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Molecular Pathways: Gene-environment interactions regulating dietary fiber induction of proliferation and apoptosis via butyrate for cancer prevention

Scott J. Bultman^{1,*}

¹Department of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599, USA

Abstract

Gene-environment interactions are so numerous and biologically complicated that it can be challenging to understand their role in cancer. However, dietary fiber and colorectal cancer prevention may represent a tractable model system. Fiber is fermented by colonic bacteria into short-chain fatty acids such as butyrate. One molecular pathway that has emerged involves butyrate having differential effects depending on its concentration and the metabolic state of the cell. Low-moderate concentrations, which are present near the base of colonic crypts, are readily metabolized in the mitochondria to stimulate cell proliferation *via* energetics. Higher concentrations, which are present near the lumen, exceed the metabolic capacity of the colonocyte. Unmetabolized butyrate enters the nucleus and functions as a histone deacetylase (HDAC) inhibitor that epigenetically regulates gene expression to inhibit cell proliferation and induce apoptosis as the colonocytes exfoliate into the lumen. Butyrate may therefore play a role in normal homeostasis by promoting turnover of the colonic epithelium. Because cancerous colonocytes undergo the Warburg effect, their preferred energy source is glucose instead of butyrate. Consequently, even moderate concentrations of butyrate accumulate in cancerous colonocytes and function as HDAC inhibitors to inhibit cell proliferation and induce apoptosis. These findings implicate a bacterial metabolite with metaboloepigenetic properties in tumor suppression.

Background

Considering that cancer susceptibility is determined by numerous gene-environment interactions, dietary factors are believed to alter the risk of cancer in general and colorectal cancer (CRC) in particular. One of the most extensively studied dietary factors has been fiber, which is defined as the edible part of plants or their extracts, or analogous carbohydrates, that are resistant to digestion and absorption in the small intestine, but are utilized after partial or complete fermentation in the colon by resident microbiota (1). Fiber includes polysaccharides (e.g., resistant starch, cellulose, hemicellulose, pectins, and gums), oligosaccharides, and lignins. As human populations have shifted away from traditional, high-fiber diets towards processed foods containing refined sugars, CRC incidence has increased markedly. CRC is now the third most diagnosed cancer in both men and women in the United States, and it is also the third most deadly (2). This trend of increasing CRC incidence is particularly evident in China and developing countries that have rapidly adopted western diets in recent years (3). The correlation between decreased fiber consumption and

To whom corresponding should be addressed. Department of Genetics, University of North Carolina. 120 Mason Farm Rd, Genetic Medicine Building Room 5060 Chapel Hill, NC 27599-7264, USA. Tel: +1 919 966 3359; Fax: +1 919 843 4683; Scott_Bultman@med.unc.edu.

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increased CRC incidence is also evident in developing countries because colonoscopies are performed on a limited basis; in contrast, widespread screening and removal of pre-cancerous adenomas in the United States has coincided with a recent plateau or slight decline in CRC incidence. More rigorous prospective-cohort studies have also been performed and have yielded both positive and negative results (4–9). Nevertheless, the most recent Expert Report from The World Cancer Research Fund (WRCF) and the American Institute of Cancer Research (AICR) has upgraded the evidence from probable to convincing that fiber has a protective effect.

It has not been established how dietary fiber might protect against CRC, but there are two general models that are not mutually exclusive (Figure 1). First, insoluble fiber bulks luminal contents and speeds colonic transit to minimize the exposure of the colonic epithelium to ingested carcinogens such as nitrosoamines from charred meat. Second, the fact that bacteria in the lumen of the colon ferment soluble fiber into short-chain fatty acids (SCFAs) is probably important. The most abundant SCFAs, such as acetate, propionate, and butyrate, are present in the lumen at very high (mM) concentrations and serve as an energy source for many species of bacteria that inhabit the colon as well as the host (10). Butyrate is selectively taken up by the colonic epithelium (*via* MCT1, SMCT1, and other transporters) and provides colonocytes with ~70% of their energy (11) and is required for energy homeostasis (12, 13), whereas acetate and propionate are primarily transported to muscle and liver tissue, respectively (14). Butyrate is a particularly good candidate for CRC prevention not only because it is metabolized by colonocytes but also because it has more potent activity as a tumor suppressor and a histone deacetylase (HDAC) inhibitor than the other SCFAs or any other known bacterial metabolites (15).

Tumor-suppressive effects of butyrate involve the Warburg effect and HDAC inhibition

Butyrate has been implicated in cancer prevention based on >100 published studies demonstrating that it inhibits cell proliferation and/or stimulates apoptosis in a variety of tumor-derived cell lines (16–19). However, the bioavailability of butyrate is primarily restricted to the colon because this is where it is produced and it is readily metabolized by colonocytes. Therefore, experiments with CRC cell lines are probably the only ones that are physiologically relevant. Because butyrate is a fatty acid and the preferred energy source of normal colonocytes, it undergoes β -oxidation in the mitochondria and relatively little accumulates in the nucleus (12, 20) (Figure 1). In contrast, glucose is the preferred energy source of cancerous colonocytes (Figure 1), which increase their glucose uptake by >10 fold (*via* increased expression of GLUTs) and rely heavily on aerobic glycolysis with a concomitant decrease in oxidative metabolism within the mitochondria. This metabolic shift, referred to as the Warburg effect, occurs in the vast majority of cancers including CRC and is the basis of FDG-PET used for tumor imaging in the clinic (21). *AKT*, *PI3K*, *KRAS*, and other mutations affect metabolism and contribute to the Warburg effect, which is selected for in cancer cells because it serves a conduit for diverting carbons into biosynthetic pathways that are utilized by rapidly dividing cells to double their biomass (22, 23). As a consequence of the Warburg effect and metabolic reprogramming in cancer cells, butyrate is metabolized to a lesser extent and accumulates in the nucleus of cancerous colonocytes where it functions as an HDAC inhibitor to epigenetically regulate gene expression (20) (Figure 1).

HDAC inhibitors such as butyrate are global transcriptional regulators because they increase histone acetylation to alter the conformation/position of nucleosomes, which consist of 147-bp segments of DNA wrapped around histone octamers (2 copies each of H2A, H2B, H3, and H4) and are the most fundamental unit of chromatin. Butyrate induces histone

acetylation at the promoters of many genes, and some direct targets, such as the *p21* cyclin-dependent kinase inhibitor and the pro-apoptotic *BAX* and *FAS* genes, contribute to the functional changes in cell proliferation and apoptosis (16–19). Butyrate can also promote cell differentiation by regulating genes such as the mucins. Thus, one may consider butyrate as a candidate “tumor-suppressor metabolite” analogous to the 2-hydroxyglutarate “oncometabolite”, which is present at high levels only in *IDH* mutant gliomas and leukemias where it inhibits the TET and JmjC families of deoxygenases that demethylate DNA and histones to alter epigenomic profiles (24).

Butyrate also has potent anti-inflammatory effects

Butyrate was the first HDAC inhibitor to be identified (15), and this mechanism is also known to regulate the transcription of certain cytokine genes including components of the interferon gamma, tumor necrosis factor alpha, and nuclear factor-kappa β signaling pathways, which are involved in both inflammation and cancer (16–18). These pathways are perturbed in intestinal epithelial cells and immune cells from individuals with Crohn’s disease and ulcerative colitis, and butyrate enemas strongly ameliorate colonic inflammation associated with these inflammatory bowel diseases (IBD) in both rodent models and human patients (16). It is noteworthy that colitis patients have a 10-fold increased risk of CRC (25). These observations are consistent with the well-accepted idea that inflammation exacerbates tumorigenesis, which is an emerging hallmark of cancer (26). This raises the possibility that butyrate might not only function cell autonomously in cancer cells but may also affect immune cells in the tumor microenvironment to influence CRC. Interestingly, activated lymphocytes undergo a metabolic shift similar or identical to the Warburg effect to support their rapid proliferation (27, 28), which can exceed that of a cancer cell and achieve doubling times of ~8 hrs. Therefore, butyrate is not expected to be readily metabolized by activated T cells or B cells but should instead function as an HDAC inhibitor similar to cancer cells.

Butyrate increases histone acetylation by two distinct mechanisms

Recent work has shown that the role of butyrate in histone acetylation is more complicated than previously appreciated (20). When cells were exposed to a relatively low dose of butyrate (0.5 mM), the intracellular concentrations of butyrate did not reach levels compatible with it acting as an HDAC inhibitor. The levels were only 0.04–0.40 relative to the IC_{50} regardless of whether or not the cells were undergoing the Warburg effect. Yet this 0.5 mM dose stimulated histone acetylation and affected cell proliferation. At this dose, butyrate undergoes β -oxidation in the mitochondria, and this leads to acetyl-CoA condensing with oxaloacetate to form citrate in the first step of the TCA cycle. Citrate can exit the mitochondria, and the enzyme ATP citrate lyase (ACL) converts it to acetyl-CoA in the cytosol and nucleus (Figure 1) (29). Cytosolic acetyl-CoA is crucial for lipid biosynthesis, whereas nuclear acetyl-CoA is an essential co-factor for histone acetyltransferases (by serving as the acetyl group donor) (29). To demonstrate that butyrate can increase histone acetylation by this mechanism, flux experiments were performed where ^{13}C -butyrate was added to cells, and ^{13}C -acetyl groups were detected on histones in an ACL-dependent manner (*via* siACL in RNAi experiments) using LC-MS/MS (20). Transcriptome-profiling experiments in siACL cells versus siMock cells identified genes that were regulated in an ACL-dependent manner and ACL-independent manner, respectively. Butyrate dosage influenced the utilization of each mechanism. At a 0.5-mM dose, the ACL-acetyl-CoA-HAT mechanism (i.e., ACL dependent) was the prominent one, accounting for 75% of the genes that were upregulated compared to cells not treated with butyrate. However, the HDAC inhibition mechanism (i.e., ACL independent) became more prevalent at 2 mM and was the prominent one at 5 mM, accounting for 75% of the upregulated genes. This mechanistic

shift can be explained by the observation that these cells reach their oxidative metabolic capacity at 1–2 mM doses of butyrate (30, 31). Therefore, when the dosage exceeds this range, butyrate molecules are not metabolized in the mitochondria and accumulate as HDAC inhibitors in the nucleus.

The transcriptome-profiling experiments also showed that the ACL-dependent genes at 0.5 mM were enriched for cell proliferation functions, whereas the ACL-independent genes at 5 mM were enriched for apoptosis (20). Because butyrate is believed to be present in a gradient with higher levels in the lumen and lower levels at the base of the crypt (due to the upward flow of mucous produced by goblet cells) (Figure 1), butyrate may promote homeostasis of the colonic epithelium, which proliferates rapidly but is continuously turned over (Figure 1) (20). Lower butyrate concentrations near the base of the crypts correlates with the position of proliferative cells, whereas higher butyrate concentrations in the lumen correlates with the position of cells that undergo apoptosis as they exfoliate into the lumen (Figure 1).

Because colorectal cancer cells undergo the Warburg effect, even lower doses of butyrate will be metabolized to a lesser extent and will function as an HDAC inhibitor to promote apoptosis rather than proliferation, which is consistent with its tumor-suppressive effects. The differential effect of butyrate in normal versus cancerous colonocytes is made even more pronounced by differences in butyrate efflux. An ABC (ATP-binding cassette) transporter in the multi-drug resistance family, named breast cancer resistance protein 1 (BRCP), transports butyrate out of cells and modulates the ability of butyrate to affect cell proliferation (32). BRCP is expressed at high levels in the normal intestine but is downregulated in IBD and in colorectal cancer cell lines compared to non-tumoral intestinal epithelial cells (32, 33). This likely contributes to higher levels of butyrate in cancerous colonocytes and further increases HDAC inhibition.

Butyrate is also an agonist for G-protein coupled receptors

Butyrate functions in multiple cell compartments. In addition to being metabolized in the mitochondria (primarily for energetics but also for histone acetylation *via* the ACL-acetyl-CoA-HAT mechanism) and the nucleus (as an HDAC inhibitor), butyrate can also function at the cell surface as an agonist for certain G-protein coupled receptors (GPRs), which function *via* the cAMP and phosphatidylinositol signaling pathways to have many effects. Butyrate binds to GPR109A, which is highly expressed on the apical membrane of colonic epithelial cells (34). GPR109A is silenced in human CRC, a mouse model of CRC, and CRC cell lines (34). GPR41 and GPR43 are bound by several SCFAs including butyrate. GPR41 is intriguing because it mediates microbiota-induced effects on host metabolism including adiposity and the production of leptin and peptide YY (PYY) that regulate feeding behavior (35). GPR43 is intriguing because it may be a tumor suppressor based on reduced or abolished expression in colon adenomas and CRC cell lines (36). Consistent with butyrate having anti-inflammatory functions relevant to cancer prevention, butyrate and other SCFAs can signal through GPR43 on the surface of T_{reg} cells to stimulate their expansion in response to fiber (37, 38).

Clinical-Translational Advances

Recent microbiome studies, which combine next-generation sequencing with computational analyses (39, 40), have revealed many differences in the relative abundance of commensal gut bacteria between individuals (41, 42). In some complex diseases, including cancer, significant differences between cases and controls have been reported. For example, at least two studies have reported that colorectal cancer cases have fewer butyrate-producing

bacteria than controls (43, 44). This raises the possibility that some of the conflicting results from epidemiology studies that have investigated whether dietary fiber protects against colorectal cancer might be due to microbiome differences between participants. To reconcile these conflicting results, it would be useful to integrate epidemiology results with data from genome-wide association studies (GWAS) and microbiome studies since the efficacy of the fiber effect is probably influenced by both genetics and gut microbiota. This approach might make it possible to discriminate between those individuals who respond favorably to increased fiber consumption and those who do not.

A number of synthetic HDAC inhibitors are currently in phase 3 clinical trials or have already received FDA approval as chemotherapeutic agents, primarily for the treatment of hematopoietic malignancies, but are known to have adverse effects (45). A chemoprevention strategy involving diet (prebiotics-fiber) and possibly dietary microbiota supplementation (probiotics-butyrate-producing bacteria) is attractive because it would involve an endogenous HDAC inhibitor (butyrate) that does not have any known adverse effects (46). As opposed to synthetic HDAC inhibitors, which are delivered systemically, butyrate is produced only in the colon. This specificity precludes collateral damage from occurring in other tissues. Furthermore, unlike synthetic HDAC inhibitors, butyrate is a fatty acid readily metabolized by normal cells and is specifically targeted to cancer cells (where it accumulates) because of the Warburg effect. Another translational possibility is to fortify foods with butyrate, but this would need to make use of a butyrate derivative such as tributyrin that it is not as readily absorbed in the upper GI tract and yields high levels of butyrate in the colon (13, 46). However, as a practical consideration, it would be necessary to utilize nanoparticles or another approach to mask the unpleasant odor of butyrate derivatives.

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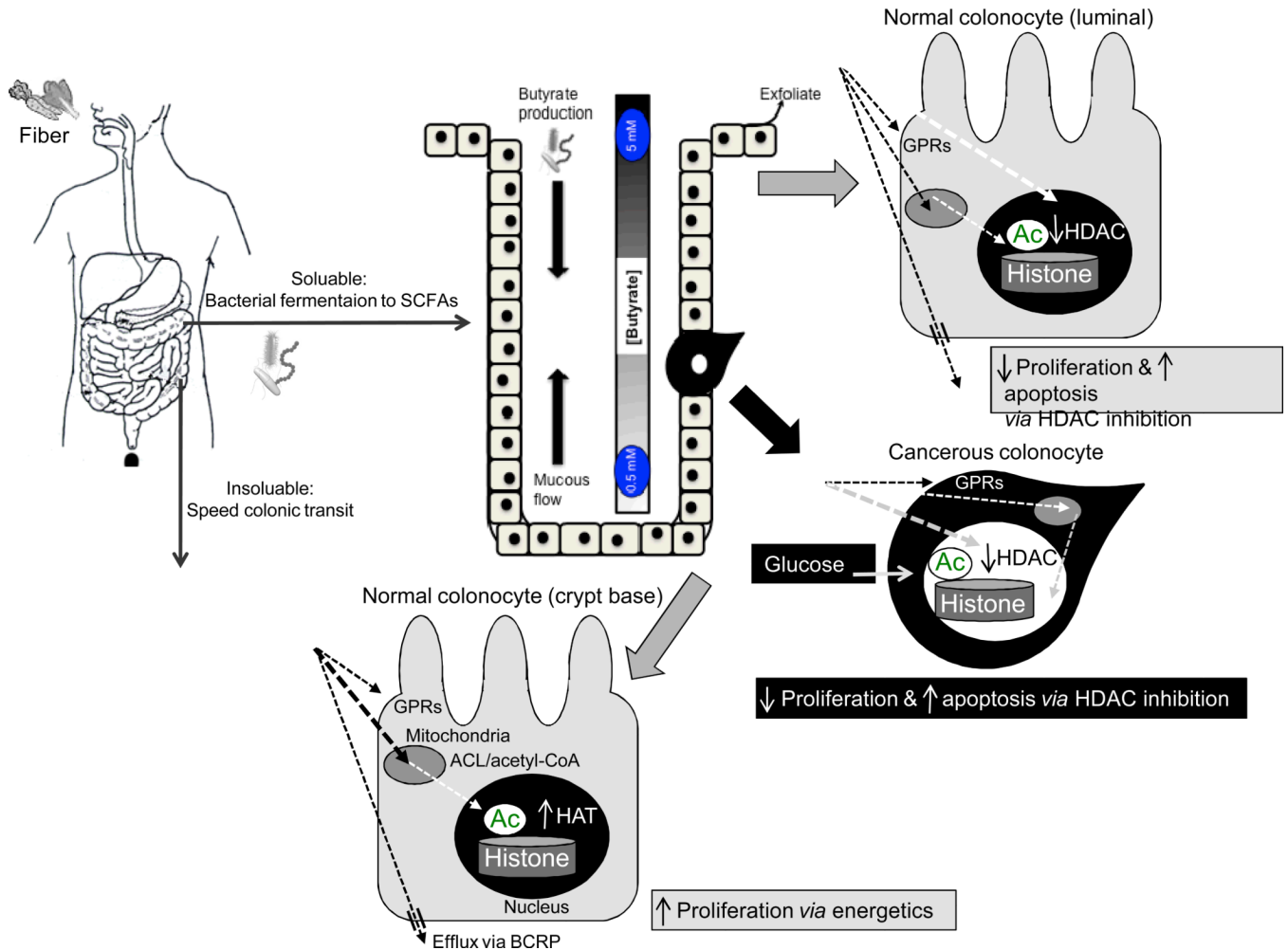


Figure 1.

A model of how fiber might protect against CRC. (Left) First, insoluble fiber bulks luminal contents and speeds colonic transit to diminish the exposure of colonocytes to ingested carcinogens. Second, soluble fiber is fermented by bacteria into SCFAs including butyrate. (Center) Butyrate is believed to be present in a gradient with 5 mM in the lumen and 0.5 mM at the crypt base. This is due to bacterial density and fermentation being highest in the lumen, and the diffusion of butyrate into the crypt is impeded by the upward flow of mucous produced by goblet cells. (Right) For normal colonocytes near the base of the crypt (bottom), butyrate is readily metabolized in the mitochondria (thick dashed arrow). This supports cell proliferation *via* energetics but also increases histone acetylation *via* an ACL-acetyl-CoA/HAT mechanism. Intracellular butyrate levels are regulated via BCRP-mediated efflux, and butyrate can also function as an agonist of GPRs. For normal colonocytes near the lumen (top), the butyrate concentration exceeds the oxidative metabolic capacity of the cell. Therefore higher levels of butyrate accumulate in the nucleus (thick dashed arrow) to increase histone acetylation *via* HDAC inhibition. This epigenetically regulates gene expression to inhibit cell proliferation and induce apoptosis as these cells exfoliate into the lumen. For cancerous colonocytes (middle), the ability of butyrate to accumulate as an HDAC inhibitor is particularly pronounced for two reasons. First, due to the Warburg effect, the preferred energy source is switched from butyrate to glucose. Second, butyrate is able to accumulate more efficiently because BCRP is often silenced so there is less efflux.