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Dietary CLA and n-3 PUFA in inflammatory bowel disease

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Abstract

Purpose of review—Inflammatory bowel disease (IBD) is a debilitating and widespread immune-mediated illness of unknown etiology. Current treatments are modestly successful and with significant side effects. The purpose of this review is to summarize the current understanding of mechanisms of action underlying the anti-inflammatory actions of CLA and n-3 PUFA in IBD.

Recent findings—Nutrition-based interventions that target peroxisome proliferator-activated receptors (PPARs) such as dietary conjugated linoleic acid (CLA) or n-3 PUFA have demonstrated anti-inflammatory efficacy in animal models of IBD. Clinical data on n-3 PUFA in IBD remains generally unimpressive, although results of a recent human study demonstrate that IBD remission can be maintained by maintaining the n-3/n-6 ratio over 0.65 *via* n-3 PUFA intervention. In mice, CLA prevented inflammation-driven colorectal cancer by activating PPAR γ and modulating regulatory T cells and macrophages. CLA is the subject of an ongoing clinical study in Crohn's disease patients.

Summary—Compelling evidence demonstrates that n-3 PUFA and CLA prevent or ameliorate IBD in animal models. However this basic knowledge has not been translated into novel nutrition-based clinical interventions. For both compounds there is an urgent need for placebo-controlled, large-scale, multi-center clinical trials.

Keywords

conjugated linoleic acid; omega-3 PUFA; immune regulation; PPARs; inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD) is a chronic, recurring immunoinflammatory illness afflicting over 1.4 million people in the United States and 0.1–24.5/100,000 people worldwide with two clinical manifestations -- Crohn's disease (CD) and ulcerative colitis (UC) (1,2). Even though IBD therapies have improved (3,4), they are modestly successful for the long-term management of the disease and result in significant side effects, including immune suppression (5). The incidence of complementary and alternative medicine use was 49.5% for IBD patients (6). Hence, developing nutritional interventions against IBD such as CLA and n-3 PUFA remains important.

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Peroxisome proliferator-activated receptors: molecular targets for dietary lipid-based intervention

A promising avenue for developing such immunonutrition-based treatments for IBD is by targeting peroxisome proliferator-activated receptors (PPARs). PPARs are nuclear receptors for endogenous lipid molecules [i.e., prostaglandins or hydroxy-containing PUFA such as 12/15-hydroxyeicosatetraenoic (HETE), 13-hydroxyoctadecadienoic (HODE)] and molecular targets for drugs against type II diabetes (7–9). They belong to the superfamily of nuclear hormone receptors with 48 members identified in the human genome. There are three known PPAR isoforms; α, β or δ, and γ, which differ in their tissue distribution and functional activity (10). PPAR activation and expression is controlled by a diverse set of natural and synthetic molecules, including nutrients, non-nutrient endogenous ligands and drugs [i.e., thiazolidinediones (TZDs) and fibrates]. In this regard, 5-ASA, a drug broadly described as an anti-inflammatory treatment for IBD, is a PPAR γ agonist (11). Some of the ligands are pan-PPAR agonists, whereas others are either isoform-specific or target two PPAR isoforms (10). PPARs have been studied primarily as drug targets. However, their main biological function is the sensing of intracellular nutrient concentrations –i.e., polyunsaturated fatty acids (PUFA), triglycerides, free fatty acids and lipoproteins- and regulation of gene expression involved in maintaining both metabolic and tissue homeostasis. Of note, results of a recent clinical study in UC patients demonstrate that rosiglitazone (Avandia™), a TZD agonist of PPAR γ and a U.S. Food and Drug Administration (FDA)-approved drug for treating type II diabetes, is also efficacious in the treatment of mild to moderately active UC (12). In spite of its efficacy, rosiglitazone is unlikely to be adopted for treating IBD due to its significant side effects (9,13) and a FDA-issued ‘Black box’ warning. Thus, there is a need to discover novel naturally occurring agonists of PPARs that exert therapeutic and prophylactic actions against IBD with limited or no adverse side effects. There is also a need to elucidate their mechanisms of action since the limited understanding about the mechanisms of action has halted further progress in the development of nutrition-based approaches for preventing IBD.

Mechanisms of Action of Conjugated Linoleic Acid (CLA) in IBD

CLA is a mixture of positional and geometric isomers of octadecadienoic acid (predominantly at position 9 and 11, or 10 and 12) appear in a conjugated double bond system (two double bonds separated by a single bond). Several CLA isomers, including cis-9, trans-11 CLA, are naturally found in milk, cheese and ruminant products (14). In 2002, we found that dietary CLA-supplementation suppresses colonic inflammation and upregulates colonic PPAR γ expression in pigs with bacterial-induced colitis (15). Since that original report we have used mice with a targeted deletion of PPAR γ in immune and epithelial cells to demonstrate that activation of colonic PPAR γ by CLA mediates protection from experimental IBD in mice (16). In addition, n-3 PUFA appear to antagonize the effects of CLA on PPAR γ in a pig model of dextran sodium sulfate (DSS) colitis (17). Several reports by others confirm increases of PPAR γ expression and activity in adipocytes (18), skeletal muscle (19), colonic mucosa (20) and macrophages (21,22) with CLA treatment or CLA-rich diets. However, a reduction in PPAR γ expression in adipocytes by CLA has also been reported (23,24). This may be due to cell-type specificity of the response to CLA or isomer specificity since the t10, c12 was able to reduce PPAR γ expression in adipocytes but the c9, t11 failed to show the same suppressive effect on PPAR γ activity (25). In RAW 264.7 mouse macrophage (RAW) cells, CLA isomers decreased the expression of COX2, TNF-α, nitric oxide, IL-1β and IL-6 mRNA via PPAR γ (21). In HT-29 and Caco-2 intestinal epithelial cell lines the generation of CLA by probiotic bacteria induced apoptosis via an increase in PPAR γ expression (26). Thus, the protective effect of CLA against IBD appears to be mediated though PPAR γ activation. However, since CLA

can also modulate the production of arachidonic acid metabolites (27,28), it is also likely that the reduced production of inflammatory lipid mediators may contribute to CLA's beneficial actions in IBD.

Evans and colleagues recently demonstrated that dietary CLA-supplementation ameliorated inflammation-driven colorectal cancer in mice (29). CLA also increased the percentages of regulatory CD4+ T cells (Treg) in mesenteric lymph nodes (MLN) of PPAR γ-expressing, but not immune cell-specific PPAR γ null mice, suggesting that CLA modulates the Treg compartment by activating PPAR γ. The results of this project are in line with the findings of previous IBD studies showing that this effect of CLA was mediated, in part, through a PPAR γ-dependent mechanism (16) as well as reports demonstrating that PPAR γ is required for Treg function (30,31).

Unlike TZDs, CLA has been shown to be safe (32). Accordingly, the FDA granted CLA generally regarded as safe (GRAS) status (GRN 00232) in July 11, 2008. In contrast to corticosteroids, CLA suppresses gut inflammatory responses while enhancing antigen-specific responsiveness of T cells against viral and bacterial pathogens (33–36). Open label clinical studies are currently underway to determine the anti-inflammatory efficacy of CLA in human patients with IBD. As a follow up of these ongoing studies, placebo-controlled, large-scale, multi-center studies should investigate the interplay between dietary CLA-supplementation, mucosal immunity and the gut microbiota.

N-3 PUFA in IBD Prevention

N-3 PUFA [i.e., linolenic acid (LN), docosahexaenoic (DHA) and eicosapentaenoic (EPA)] elicit potent anti-inflammatory and immunoregulatory properties either directly (37,38) or following transcellular processing that results in the generation of hydroxy-containing n-3 PUFA metabolites (39). In similar action to dietary CLA, n-3 PUFA have been reported to ameliorate intestinal inflammation in animal models of IBD (40). However, previous IBD pre-clinical studies examined the efficacy of doses over 4 g of *n-3* PUFA per 100 g diet, which would be unattainable in a human clinical setting. Thus, while the pre-clinical story in animal models is strong, the translational value of the doses of n-3 PUFA utilized is questionable.

In this regard, in 2005 MacLean and colleagues (41) reviewed 13 controlled trials that investigated the effects of n-3 PUFA on clinical, sigmoidoscopic or histologic scores. Only 3 studies found that n-3 PUFA administration decreased the corticosteroid requirement. Based on these findings, it was concluded that the available data are insufficient to recommend n-3 PUFA for the management of IBD in humans (e.g., GRAS Notice No. GRN 000105).

In 2006 we used a pig model of experimental IBD to examine the clinical activity of two fatty acid mixtures (i.e., n-3 PUFA and CLA) that have been proposed to prevent or ameliorate IBD (17). Our data demonstrate that during a 7-day challenge with DSS, *n*-3 PUFA failed to ameliorate clinical disease but favored a faster remission. Mechanistically, the effects of n-3 PUFA on epithelial regeneration appeared to be dependent on activation of PPAR δ (17).

A more recent study in human patients with CD and UC published by Uchiyama and colleagues published in 2010 (42) suggests a relationship between the accumulation of n-3 PUFA in the cell membranes and remission from IBD. Interestingly, in this study 2,250–3000 mg/day 5-ASA was administered to all patients. Since 5-ASA is a known PPAR γ agonist, it is possible that 5-ASA may have interacted with n-3 PUFA to favor remission.

Brix et al provided evidence demonstrating that $CD4^+$ T cell activation is differentially modulated by bacteria-primed dendritic cells, but is down-regulated by n-3 PUFA (43). However, the underlying mechanisms mediating this effect have not been fully characterized. Since PPARs can modulate the function of effector and regulatory T cells (30,31,44) and given the established role of PUFA as PPAR agonists (45), it is puzzling that PPAR-dependent mechanisms were not investigated in this study. Nonetheless, the ability of n-3 PUFA to modulate immune responses to bacterial antigens is novel and it should be further explored. It is also important to investigate the direct effect of nutritional compounds on gut microbial populations.

Diet-Microbiome Interactions in IBD

The pathogenesis of IBD involves an interaction among the genetic predisposition of the individual, the environment and the gut microbiota. Understanding how n-3 PUFA and CLA favorably modulate the interface between diet, mucosal immunity and gut microbiota is of crucial importance for gaining useful insights regarding both clinical efficacy and mechanism of action. This will require a comprehensive assessment of the effects of the compounds on mucosal immune responses and gut microbial populations and host-bacterial interaction networks.

Sequence-based metagenomics technology has enabled the study of uncultured bacteria and archea by culture-independent identification and characterization of microorganisms using direct DNA sequencing. Recent advances in sequencing technology have made large characterization of complete metagenomic sequencing more accessible (46–48). For instance, pyrosequencing has been applied to study characterization of microbial biodiversity and/or relative abundance of proteins specific to ecological niches such as seas (49), drainage (50) and waste water (51), soil and carcasses (52), worms (53), human skin (54) and gut (55). Analysis of 16S rRNA genes provides insight into the phylogenetic structure, composition and community dynamics of microbiota in their host environments. These new technologies will facilitate high-throughput and comprehensive analyses of the effect of dietary compounds in the gut microbiota.

Progress is underway in investigating the relationship between obesity and gut microbiota. For instance, at higher taxonomic classification two bacterial phyla that dominate this ecosystem belong to Firmicutes (Gram-positive bacteria) and Bacteroidetes (Gram-negative bacteria) (56) with Firmicutes dominating the guts of the obese individuals. Recent studies have also shown that diet and obesity influence the composition of gut microbial populations (57–61). Thus, it is novel and important to examine how dietary components and IBD interact to modulate resident gut microbial populations. The gut microbiota may be manipulated by dietary components such as n-3 PUFA and CLA to favorably influence inflammatory disease risk by reducing endotoxin load via shifts in the composition and metabolic activity of the microbial community. There is some evidence suggesting that probiotic bacteria (i.e., VSL3) can produce CLA (26). However, very little is known about the extent to which the gut microbial environment mediates the associations between specific dietary components and IBD. Given that *Bacteroidetes* are the main source of lipopolysaccharide (LPS) and the established role of LPS in mediating low-grade chronic inflammation, the characterization of gut microbial communities during IBD as well as the modulation by dietary CLA, n-3 PUFA and other PPAR γ and δ agonists such as abscisic acid (ABA) (62) will provide novel and important insights on how to suppress intestinal inflammation in CD and UC patients.

Modeling Nutritional Interventions in IBD

Since PPAR γ and other molecular targets for IBD therapeutics are ubiquitously expressed in the gut, tracing clinical improvements from nutritional interventions back to concrete PPAR γ-initiated immunological mechanisms has proven extremely challenging. PPAR γ activity delineates the susceptibility to intestinal inflammation ranging from highly pro-inflammatory (low expression or activation) to anti-inflammatory (high expression or activation) states. In addition to testing the efficacy of such compounds in animal models and in patients with IBD, there is a need to build predictive, multiscale models of the intestine for understanding how important therapeutic targets modulate the immune response dynamics, gut pathology and anti-inflammatory responses.

Highly relevant to the discovery of novel PPAR γ-based therapeutic and prophylactic strategies for IBD is the identification of the most critical immunoregulatory mechanisms of the mucosal immune system that prevent inflammation and the subsequent destruction of the gut mucosa. For instance, computational/mathematical models of the gut will facilitate performing *in silico* deletions of putative regulatory mechanisms (i.e., regulatory T cells, M2 macrophages, tolerogenic dendritic cells) during an inflammatory challenge and investigate the consequences on indicators of enteric pathology such as epithelial erosion, immune cell infiltration or increased concentrations of pro-inflammatory cytokines in the mucosa. We constructed for the first time a model with an initial level of granularity at the cellular (immune and epithelial cells), with multiple tissues and compartments such as lumen, colonic lamina propria (LP) and MLN (63). We next asked which immune cell subsets would be more greatly associated with the recovery from disease. The model predicted that allowing the reversion rate from M1 macrophages to M2 macrophages facilitates recovery from colitis, indicating that M2 macrophages suppress gut inflammation. Validation of this prediction in a mouse model of experimental IBD demonstrated that pharmacologically inducing differentiation of macrophages into an M2 phenotype (64) by activating PPAR γ with pioglitazone, a TZD, facilitated recovery from colonic inflammation, as measured by a disease activity index. Moreover, the deletion of PPAR γ in macrophages (but not in other immune or epithelial cells) in Lysozyme M-Cre+ mice abrogated the ability of PIA to induce recovery from colitis. Further studies are required to track clinical and pathological improvements caused by naturally occurring PPAR γ agonists back to specific cellular and molecular interactions within the mucosal immune system network.

Conclusions

Insufficient progress has been made in translating the basic knowledge on the prevention of IBD by n-3 PUFA and CLA into actionable information for implementing nutrition-based interventions in the clinic. There is an urgent need for data from placebo-controlled, large-scale, multi-center clinical trials designed to perform a comprehensive assessment of the effects of such interventions on mucosal immune responses and gut microbial populations. A better mechanistic understanding in combination with more comprehensive data from well-designed clinical studies will lay the groundwork for accelerating the development of safer and more efficacious nutrition-based therapies against IBD.

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