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REVIEW ARTICLE

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# Recent advances on the impact of protumorigenic dietary-derived bacterial metabolites on the intestinal stem cell

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**Abstract**

The links between diet, microbiome, immunity, and colorectal cancer are well established. The metabolite output of the microbiome, which has a large influence over host health and disease, is related to the composition of the diet. These metabolites subsequently impact on immune and intestinal epithelial either directly or indirectly via production of secondary metabolites. Here we summarize the latest findings and briefly discuss their potential for managing disease risk.

**KEYWORDS**

colorectal cancer, diet, intestinal stem cell, microbiome, secondary metabolites

## 1 | INTRODUCTION

The gut microbiota is a diverse and dynamic community of microorganisms that includes bacteria, viruses, and fungi, these commensal organisms play key roles in human health and disease (Hou et al., 2022). A considerable amount of data is now available on the relationship between the intestinal microbiome and colorectal cancer (CRC), recently reviewed by Anderson and Sears (2023). CRC is the second leading cause of cancer death (Fang et al., 2021) with 600,000 annual deaths worldwide (GLOBOCAN, 2020: New Global Cancer Data, 2024). While research into new therapies and management of CRC continues apace it is of note that ~50% of cases are estimated to be preventable by dietary and lifestyle changes (Brown et al., 2018). For example, obesity is linked to around 11% of colorectal cancer (CRC) cases (Safizadeh et al., 2023). Due, at least in part, to dietary factors that affect the composition of the intestinal microbiome eliciting an immune response which ultimately leads to inflammation and increased CRC risk (Riazati et al., 2023). A position supported by the links and associations between gut dysbiosis, inflammatory bowel disease and CRC (Markandey et al., 2021). Thus, our greater understanding of the microbiota role in CRC risk has potential to make a significant impact on CRC incidence. For example, within the intestines the microbiome's bacterial component plays a key role in converting dietary components, via fermentation, into metabolites for utilization by the host. Short chain fatty acids, in particular butyrate, produced by fermentation of dietary fiber by primarily the Clostridium cluster of the phylum Firmicutes (e.g. *Faecalibacterium prasunitzi*, Louis & Flint, 2009) provide the main energy source for colonocytes (Donohoe et al., 2011; Roediger, 1982) and contribute to enterocyte support (Newsholme et al., 2003). While the SCFA propionate, produced predominantly by bacteria of the phylum Bacteroidetes (Reichardt et al., 2014), has been shown to stimulate cell migration from the intestinal stem cell niche to the luminal surface (Bilotta et al., 2021) (Figure 1).

As the metabolite output of the microbiome is related to the composition of the diet and the gut microbiota; it has a large influence over host health and

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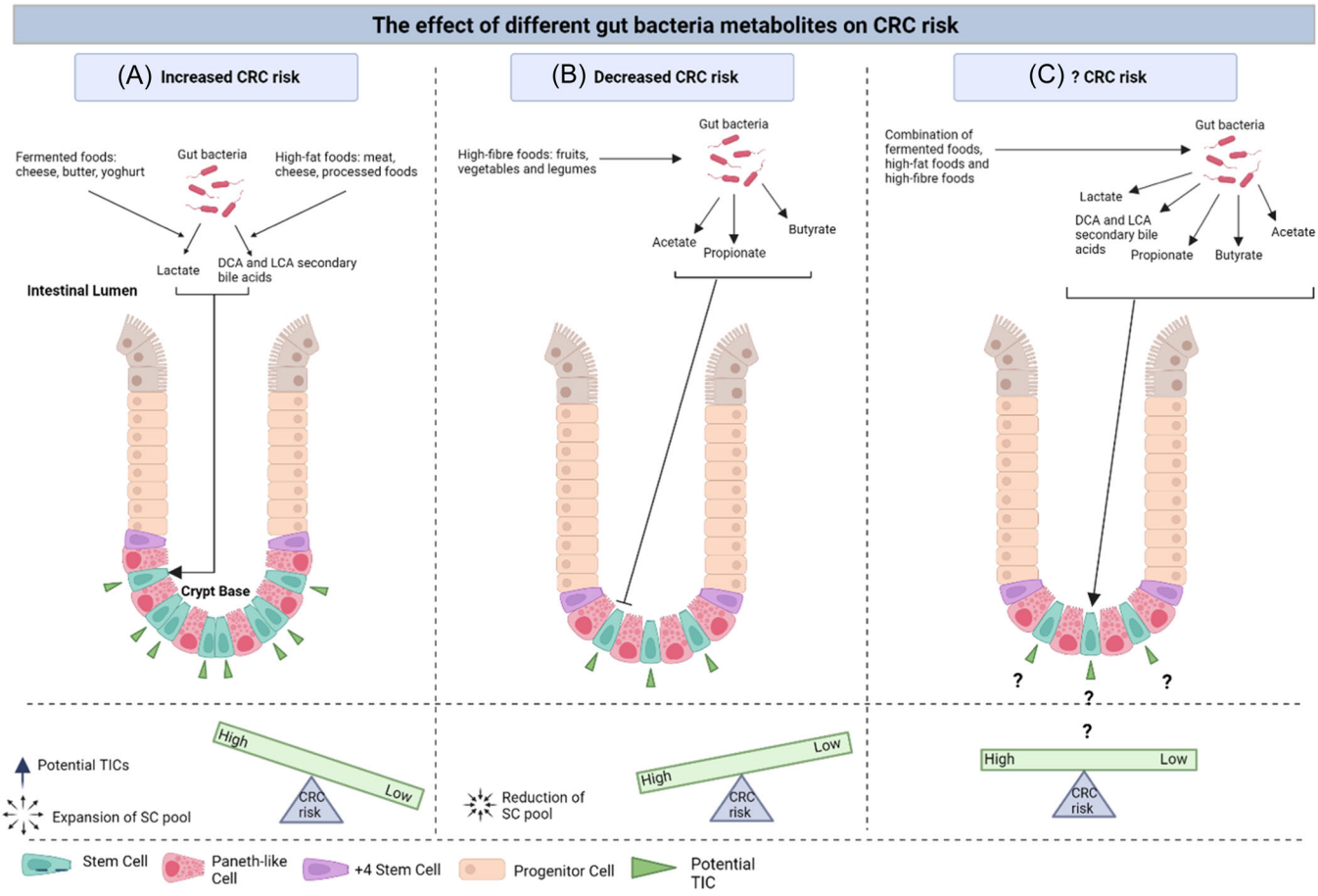


**FIGURE 1** Impact of microbial metabolites on intestinal stem cells and CRC risk. ISC daughter cells proliferate and differentiate as the migrate from the base of the crypt to the luminal surface. (A) Higher levels of microbial-produced lactate and SBAs drive proliferation and expansion of the ISCs (green), increasing the number of cells capable of initiating a tumor if mutated. (B) Bacterial metabolites derived from high-fibre foods produce SCFAs which fuel colonocytes, reduce inflammation and lower the number of ISCs required to maintain homeostasis, thereby reducing CRC risk. (C) Understanding how these pro- and anti-tumorigenic dietary-derived microbial metabolites factors interact in individuals whose diet leads to physiologically relevant of both types will provide significant insight into how we can manage CRC risk and improve public health advice. CRC, colorectal cancer; DCA, deoxycholic acid; LCA, lithocholic acid; PC, progenitor cell; SC, stem cell; TIC, tumor-initiating cell.

disease (Hou et al., 2022; Liu, Tan, et al., 2022) (Hou et al., 2022). The interactions between the microbiome and diet can influence immunity, cell biology and the intestinal stem cells (Figure 1). The epithelial surface of the intestine is maintained by a pool of rapidly dividing ISCs, marked by expression of *Lgr5* (Barker et al., 2007), that reside in the intestinal crypts and have been demonstrated to be the cells of origin for CRC (Barker et al., 2009; Buczacki et al., 2013; Huels et al., 2018; Vermeulen et al., 2013). The identification of these ISCs has greatly aided our ability to study lifestyle and CRC risk (Beyaz et al., 2016; Fu et al., 2019; May et al., 2022). This diet:microbiome interaction ultimately must impact on the intestinal stem cells (ISCs) if it is to underpin the association between diet and altered CRC risk (Figure 1) (Aliluev et al., 2021). In this context bacterial SCFA metabolite butyrate is the most widely studied with many reviews available on its tumor suppressive and oncometabolite roles (Bultman & Jobin, 2014). To supplement these here we summarize recent developments of other non-SCFA microbial metabolites demonstrated to impact on the ISC population and alter CRC risk.

## 2 | HIGH-FAT DIET-DERIVED BACTERIAL METABOLITES LINKED TO INCREASED TUMORIGENICITY OF ISCS

Obesity, a pivotal health burden, is closely associated with colorectal cancer (Pourvali & Monji, 2021). In 2016, Beyaz et al. (Beyaz et al., 2016) reported that a high-fat diet (HFD) elevated the number and ability of the *Lgr5*+ ISCs to form 3D organoids in ex vivo culture. A HFD was shown to induce erosion of the intestinal crypt-villus structures exposing the ISCs and their progenitors to fatty acids within the diet. While the types of fatty

acids vary depending on the dietary source the saturated palmitic acid, poly-unsaturated linoleic & linolenic and mono-unsaturated oleic fatty acids are consistently found elevated in the serum of rodents fed a high-fat diet (Buettner et al., 2006). With mouse and human organoids exposed to palmitic and oleic acid containing significantly more *Lgr5*+ ISCs (Beyaz et al., 2016). This instigated a fatty acid-dependent response via the peroxisome proliferator-activated receptor-delta (PPAR-δ) (Beyaz et al., 2016) and farnesoid-X-receptor (Fu et al., 2019) that enhanced canonical Wnt signalling, stemness and tumorigenesis (Figure 1). Aberrant activation of the Wnt pathway drives ~80% of CRC (Guinney et al., 2015) and increases stemness and tumorigenicity (Sansom et al., 2004). Thus, at the dietary level an excess of intake of fatty acids can directly increase ISC numbers and CRC risk. Recent work has now described how this increased CRC risk is further compounded by these saturated fats raising cholesterol levels. With the demonstration that the bile acids, produced by microbial transformation of cholesterol, also have protumorigenic effects on ISCs (Guzior & Quinn, 2021).

### 2.1 | ISC impact of microbial biotransformation of cholesterol into secondary bile acids (SBAs)

Secondary bile acids (SBAs) are metabolites produced by gut bacteria capable of bio-transforming primary bile acids (PBAs) via processes such as deconjugation, reviewed by Collins et al. (2023) and Guzior and Quinn (2021). This biotransformation is carried out by bile salt hydrolase producing bacteria, most commonly from the Gram-positive *Clostridium* sp. (Ridlon et al., 2006). The two main SBAs deoxycholic acid (DCA) and lithocholic acid (LCA) are derived from PBAs which are synthesized from cholesterol (Sah et al., 2022). Cholesterol and its PBA and SBA derivatives are increased by high fat diets, such as the Western-style diet which is characterized by high saturated and trans fats (Clemente-Suarez et al., 2023). High concentrations of SBAs are associated with an increased risk of and presence of CRC, with elevated levels present in CRC patients (Liu, Zhang, et al., 2022). With multiple reports demonstrating LCA and DCA inducing hyperproliferation, increased survival and invasion in CRC cells, reviewed in Rezen et al. (2022). These SBAs have been shown to be important to ISC function and renewal, with their exposure to isolated mouse intestinal crypts triggering *de novo* crypt formation (Figure 1). This SBA induced expansion of the LGR5+ ISCs via a process dependent on the G protein-coupled bile acid receptor 1 (GPBAR1, also called TGR5) (Sorrentino et al., 2020). However, whether it was the PBA or SBA component of the high-fat diet involved in this TGR5 axis was not determined, as they were collectively considered. Thus, SBAs in general are carcinogenic due to having the ability to transform human colonic epithelial cells to cancer stem cells (CSCs) that have express CSC markers and gain the ability to self-renew, generate spheroids and an ability to resist chemotherapy (Farhana et al., 2016). However, another type of SBA called ursodeoxycholic acid (UDCA) has antitumor effects, with it being protective against CRC at low doses (Guzior & Quinn, 2021) by inducing apoptosis of CRC cells and inhibiting many of DCA's protumorigenic effects (Guzior & Quinn, 2021; Režen et al., 2022; Sorrentino et al., 2020). Highlighting the importance of taking a holistic view of the microbiota's roles and consideration of the indirect impact SBAs may have on the ISC population via the immune system and cancer risk; as SBAs have been shown to act as carcinogens in the mouse colon (Bernstein et al., 2011; Prasad, 2014; Wan et al., 2019; reviewed in Bernstein & Bernstein, 2023).

A role for the immune system in mediating the effects of bile acids is supported by data from mouse models (Lajczak-McGinley et al., 2020; Sorrentino et al., 2020) and anecdotally in IBD patients, who have lower SBA concentrations and higher PBA concentrations compared to healthy individuals (Duboc et al., 2013). This may be due to the characteristic dysbiosis of IBD, with patients often having a lower abundance of bacteria species which biotransform PBAs into SBAs (Das et al., 2019). This biotransformation may also be decreased by IBD patients having fewer bile salt biotransformation genes that are involved in the biotransformation of PBAs to SBAs. Receptors for SBAs are on various cell types including immune cells such as T-cells, macrophages, and dendritic cells, which when stimulated result in anti-inflammatory effects, reviewed in Sun et al. (2021). A significant caveat when considering that ISC number and status is influenced by crosstalk between T cells and the intestinal crypt. With T helper cell cytokine inducing ISC differentiation and Tregs ISC proliferation (Biton et al., 2018). With SBAs being anti-inflammatory, their reduced levels in IBD likely contribute to disease severity, supported by treatment of different animal models of colitis showing decreased inflammation and improved symptoms (Sinha et al., 2020; Zhou et al., 2023). However, paradoxically an increase in anti-inflammatory Treg cells may increase ISC number and improve repair at the expense of increased CRC risk.

## 3 | ISC IMPACT OF MICROBIAL BIOTRANSFORMATION OF CARBOHYDRATES INTO LACTATE

Lactate is a metabolite produced by lactic acid bacteria (LAB) in the gut by fermentation of carbohydrates such as lactose (De Filippis et al., 2020), familiar components of probiotic preparations. LAB are phylogenetically located in the Clostridia branch of Gram-positive bacteria cultures, and are some of the most widely studied bacteria, being used to produce fermented foods such as cheese, butter, yoghurt, fermented meats, and fermented vegetables (Leroy & De Vuyst, 2004). It is thought that

consuming these fermented foods is a source of LAB (Pasolli et al., 2020), resulting in increased LAB metabolites. A LAB population are also harbored in the human gut, for example, *Lactobacillus acidophilus* and *L. caesei* (Walter, 2008), with consistent interindividual variations driven by multiple factors such as diet (David et al., 2014) and the ingestion of LAB-enriched foods. Due to lactic acid being unstable at physiological pH, it is mostly converted into lactate and hydrogen (Macharia et al., 2023), thus lactate is considered a LAB metabolite.

When lactate stimulates its specific GPR81 receptor on intestinal stromal cells it significantly increases Wnt 3 expression, driving the Wnt/β-catenin pathway and inducing proliferation and differentiation of LGR5+ ISCs (Lee et al., 2018). Through this interaction, lactate induces intestinal epithelial regeneration with increased crypt height and more LGR5+ stem cells in mice orally administered the VSL#3 probiotic containing LAB (Lee et al., 2018). These effects were due to lactate and not the LAB itself or a different metabolite, as they were not observed in mice fed a LAB strain lacking lactate dehydrogenase activity with defective lactate secretion. The pathway by which lactate increases ISC proliferation is not wholly agreed on, with evidence indicating that lactate triggers reactive oxygen species (ROS) which increases ISC proliferation (Neophytou & Pitsouli, 2022).

As with SBAs, lactate acts on immune cells through its various receptors and transporters including GPR81, MCT-1 and SL15a12 and its signalling brings about both pro- and anti-inflammatory effects (Caslin et al., 2021). Its effects are thought to be dependent on the cell type which it is stimulating, its microenvironment, and the receptor/transporter it is acting through. Lactate levels are often high in disease; however, it has contradictory effects depending on the individual's condition. For example, high lactate indicates increased metastasis and poor survival in cancer but contrastingly, its high levels following injury indicate increased wound healing (Caslin et al., 2021). Supportive of lactate expanding the ISC populations. However, meta-analysis studies have found conflicting results on whether LAB probiotic administration improves IBD symptoms (De Filippis et al., 2020) or improves CRC (Macharia et al., 2023). With conflicting evidence for LAB strains increasing CRC cell proliferation and chemoresistance alongside reported anticarcinogenic effects. However, the benefits or risks of LAB to health may not be due to lactate but other metabolites and products of LAB such as SCFAs, bacteriocins, and exopolysaccharides, reviewed by Guo et al. (2023).

## 4 | DISCUSSION

It has been brought to light that a high-fat or western diet can increases ISCs through production of bacterial metabolites, such as lactate or SBAs, that leads to an increased CRC risk (Figure 1A). This contrasts with the impact of fibre and fruit-derived metabolites which reduce ISC number and CRC risk (Donohoe et al., 2014; May et al., 2022) (Figure 1B). Although further studies to validate these findings are imperative due to the limitations these results hold, such as the mouse models used to generate the conclusions.

Further consideration needs to be applied to how combinations of these metabolites impact on the ISCs and cellular plasticity within the intestinal epithelium (Choi et al., 2023; de Sousa & de Sauvage, 2019) which is crucial for response to injury and inflammation (Figure 1). The potential for non-ISCs to revert to ISCs is a topic of great interest in medicine and stem cell biology. A greater understanding of these relationships could help shape effective novel cancer prevention strategies for those obese individuals at high risk of CRC (Figure 1C). As lifestyle changes to reduce weight are often successful in the short term but ultimately unsuccessful in the long term, with most people returning to their original weight within 1 year. Potentially, dietary components, microbial metabolites, or exercise, which is strongly correlated with lowered risk, may be capable of reducing ISCs and CRC risk in obese people without being wholly reliant on significant or maintained weight loss.

## AUTHOR CONTRIBUTIONS

**Carys Holmes**: Writing—original draft. **Charlotte H. Illingworth**: Writing—original draft. **Lee Parry**: Conceptualization; supervision; writing—original draft; writing—review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ETHICS STATEMENT

None declared.

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