expression of certain antimicrobial elicitors and cytokines/chemokines by activating downstream kinases and transcription factors, including nuclear factor-κB (Cell Host Microbe 2008;3:352–363). Others and we have recently emphasized the important role of NOD2 in the pathogenesis of Crohn's disease (CD). NOD2 is involved in innate and adaptive immunity by enabling cell-intrinsic responsiveness to the muramyl dipeptide MurNAc-L-Ala-D-isoGln (MDP), which is a common motif found in the peptidoglycan of both Gram-positive and Gram-negative bacteria. Interestingly, systemic administration of MDP protects against dextran sulphate sodium–induced colitis (J Clin Invest 2008;118:545–559) and streptozotocin-induced T1D (Int J Immunopharmacol 1988;10:293–298). However, the CD-associated *NOD2* variants were not predisposing to T1D (Mol Genet Metab 2005;86:379–383). In genetically predisposed individuals, T1D or CD development may be accelerated by the host's failure to prevent tissue damage and to drive an optimal immunologic response to distinct signals derived from the microbiota (Nature 2007;448:427–434; Cell 2007;131:33–45). Noteworthy, shifts of the microbiota seem to be disease-specific (Gastroenterology 2008;134:577–594). Several fundamental issues remained, therefore, to be elucidated. Which host molecules and which cognate microbiota-derived agonists are sufficient to prevent destruction of insulin-secreting β-cells independently of MyD88?

Beside bacterial threats, epidemiologic studies unveiled that certain chronic picornaviruses infections, including the B4 Coxsackievirus that is replicating in the gut, may be involved in T1D pathogenesis (Lancet 1995;346:221–223). In mice, diabetes may be accelerated by type 1 interferon-mediated antiviral response (Proc Natl Acad Sci U S A 2008;105:12439–12444; Nat Med 2005;11:120–121). Genetic and biochemical analyses recently identified the RIGI-like receptor (RLR) family member melanoma differentiation-associated gene-5 (Mda-5) in host defence against picornaviruses and in T1D pathogenesis (Nat Genet 2006;38:617–619; Nature. 2006;441:101–105). Notably, Mda-5, also referred as interferon-induced helicase or IFIH1, functions as an essential *hitherto* cytosolic sensors that regulate type I interferon-mediated response to viral double-stranded RNA. The A946T IFIH1 mutation (referred as rs1990760) confers strong protection against T1D (Nat Genet 2006;38:617–619). It begs, therefore, the question of whether impaired engagement of Mda-5 may predispose or protect to T1D independently of MyD88. Viral epidemic gastroenteritis are primarily caused by norovirus infection, which is also sensed by Mda-5 (PLoS Pathog 2008;4:e1000108). Whether the apparently controversial role of the microbiota in immunocompetent hosts between SPF animal facilities may result from mouse norovirus infection remains to be investigated (PLoS Pathog 2008;4:e1000108; Nature 2008;455:1109–1113).

In 1989, Strachan proposed the hygiene hypothesis to account for the increased incidence of allergic diseases in developed countries (BMJ 1989;299:1259–1260). More recently, Bach hypothesized that T1D may be favoured by changes of the composition of the microbiota at early days of life through antibiotic use and/or attendance to day-care centers (N Engl J Med 2002;347:911–920). Integrated evaluation of the functional impact of changes in microbiome composition, together with the elucidation of the pivotal role of viral infections, will yield a better understanding of the pathogenesis of T1D. In the future, targeting Mda-5 or an as-yet uncharacterized T1D-protective RLR/NLR might represent a novel anti-diabetogenic strategy aimed at restoring gut integrity and/or preventing apoptosis of insulin-secreting β-cells. Noteworthy, correcting T1D-associated shifts of the microbiota might ultimately represent rational therapeutic approaches designed at preventing autoimmunity.

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## THE FODMAP DIET FOR IRRITABLE BOWEL SYNDROME: FOOD FAD OR ROADMAP TO A NEW TREATMENT PARADIGM?

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The role of restricting dietary fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in patients with irritable bowel syndrome (IBS) was recently evaluated by Shepherd et al in a randomized, double-blinded, quadruple-arm, crossover, placebo-controlled, rechallenge trial. The investigators studied 25 Australian patients with IBS as defined by the Rome II criteria and fructose malabsorption (FM) diagnosed by a positive fructose hydrogen breath test (HBT) following a 35-g fructose load. Notably, all 3 IBS subtypes—constipation-predominant, diarrhea-predominant, and mixed bowel habits—were included. Eligible subjects had received instruction in a low FODMAP diet ≥3 months before recruitment, and experienced marked and sustained global improvement in gastrointestinal (GI) symptoms on the low FODMAP diet. Celiac disease, inflammatory bowel disease, other serious comorbidities, or medications influencing GI symptoms were all exclusion criteria.

All patients were provided with a low FODMAP diet for the duration of the study. The diet was a 4-week rotation of foods low in FODMAPs calculated for the specific energy requirements of each patient and in compliance with the Australian Recommended Daily Intakes for macronutrients and micronutrients. Excluded foods (those high in FODMAPs) were fruits containing fructose in excess of glucose (apples, pears, watermelon), vegetables containing fructan (onions, leeks, asparagus, artichokes), wheat-based products, foods containing sorbitol, foods containing raffinose (legumes, lentils, cabbage, brussel sprouts), and foods containing lactose (if the patient had lactase deficiency as diagnosed by a HBT after a 50-g lactose load). Patients were also provided with a list of suitable foods when dining out. Patient adherence to diet was determined by diary entries. Patients' specific symptoms (overall abdominal symptoms, wind, bloating, abdominal pain, tiredness, nausea) were assessed by a severity score on the 100-mm visual analog score (VAS), whereas more general assessments were obtained by daily diary entries comprising the global symptom question, "Were your symptoms adequately controlled in this phase?" This latter question was answered at the end of each dose phase and weekly during washout periods.

The subjects were provided with a low FODMAP diet for ≥10 days at the start of the study, and subsequently underwent 3 phases of the study in which they ingested premixed drinks containing 1 of 4 test substances (fructans, fructose alone, fructan and fructose mix, and glucose) at varying doses (low, medium, or high). The subjects consumed low-dose drinks with 3 meals per day for 3 days, followed by medium-dose drinks with meals for 3 days, and finally high-dose drinks with meals for the remainder of 2 weeks. Patients were allowed to withdraw from a phase early if they experienced intolerable symptoms. A washout period of ≥10 days was used between test phases with patients continuing a low FODMAP diet throughout. A subsequent test substance challenge was not permitted until a patient returned to his or her baseline symptom level for ≥7 days. The primary end point was the answer to the question, "Were your symptoms adequately controlled in this phase?"; secondary end points were VAS scores for individual symptoms at the highest test substance dose taken as well as at each specific dose.

With regard to the primary end point question—"Were your symptoms adequately controlled in this phase?"—a similar proportion of patients receiving fructose, fructans, or a mix of the 2 answered positively. However, a significantly greater proportion of patients receiving glucose answered this question positively as compared with patients receiving fructose, fructans, or a mix of the 2.

As compared with the glucose phase, patients in the fructose, fructans, or fructose and fructans mix phase reported significantly higher VAS scores for overall abdominal symptoms, abdominal pain, wind, and bloating. In addition, the reported intensity of each of these symptoms increased in relation to increasing doses of fructose, fructans, or a mix of the 2. There was no similar dose-dependent symptom intensity variation for glucose. There were no statistically significant differences in VAS scores for nausea or tiredness across all groups. As compared with fructose alone, a combination of fructose and fructans was associated with significantly higher symptom severity. A similar difference was not identified when comparing fructose to fructans, or fructans to a fructose and fructan mix.

**Comment.** IBS remains a disorder defined by the presence of characteristic symptoms, including some combination of abdominal pain and altered bowel habits. The clinical presentation of patients with IBS is highly variable. Not surprisingly, then, a unifying physiologic abnormality or biomarker has thus far not been identified for IBS. In fact, recent studies suggesting that celiac disease, microscopic colitis, and small intestinal bacterial overgrowth can masquerade as IBS should teach us that this condition likely represents a number of different diseases that happen to present with similar symptoms. As our understanding of the physiologic abnormalities that underlie the different disease subgroups that constitute IBS improves, so too will diagnostic testing strategies and, ultimately, our ability to choose the most appropriate therapy for an individual patient. However, until such a time, we are left with symptoms as the primary guide to the management of IBS patients.

One of the more consistent clinical features of IBS is an association between the development of symptoms and the ingestion of food. Nearly two thirds of patients with IBS associate symptoms with eating a meal, and this finding is particularly common in female patients who have underlying anxiety (Digestion 2001;63:108–115). Despite this very practical clinical observation, surprisingly little attention has been paid to the role of specific foods in the genesis of IBS symptoms.

IBS patients frequently report multiple food "allergies." However, only a small subset of IBS patients have true food allergies based on serum immunoglobulin E testing (Eur J Clin Nutr 2006;60:667–672). The most common true food allergies include peanuts, tree nuts, fish, shellfish, milk, eggs, soy, and wheat (www.cfsan.fda.gov/~dms/wh-alrgy.html). On the other hand, the prevalence of less well-characterized food hypersensitivities and intolerances remain unclear, but is likely to be higher than true food allergies (Ann Allergy 1989;62:94–99; Am J Gastroenterol 2005;100:1550–1557). The potentially important role of food in IBS symptoms is underscored by studies reporting benefits for exclusion diets (J Am Coll Nutr 2006;25:514–522; Gut 2004;53:1459–1464) as well as oral cromolyn sulfate, a mast cell inhib-