GUT MICROBIOTA

Diet promotes dysbiosis and colitis in susceptible hosts

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New findings demonstrate novel interactions between diet, bacteria, genetic susceptibility and immune responses in IBD. Milk fat increases production of taurocholine-conjugated bile acids, which promotes growth of sulphate-reducing bacteria that cause immune-mediated colitis in susceptible mice. These observations will guide human studies that might improve dietary advice for patients with IBD.

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Physicians are poorly equipped to answer one of the questions most frequently posed by patients with Crohn's disease and ulcerative colitis: how should I alter my diet to control my disease?[1] Many patients are convinced that diet affects their disease course and symptoms, and consequently alter their food intake on the basis of their personal experiences.[2] Evolving dietary patterns are plausible environmental mediators of the increased incidence of IBD in the second half of the 20th century in North America and Western Europe, and of the more recent explosion in incidence of these diseases in Asian, Eastern European and South American countries that have adopted Western lifestyle practices.[3] Now, in elegantly designed experiments in mice, Devkota and colleagues[4] convincingly demonstrate that ingesting saturated milk fat promotes more aggressive colitis in IL-10-deficient mice, by expanding a normally rare bacterial population that induces pathogenic T-helper-1 (T_H1) immune responses.

The investigators carefully dissected how consuming milk fat indirectly altered the bacterial community structure.[4] Ingestion of saturated milk fat (37% of consumed calories) by mice selectively expanded a population of normally low abundance sulphate-reducing Deltaproteobacteria, of which *Bilophilia wadsworthia* is prototypical. Isocaloric consumption of polyunsaturated fat (safflower oil) altered faecal bacterial profiles in the mice, but did not promote growth of Deltaproteobacteria or *B. wadsworthia*. High levels of milk-fat consumption also increased the incidence and aggressiveness of experimental colitis and proinflammatory cytokine production in IL-10-deficient mice, but had no detrimental effect on wild-type mice. Expansion of the *B. wadsworthia* population was dependent on increased concentrations of taurine-conjugated bile acids as a result of ingestion of milk fat. As its name implies, *B. wadsworthia*—and other functionally

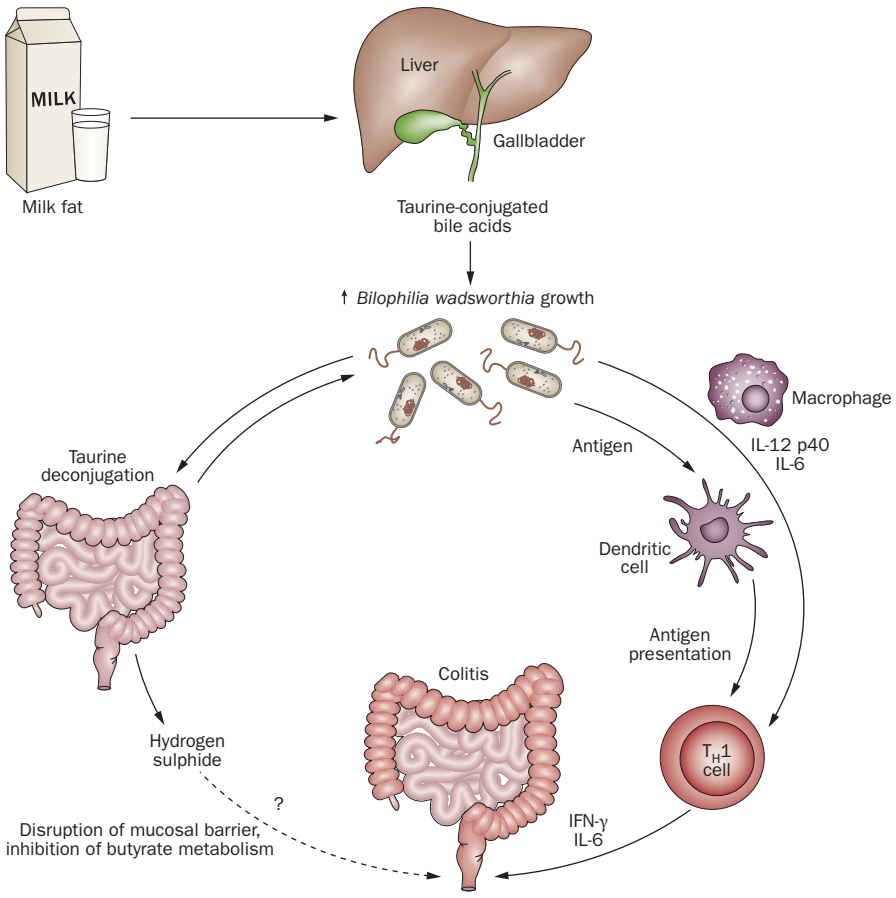

Figure 1 | Diet promotes dysbiosis and colitis in susceptible hosts. Milk fat stimulates production of taurine-conjugated bile acids, which in turn increases intraluminal growth of *Bilophilia wadsworthia*. This organism then stimulates production of immune cytokines by macrophages and dendritic cells, which then stimulate bacterial-antigen-specific T_H1 cells to secrete IFN-γ that causes colitis. An alternative pathway that might be involved, hence the question mark, is *B. wadsworthia* deconjugation of taurine leading to hydrogen sulphide formation that possibly disrupts the mucosal barrier and inhibits colonic epithelial metabolism. Abbreviations: IFN, interferon; IL, interleukin; T_H1, T-helper-1.

similar bacterial species containing the dissimatory sulphite reductase A gene (*dsrA*)—flourish in the presence of taurocholate (taurocholic acid, a sulphur-containing bile acid) owing to their ability to reduce sulphur, which generates hydrogen sulphide. Growth of *B. wadsworthia* in selectively colonized (monoassociated) gnotobiotic *Il10*$^{-/-}$ mice required exogenous taurocholine in the absence of milk-fat consumption, and taurocholine-fed monoassociated *Il10*$^{-/-}$ mice developed colitis and had increased IFN-γ production. Thus, ingestion of saturated milk fat promotes a progression of events that culminates in potentiated risk of colitis in a susceptible host (Figure 1). Milk fats increase the amount of taurine-conjugated bile acids that promote growth and metabolic activity of sulphate-reducing, bile-acid-tolerant bacterial species, such as *B. wadsworthia*, which in turn stimulate pathogenic immune responses in genetically susceptible hosts.

The inherent complexity of this disease model, in which environmental (dietary), microbial, immunological and genetic variables interact to cause inflammation, might help explain several unresolved clinical observations in patients with IBD. Incomplete disease penetrance in monozygotic twins, rapid changes in disease incidence, asymmetric geographical distribution and reactivation of clinical activity after long quiescent periods strongly implicate environmental influences in IBD, but characterizing these influences and the mechanisms by which they affect disease susceptibility has been challenging.[5] In parallel, our understanding of the influence of diet on inflammation, microbiota composition and bacterial function has lagged considerably behind the widespread belief of patients that dietary consumption influences their symptoms and disease activity.[2]

Enteric microbiota are firmly implicated in the pathogenesis of IBD,[6] and food and bacteria are most probably integrally linked in the development of the disease.[7] Diet can influence enteric bacteria in several ways. Sustained consumption of foods high in fat and low in fibre is associated with a different bacterial profile, a *Bacteroides* enterotype, compared with individuals consuming high-fibre, low-fat diets, who exhibit a *Prevotella* enterotype.[8] In addition, dietary substrates profoundly influence bacterial metabolism. For example, nonabsorbed dietary fibre and prebiotic compounds such as inulin are metabolized by colonic bacteria to produce short-chain fatty acids, including butyrate. Moreover, sulphate-reducing bacteria, including *B. wadsworthia*, metabolize dietary sulphur to produce hydrogen sulphide. These metabolites have important physiological effects on the intestine—butyrate is an essential energy source for the distal colonocyte and hydrogen sulphide damages mucosal integrity and inhibits butyrate metabolism.[9] Induction of taurocholic acid secretion by consumption of milk fat provides metabolic substrates for sulphate-reducing bacterial species. Finally, dietary carbohydrates rapidly alter gene expression in gut bacteria, including mucolytic enzyme activity that can diminish mucosal protection by decreasing the mucus barrier as a result of bacterial utilization of host mucus glycans.[10]

Complete understanding of the progressive events described by Devkota and colleagues[4] will require mechanistic studies. A primary unresolved question is the relative contribution of bacterial-antigen-induced T_H1 responses versus the toxic effects of hydrogen sulphide and other *B. wadsworthia* metabolites on the mucosal barrier. IFN-γ production by CD4$^+$ T cells co-cultured with dendritic cells that have been exposed to *B. wadsworthia* lysate demonstrates that this organism can activate aggressive effector T cells.[4] The potentially toxic role of hydrogen sulphide on the epithelium barrier can be most definitively addressed by selective colonization of *Il10*$^{-/-}$ mice with *B. wadsworthia* strains lacking *dsrA*. The component of milk fat that induces hepatic production of taurocholic acid needs to be determined, and dose response studies of dietary milk fat should be performed to elucidate whether consumption of low-fat milk alters Deltaproteobacteria populations and induces colitis. The effect of milk-fat consumption on other T_H1-mediated conditions such as coeliac disease, rheumatoid arthritis, psoriasis and multiple sclerosis needs to be addressed. Most importantly, the clinical implications of these observations in a mouse model must be pursued in humans.

The Devkota *et al.*[4] study identifies a putative immunologically active commensal pathobiont that could serve as a diagnostic biomarker for clinically relevant subsets of patients with IBD and as a target for therapeutic interventions, including selective antibiotics, dietary manipulation or novel inhibitors of sulphite reductase activity or taurine conjugation of bile acids. Interestingly, *B. wadsworthia* and other sulphate-reducing bacteria are normally found in the intestines of healthy humans, and their populations are increased in patients with ulcerative colitis.[9] These innovative observations could potentially help guide clinicians in providing better recommendations to their patients. To realize this goal, however, essential translational and clinical studies must be performed to verify whether *B. wadsworthia* and related sulphate-reducing Deltaproteobacteria define IBD subsets in patients and whether altering milk-fat intake influences human microbiota community profiles and, most importantly, IBD disease activity. By stimulating such clinical and translational investigations, the innovative study by Devkota *et al.*[4] could ultimately influence clinical care and even provide a dietary guide to prevent disease in genetically at-risk individuals. Meanwhile, from the broader perspective, these results validate a renewed mandate to better understand the influence of the Western diet on the pathogenesis of rapidly increasing immune-mediated diseases and, in a global context, the mechanisms by which diet affects the composition and function of the enteric microbiota.

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Competing interests
The author declares no competing interests.

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