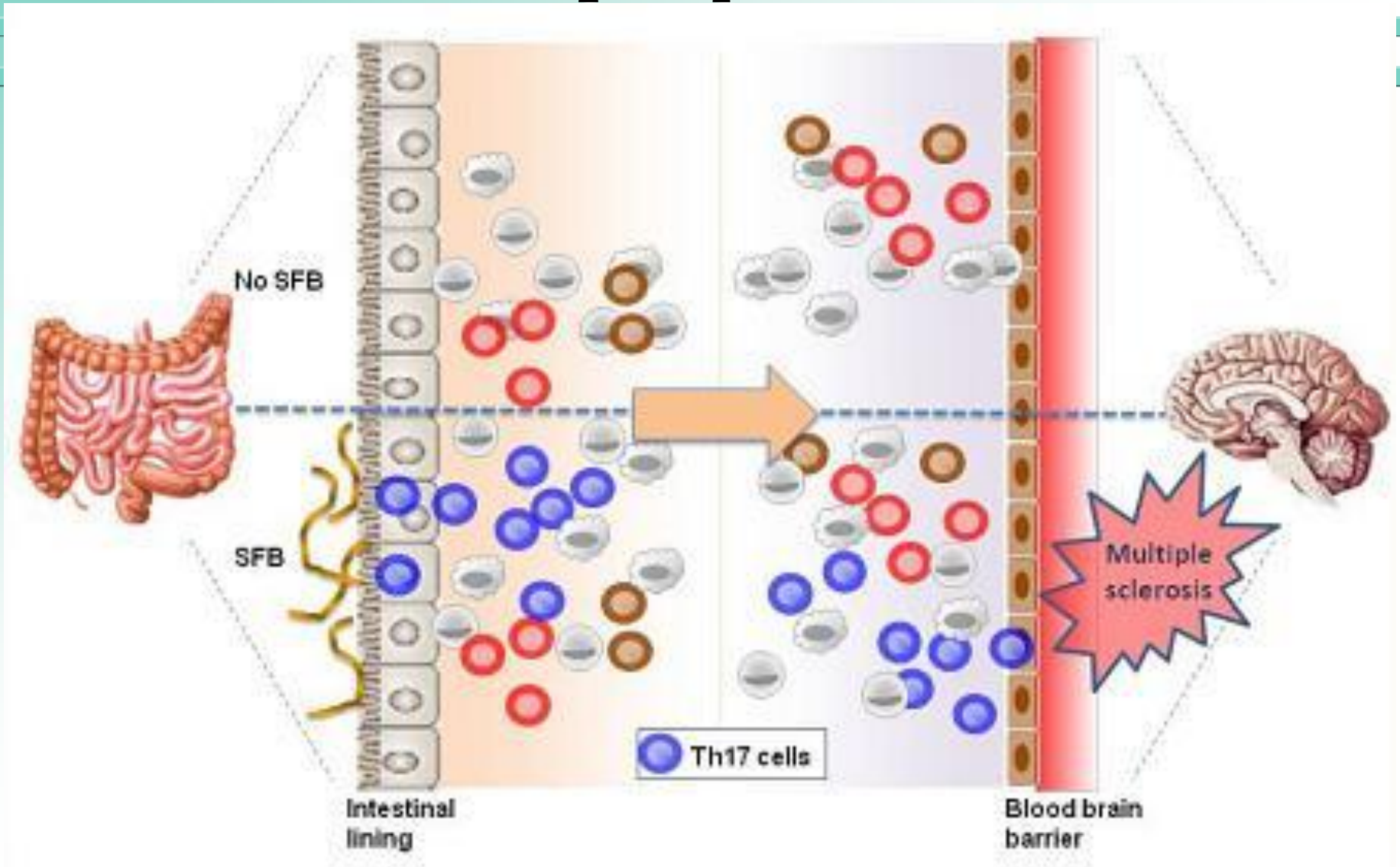
- Il y a production d'anticorps et/ou de cellules qui s'attaquent à la myéline

- La plupart des médicaments utilisés sont des immunomodulateurs visant à désactiver la réponse immunitaire productrice d'anticorps (anti-CD52, anti-CD25, anti-CD20) ou a reprogrammer la réponse immune (glatiramer)

Les cellules T_H17

- Les cellules Th17reg induisent une tolérance aux protéines du soi (IL-6 et TGF-beta)
- Les cellules Th17 induisent une réponse inflammatoire en présence de protéines étrangères (IL-23 et IL-1)
- Une même substance selon l'environnement peut induire une tolérance ou une défense.

La Sclérose en plaques



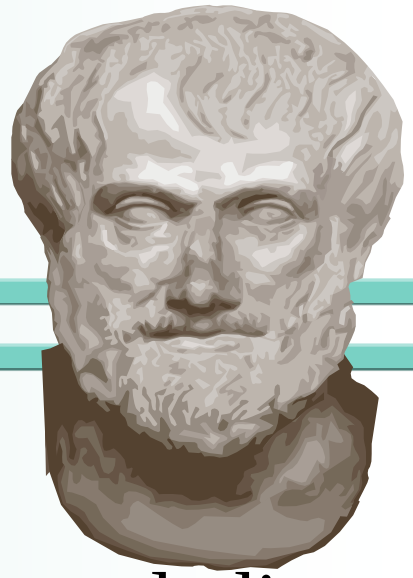
Les premières études 2014-2015

- Importantes anomalies ou différences dans les profils méta génomiques dans la majorité des cas de SEP avec récidives (Relapsing MS)
- Les études en cours visent à savoir si les modifications observées du microbiome précèdent ou sont la conséquence de la maladie.
- Des études pilotes visant à modifier le microbiome sont en élaboration ou en route.

La ou les conditions responsables ?

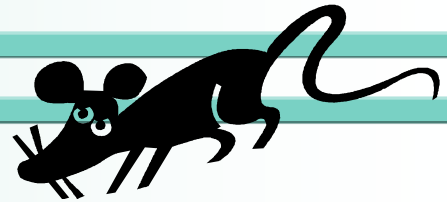
- La présence d'une substance analogue à la myéline (bactérienne ou alimentaire)
- La présence d'un environnement inflammatoire (gluten, lait cru, acrilamide etc.)
- L'absence des bon microbes inducteur de la tolérance (microbiote pauvre)
- Présence ou non de mauvais locataires (virus, bactéries, parasites)

La surprise ?



- On est ce que l'On mange
- Il y a un lien en notre alimentation et les maladies inflammatoires
- Néanmoins: les données scientifiques actuelles sont perçues comme une menace dérangeante
- Les microbes sont impliqués (et la solution?)
- Il faut penser à adapter notre nourriture pour ce quoi on est fait

L’alimentation et nos locataires



- Si on prend soins de nos locataires ils nous le rendent bien (croissance et protection)
- Si on les « empoisonnent », ils nous le font savoir: production d’hormones inflammatoires et maladies
  - Maladies inflammatoire de l’intestin
  - Intolérance
  - Maladies à distance

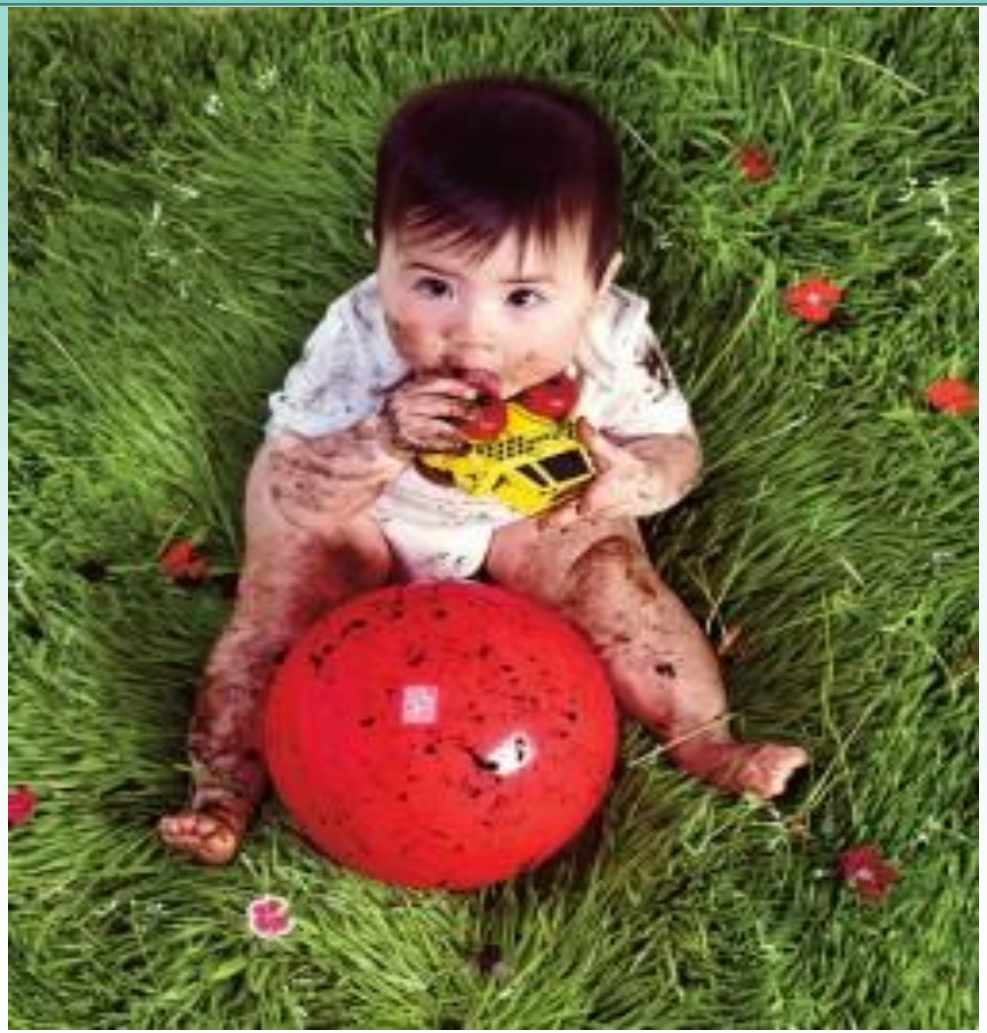
Prendre soins de nos microbes

- Diète proche de la nature
  - Fruits et légumes frais
  - Diminuer la bouffe industrielle
- Le moins possible d'antibiotiques

Les mauvaises nouvelles

- On leur fais de la misère depuis 70 ans
- La résistance aux antibiotiques était PRÉVISIBLE
- Les microbes s'échangent les gènes nécessaires à leur défense
- Si on continue comme on le fait maintenant: LA GUERRE EST INÉVITABLE (CDC)

Se construire un bon microbiome



Questions ?

LA FIN DES ANTI-BIOTIQUES EST PROCHE !
Sais-tu, j'ai plutôt envie d'un repas végétarien, finalement...
Rotisse
POULET BARBEC
Pascal

ARTICLE

doi:10.1038/nature11319

Gut microbiota composition correlates with diet and health in the elderly

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Alterations in intestinal microbiota composition are associated with several chronic conditions, including obesity and inflammatory diseases. The microbiota of older people displays greater inter-individual variation than that of younger adults. Here we show that the faecal microbiota composition from 178 elderly subjects formed groups, correlating with residence location in the community, day-hospital, rehabilitation or in long-term residential care. However, clustering of subjects by diet separated them by the same residence location and microbiota groupings. The separation of microbiota composition significantly correlated with measures of frailty, co-morbidity, nutritional status, markers of inflammation

Table 1. Comparison of Vegetarian With Nonvegetarian Dietary Patterns With Respect to All-Cause and Cause-Specific Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009

Characteristic	Deaths, Hazard Ratio (95% CI)				
	All-Cause	Ischemic Heart Disease	Cardiovascular Disease	Cancer	Other
All (N = 73 308), No. of deaths[a,b]	2560	372	987	706	867
Vegetarian	0.88 (0.80-0.97)	0.81 (0.64-1.02)	0.87 (0.75-1.01)	0.92 (0.78-1.08)	0.85 (0.73-0.99)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Men (n = 25 105), No. of deaths[a]	1031	169	390	273	368
Vegetarian	0.82 (0.72-0.94)	0.71 (0.51-1.00)	0.71 (0.57-0.90)	1.02 (0.78-1.32)	0.83 (0.66-1.04)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Women (n = 48 203), No. of deaths[a,c]	1529	203	597	433	499
Vegetarian	0.93 (0.82-1.05)	0.88 (0.65-1.20)	0.99 (0.83-1.18)	0.87 (0.71-1.07)	0.88 (0.72-1.08)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

[a] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/wk, 21-60 min/wk, 61-150 min/wk, and ≥151 min/wk), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night);

[b] Also adjusted by sex (male and female), menopause (in women) (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

[c] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

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Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Virgin olive oil and nuts as key foods of the Mediterranean diet effects on inflammatory biomarkers related to atherosclerosis

Mireia Urpi-Sarda[a,b], Rosa Casas[a,b], Gemma Chiva-Blanch[a,b], Edwin Saúl Romero-Mamani[a,b], Palmira Valderas-Martínez[a,b], Sara Arranz[a,b], Cristina Andres-Lacueva[c,d], Rafael Llorach[c,d], Alex Medina-Remón[b,c], Rosa M. Lamuela-Raventos[b,c], Ramon Estruch[a,b,*]

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[b] *CIBER 08/08: Fisiopatología de la Obesidad y la Nutrición and RD06/0045 Alimentación Saludable, Instituto de Salud Carlos III, Spain*
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Table 1
Concentrations of circulating inflammatory molecules at baseline and after 3 months of intervention with Med-Diet supplemented with virgin olive oil (Med-Diet with VOO), Med-Diet supplemented with nuts (Med-Diet with Nuts) or LFD in patients at high risk for cardiovascular disease.

	Med-diet with VOO ($n=35$)	Med-diet with nuts ($n=35$)	LFD ($n=36$)	Repeated-measures ANOVA[a]	*P* value for differences[b]		
				Time × treatment	MD-VOO vs MD-nuts	MD-VOO vs LFD	MD-nuts vs LFD
ICAM-1, μg/L							
Baseline	290 ± 104	270 ± 113	239 ± 103				
3 months	212 ± 93b[c]	208 ± 85b[c]	315 ± 148a[c]	<0.001	1.00	<0.001	<0.001
Change	−78 ± 122	−63 ± 118	76 ± 85				
VCAM-1, μg/L							
Baseline	1033 ± 311	962 ± 363	1023 ± 298				
3 months	857 ± 252b[c]	883 ± 329b	1147 ± 318a[c]	0.003	0.85	0.002	0.08
Change	−176 ± 275	−79 ± 440	124 ± 325				
IL6, ng/L							
Baseline	6.8 ± 4.6	6.8 ± 6.0	5.9 ± 5.3				
3 months	5.7 ± 3.7[c]	5.9 ± 5.5	7.3 ± 5.8[c]	0.002	1.00	0.004	0.019
Change	−1.2 ± 2.5	−0.9 ± 0.9	1.4 ± 2.7				
CRP, μg/L							
Baseline	4.0 ± 4.9	2.2 ± 1.9	2.8 ± 2.7				
3 months	2.5 ± 2.4[c]	2.5 ± 3.2	3.9 ± 5.7	0.024	0.20	0.025	1.00
Change	−1.5 ± 4.9	0.3 ± 2.5	1.1 ± 4.1				

Modified from Mena et al. [19].

Values are means ± SD. Means in a row with online letter (a,b) without a common letter differ, $P<0.05$ (Bonferroni post hoc test).

[a] Data were analyzed by repeated-measures 2-factor ANOVA ($P<0.05$).

[b] Data were analyzed by ANOVA ($P<0.05$).

[c] Different from baseline, $P<0.05$ (Bonferroni post hoc test).

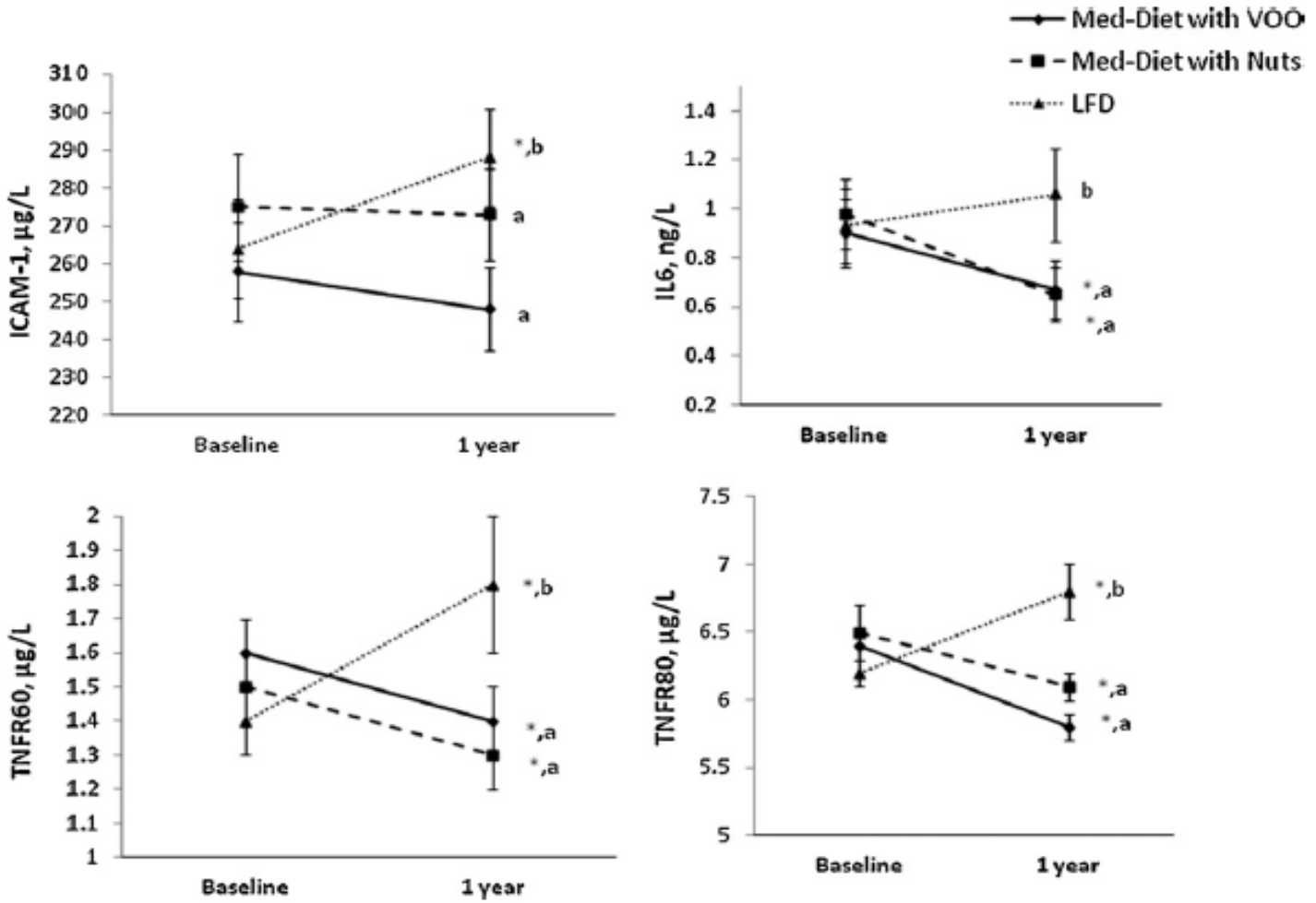

Fig. 2. Concentrations of circulating inflammatory molecules at baseline and after 1 year of intervention with Med-Diet supplemented with VOO, Med-Diet supplemented with nuts or LFD in patients at high risk for cardiovascular disease. Values are geometric means (95% CI). Data were analyzed by repeated-measures 2-factor ANOVA ($P < 0.05$). Changes between 1 year and baseline in response to the intervention treatment were analyzed by ANCOVA ($P < 0.05$). Repeated measures and ANCOVA were adjusted for age, gender, BMI, smoking status, physical activity and drugs (aspirin and statins). *Different from baseline, $P < 0.05$ (Bonferroni post hoc test). Changes in response to the intervention without a common letter differ ($P < 0.05$).

Modified from Urpi-Sarda et al. [20].

Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

Amandine Everard[a], Clara Belzer[b], Lucie Geurts[a], Janneke P. Ouwerkerk[b], Céline Druart[a], Laure B. Bindels[a], Yves Guiot[c], Muriel Derrien[b], Giulio G. Muccioli[d], Nathalie M. Delzenne[a], Willem M. de Vos[b,e], and Patrice D. Cani[a,1]

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Edited* by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved March 28, 2013 (received for review November 8, 2012)

Obesity and type 2 diabetes are characterized by altered gut microbiota, inflammation, and gut barrier disruption. Microbial composition and the mechanisms of interaction with the host that affect gut barrier function during obesity and type 2 diabetes have not been elucidated. We recently isolated *Akkermansia muciniphila*, which is a mucin-degrading bacterium that resides in the mucus layer. The presence of this bacterium inversely correlates with body weight in rodents and humans. However, the precise physiological roles played by this bacterium during obesity and metabolic disorders are unknown. This study demonstrated that the abundance of *A. muciniphila* decreased in obese and type 2 diabetic mice. We also observed that prebiotic feeding normalized *A. muciniphila* abun-

derived 3-gamma, RegIIIγ) or enterocytes (RegIIIγ) (10–12). Adaptive immune system effectors that are secreted into the intestinal lumen, such as IgA, may also restrict bacterial penetration into the host mucus and mucosal tissue (13). These immune factors allow the host to control its interactions with gut microbiota and shape its microbial communities (11).

The endocannabinoid system has also been implicated in the control of the gut barrier and inflammation (5, 14). One lipid in this system, 2-arachidonoylglycerol (2-AG), reduces metabolic endotoxemia and systemic inflammation (15). Another acylglycerol, 2-palmitoylglycerol (2-PG), potentiates the antiinflammatory effects

.pnas.org/cgi/doi/10.1073/pnas.1219451110

OPEN ACCESS Freely available online

PLoS MEDICINE

The Effect of Chromosome 9p21 Variants on Cardiovascular Disease May Be Modified by Dietary Intake: Evidence from a Case/Control and a Prospective Study

Ron Do[1], Changchun Xie[2,3], Xiaohe Zhang[2], Satu Männistö[4], Kennet Harald[4], Shofiqul Islam[2,3], Swneke D. Bailey[1], Sumathy Rangarajan[2], Matthew J. McQueen[2], Rafael Diaz[5], Liu Lisheng[6], Xingyu Wang[7], Kaisa Silander[4,8], Leena Peltonen[4,8†], Salim Yusuf[2], Veikko Salomaa[4], James C. Engert[1,9,10*], Sonia S. Anand[2,3*], on behalf of the INTERHEART investigators

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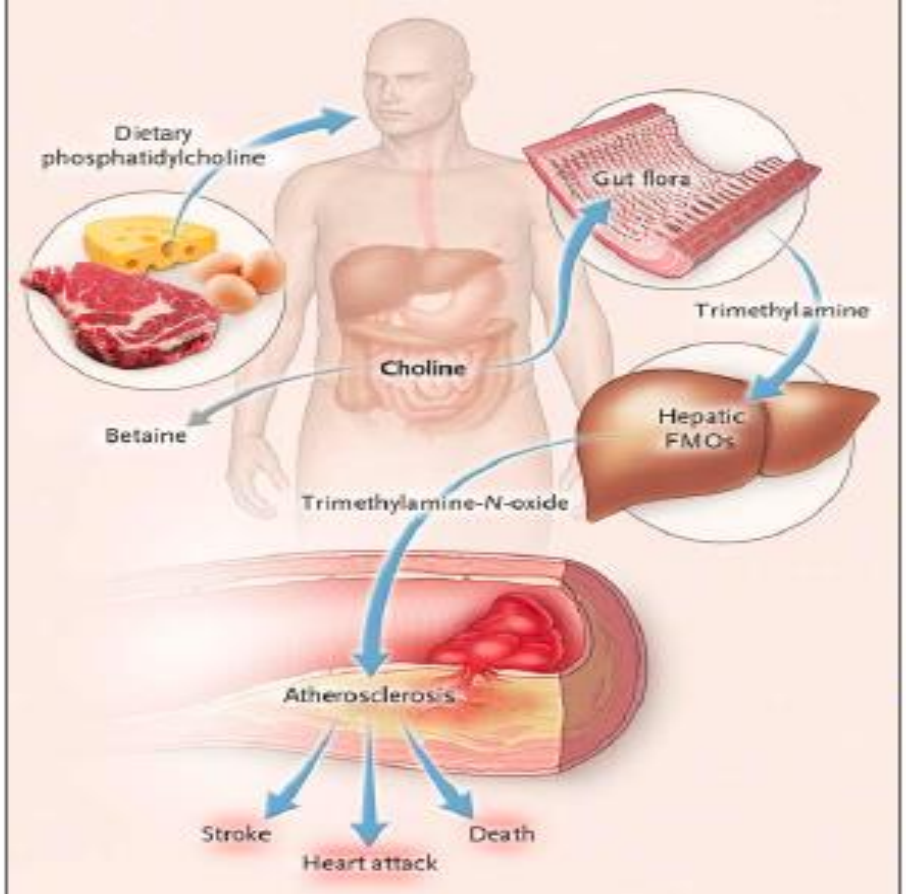

Figure 3. Pathways Linking Dietary Phosphatidylcholine, Intestinal Microbiota, and Incident Adverse Cardiovascular Events.

Ingested phosphatidylcholine (lecithin), the major dietary source of total choline, is acted on by intestinal lipases to form a variety of metabolic products, including the choline-containing nutrients glycerophosphocholine, phosphocholine, and choline. Choline-containing nutrients that reach the cecum and large bowel may serve as fuel for intestinal microbiota (gut flora), producing trimethylamine (TMA). TMA is rapidly further oxidized to trimethylamine-*N*-oxide (TMAO) by hepatic flavin-containing monooxygenases (FMOs). TMAO enhances the accumulation of cholesterol in macrophages, the accumulation of foam cells in artery walls, and atherosclerosis,[7] all factors that are associated with an increased risk of heart attack, stroke, and death. Choline can also be oxidized to betaine in both the liver and kidneys.[20] Dietary betaine can serve as a substrate for bacteria to form TMA[21] and presumably TMAO.

ORIGINAL INVESTIGATION

ONLINE FIRST

Vegetarian Dietary Patterns and Mortality in Adventist Health Study 2

Michael J. Orlich, MD; Pramil N Singh, DrPH; Joan Sabaté, MD, DrPH; Karen Jaceldo-Siegl, DrPH; Jing Fan, MS; Synnove Knutsen, MD, PhD; W. Lawrence Beeson, DrPH; Gary E. Fraser, MBchB, PhD

- **73 308 participants followed for a mean of 5.79 years**

Conclusions and Relevance: Vegetarian diets are associated with lower all-cause mortality and with some reductions in cause-specific mortality. Results appeared to be more robust in males. These favorable associations should be considered carefully by those offering dietary guidance.

JAMA Intern Med.
Published online June 3, 2013.

nature immunology

Lymphotoxin regulates commensal responses to enable diet-induced obesity

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Microbiota are essential for weight gain in mouse models of diet-induced obesity (DIO), but the pathways that cause the microbiota to induce weight gain are unknown. We report that mice deficient in lymphotoxin, a key molecule in gut immunity, were resistant to DIO. *Ltbr*$^{-/-}$ mice had different microbial community composition compared to their heterozygous littermates, including an overgrowth of segmented filamentous bacteria (SFB). Furthermore, cecal transplantation conferred leanness to germ-free recipients. Housing *Ltbr*$^{-/-}$ mice with their obese siblings rescued weight gain in *Ltbr*$^{-/-}$ mice, demonstrating the communicability of the obese phenotype. *Ltbr*$^{-/-}$ mice lacked interleukin 23 (IL-23) and IL-22, which can regulate SFB. Mice

published online 26 August 2012; doi:10.1038/ni.2403

Microbiota are essential for weight gain in mouse models of diet-induced obesity (DIO), but the pathways that cause the microbiota to induce weight gain are unknown. We report that mice deficient in lymphotoxin, a key molecule in gut immunity, were resistant to DIO. *Ltbr*$^{-/-}$ mice had different microbial community composition compared to their heterozygous littermates, including an overgrowth of segmented filamentous bacteria (SFB). Furthermore, cecal transplantation conferred leanness to germ-free recipients. Housing *Ltbr*$^{-/-}$ mice with their obese siblings rescued weight gain in *Ltbr*$^{-/-}$ mice, demonstrating the communicability of the obese phenotype. *Ltbr*$^{-/-}$ mice lacked interleukin 23 (IL-23) and IL-22, which can regulate SFB. Mice deficient in these pathways also resisted DIO, demonstrating that intact mucosal immunity guides diet-induced changes to the microbiota to enable obesity.