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Short-Chain Fatty Acids

A Potential Therapy for Colorectal Cancer

By Samia Chergui

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, have garnered significant attention due to their anti-inflammatory properties within the human body.[1] Expanding on these studies, recent research has revealed that SCFAs exhibit selective antitumor effects on colorectal cancer cells (CRC cells). The findings from these investigations have illuminated the influence SCFAs can have on the development and progression of colorectal cancer. These discoveries underscore the therapeutic potential SCFAs might offer in the management and treatment of colorectal cancer.

Short-chain fatty acids (SCFAs) are produced in the colon during the fermentation of indigestible dietary fibers. The average molar ratio of acetate: propionate: butyrate found in the colon and feces at physiological conditions is 60:25:10 mmol/L.[2] These SCFAs can exert regulatory effects on various processes, including phagocytosis, the production of chemokines, and signaling pathways that control cell growth and apoptosis. Although a significant portion of research has been dedicated to exploring the specificity of the individual SCFAs toward CRC cells, the recent study by Gomes et al. instead focuses on evaluating the additive anti-cancer and possible synergism of SCFA mixtures. The results of this study provide a promising foundation for exploring the modulation of the gut microbiota-SCFAs axis as a potential avenue for CRC treatment or prevention.[3]

Previous studies have primarily investigated the impact of SCFA treatments on immune cells, cell cycle control and apoptosis, metabolic processes, and other aspects of cellular physiology. SCFAs, particularly butyrate, have demonstrated a role in stabilizing hypoxia-inducing factor (HIF), which is disease-protective against colitis.1 Individual SCFA exposure has also been shown to reduce cell proliferation rates on cultured cell lines derived from normal human colon mucosal epithelium (NCM460), colon carcinoma (RKO), and colorectal adenocarcinoma (HCT-15) with more selectivity toward CRCs.[3] RKO colon cancer cells exposed to butyrate were observed to have suppressed MAPK/ERK signaling, leading to upregulation of the endocan gene, which is thought to contribute to anti-cancer effects such as inhibition of cellular proliferation and migration.[4] The SCFA propionate was shown to promote proteasomal degradation of euchromatic histone-Lysine N-methyltransferase 2 (EHMT2) in cultured adenocarcinoma cell lines HCT116 and LS174T cell line. This epigenetic control influences the downstream pathways involved in cell proliferation. One direct target that EHMT2 acts on can induce apoptosis in colorectal cancer cells. By promoting EHMT2 degradation, propionate inhibits the growth of colorectal cancer cells.[5] Acetate treatment was observed to inhibit cell proliferation and viability of the colorectal cancer cell lines HT29 and HCT116. Additionally, under normoxic conditions, acetate modulates the mitochondrial function. It diminishes glycolysis activity, a metabolic pathway cancer cells rely heavily on for energy production to support their rapid cell growth and division.[6]

To evaluate the additive effect of SCFAs, Gomes et al. first predicted the joint toxic effects using a concentration addition model. The SCFAs were combined at the molar ratio typically found in the human colon (60 acetate:15 butyrate:25 propionate). In the RKO cell line, the experimentally observed effects of the SCFA mixtures closely matched the effects predicted by the CA model, indicating that the SCFAs exhibited an additive effect when combined. The observed effects were more pronounced for the HCT-15 cell line than the predicted additive effects, suggesting a potential synergistic interaction at these concentrations. The SCFAs, individually and in the mixture, induced cell-cycle arrest, lysosomal membrane permeabilization (LMP), and decreased cytosolic pH in CRC cells (**Fig. 1**). The lysosomal dysfunction and acidification of the cytosol are proposed to be part of the mechanism leading to apoptosis.[7] The sensitivity of CRC cells to the effect of SCFAs could be explained by the higher activity of multiple lysosomal enzymes in many cancer tissues compared to normal cells. The compromised lysosomal membrane releases lysosomal enzymes, such as cathepsins, into the cytosol. The released cathepsins can then trigger apoptosis by activating various apoptotic pathways.[3]

The data from the study by Gomes et al. implies that butyrate, even at a relatively lower concentration than acetate and propionate, exerted a dominant influence on the mixture effects.[3] From the individual dose-response curves and IC50 calculations (concentration required for 50% inhibition of cell growth), butyrate was shown to have a lower IC50 among the three SCFAs. This indicates that butyrate has a higher potency in inhibiting the growth of colorectal cancer cells. Although the potentially dominant mechanisms of butyrate-induced cell growth inhibition are not explicitly stated, butyrate's specific mechanisms of action, such as histone deacetylase inhibition or other epigenetic modulations, could explain why it is the more potent component of the SCFA mixture.[8]

In conclusion, the study by Gomes et al. highlights the important effects SCFAs have on CRC cells. However, relying on in-vitro experiments alone fails to recapitulate the complex tumor microenvironment and systemic effects observed in vivo. Furthermore, the study may have overlooked the potential synergistic or antagonistic effects of other untested SCFAs and other metabolic byproducts of the gut microbiota. Overall, to translate these findings into effective therapeutic approaches for treating colorectal cancers, it is crucial to conduct further investigations into the possible synergistic or antagonistic effects of a much larger array of SCFAs and to understand better how diet can impact the variety of metabolic byproducts produced by the gut microbiota.

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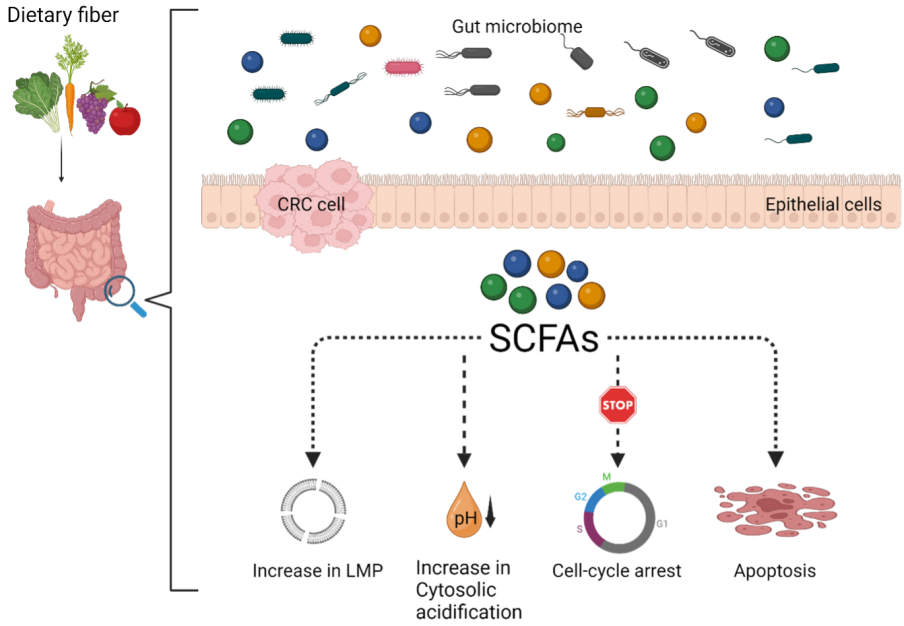

Figure 1 | The effect of short-chain fatty acids (SCFAs) on CRC cells. Gut microbiota ferments dietary fiber and produces the SCFAs acetate, butyrate, and propionate. In CRC cells, the combination of SCFAs shows an additive effect in inducing cell apoptosis and cell cycle arrest. They also lower the pH of the cytosol and promote an increase in lysosomal membrane permeability (LMP).