

Role of intestinal flora in colorectal cancer from the metabolite perspective: a systematic review

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Abstract: Colorectal cancer is one of the most common human malignant tumors. Recent research has shown that colorectal cancer is a dysbacteriosis-induced disease; however, the role of intestinal bacteria in colorectal cancer is unclear. This review explores the role of intestinal flora in colorectal cancer. In total, 57 articles were included after identification and screening. The pertinent literature on floral metabolites in colorectal cancer from three metabolic perspectives – including carbohydrate, lipid, and amino acid metabolism – was analyzed. An association network regarding the role of intestinal flora from a metabolic perspective was constructed by analyzing the previous literature to provide direction and insight for further research on intestinal flora in colorectal cancer.

Keywords: colorectal cancer, bacteria, microbiology, carbohydrate metabolism, lipid metabolism, amino acids, inflammation

Introduction

Colorectal cancer is the third leading cancer in humans and the fourth most common cause of cancer-related death.¹ The causes of the occurrence and development of colorectal cancer are unclear, but it is thought to result from a combination of genetic and environmental factors.² Intestinal flora and their metabolites, as environmental factors, play important roles in colorectal cancer by regulating related genes.³

The main function of the colorectum is to store feces while under siege from complex intestinal flora. Several probiotics,^{4–6} including *Lactobacillus acidophilus*, *Bifidobacterium*, *Lactobacillus rhamnosus*, and *Streptococcus thermophilus*, as well as pathogenic bacteria,^{7–9} including *Enterococcus faecalis*, *Enterotoxigenic bacteroides fragilis*, *Streptococcus bovis*, *Salmonella*, *Clostridia*, and *Fusobacterium nucleatum*, comprise the diverse intestinal flora. This intestinal flora, mucosal epithelial cells, foodborne probiotic components, and small molecules – including hormones, enzymes, mucus, and bile salts – constitute a complex intestinal micro-ecosystem.¹⁰ Although individual substances vary, the intestinal micro-ecosystem is relatively stable under physiological conditions. Multiple diseases may result if changes occur beyond the ability of compensatory adjustment.^{11,12} Studies have shown that the micro-ecosystem equilibrium in patients with colorectal cancer is disrupted.¹³ Various intestinal flora and metabolites are closely related to colorectal cancer.¹⁴

With advanced developments in microbiome and microbial metabolomics, especially rapid advancements in high-throughput sequencing technology, increasing attention has been given to studying intestinal flora and intestinal microecology in recent years.¹⁵ Current research has focused on the relationship between intestinal flora and

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colorectal cancer; however, the specific mechanism of the intestinal flora in causing colorectal cancer is unclear.^{16,17} Microbial primary metabolites, including amino acids, nucleotides, polysaccharides, lipids, and vitamins, are necessary to sustain intestinal flora growth and reproduction.¹⁸ Microbial primary metabolites are similar in most microbial cells. The synthesis of primary metabolites is a constant process, and synthetic obstacles affect normal microbial activities.^{19,20} Microbial secondary metabolites, including alkaloids, phenols, antibiotics, and pigments, determine the specificity and function of the flora. Microbes are valuable in maintaining the balance of the intestinal microecology;^{21,22} however, the significance of microbial metabolites in colorectal cancer is unclear. Given that the metabolism of three substances, including carbohydrate, lipid, and amino acid metabolism, is the general metabolic mechanism among all creatures, we tried to build a link between the intestinal flora and colorectal cancer from this angle.

In this review, we comprehensively analyzed and classified the pertinent literature on microflora metabolites in colorectal cancer from three metabolic perspectives, including carbohydrate, lipid, and amino acid metabolism. An association network of intestinal flora, their metabolites, and colorectal cancer was built that may provide direction and insight for further research on intestinal flora in colorectal cancer.

Methods

Literature search

We searched the “PubMed”, “Embase”, and “Cochrane” databases for literature published up to August 11, 2017. To achieve maximum sensitivity of the search strategy and identify all studies, the following terms were combined: (“colorectal or colon or rectal, large intestine or large bowel or intestinum crassum” and “neoplasms or tumor or carcinoma or cancer” and “flora or microflora or microorganism or microbiome or microbiota or microbe or microbiology or germ or bacteria or bacterium or fungus”) and (“glucose or adenosine triphosphate or lactic acid or mitochondria or galactose or sucrase or amylase or hexokinase or glucokinase or pyruvate kinase or glucuronidase” OR “triglyceride or fat or aliphatic acid or lipoprotein or cholesterol or cholesterin or bile acid or lithocholic acid or vitamin d or dehydroxylase” OR “amino acid or ammonia or amine or urea or carbamide or ureophil or mucin or mucoprotein or nitrosamines or nitroguanidine or nitrosoarea or aromatic amines or mycotoxin or endotoxin or exotoxin or sulfuretted hydrogen or hydrogen sulfide or hydrothion”). All relevant abstracts were

retrieved independently by two authors, and articles with available information for the present systematic review were fully reviewed. In total, 42 articles were included. To present a more comprehensive role of flora in colorectal cancer, flora appearing in the 42 articles were used as the medical subject headings (MeSH) and the pertinent literature was retrieved. Finally, 15 articles were added after identification and screening. Moreover, pertinent literature from the searched studies was analyzed. A detailed search strategy is presented in Figure 1.

Study selection

Studies catering to the following criteria were considered for inclusion: 1) studies that were published in English and 2) studies that involved intestinal flora and intestinal flora metabolism in colorectal cancer, both in vivo and in vitro. Exclusion criteria were as follows: 1) letters, case reports, reviews, or conference reports; 2) predominant studies that were not on intestinal flora metabolism in colorectal cancer; and 3) correlation studies did not involve flora metabolism.

Role of flora metabolites in colorectal cancer

Intestinal flora and carbohydrate metabolism in colorectal cancer

Carbohydrate metabolism refers to a series of complex chemical reactions in vivo. The tricarboxylic acid cycle, as the principal pathway of carbohydrate metabolism, is the final metabolic pathway and metabolic hub of the three major nutrients, including carbohydrates, lipids, and amino acids.^{23,24} Carbohydrate metabolism is important for intestinal flora and colorectal cancer. First, oxygen plays a decisive role in choosing the carbohydrate metabolic pathway. Both anaerobic and aerobic bacteria coexist in the intestinal tract. Superoxide, oxygen radicals, and oxygen molecules are closely related to the development of colorectal cancer.^{25,26} Second, carbon dioxide and water are the primary producers in carbohydrate metabolism.²⁷ Various bacteria decompose glucose and lactose and produce acid.²⁸ Intestinal microecology is regulated by maintaining the acid–base balance and regulating osmotic pressure. Third, adenosine triphosphate (ATP) is produced during carbohydrate metabolism and is an important compound that supplies energy to all living cells. Phosphoribose produced during the metabolism of pentose phosphate is necessary to synthesize DNA and RNA, and they are especially important for rapidly reproducing bacteria and infinitely replicating cancer cells.²⁹ Fourth, nicotinamide adenine dinucleotide phosphate (NADPH) is

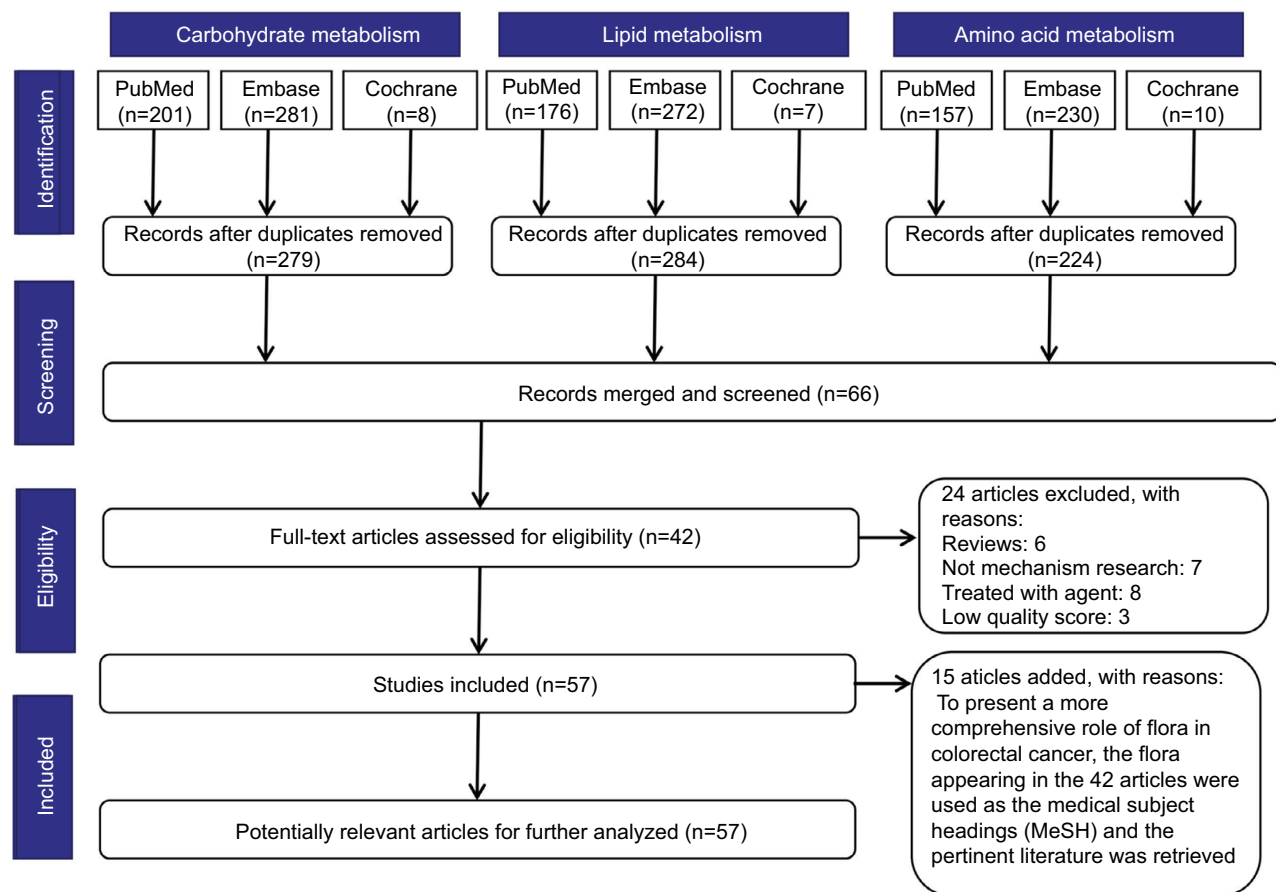


Figure 1 Literature search strategy.

Notes: The databases “PubMed”, “Embase”, and “Cochrane” were searched for literature published up to August 11, 2017. Forty-two articles were assessed for eligibility after identification and screening. To present a more comprehensive role of flora in colorectal cancer, the flora appearing in the 42 articles were used as the medical subject headings (MeSH) and the pertinent literature was retrieved. A further 15 articles were added after identification and screening.

the intermediate metabolite in carbohydrate metabolism, and it participates in phosphorylating proteins and genes. It may be involved in microbial variation and epigenetic regulation of colorectal cancer.³⁰ Finally, mitochondria are the key location for carbohydrate metabolism, and mitochondrial dysfunction is one the most important features in colorectal cancer and intestinal flora imbalance.^{31,32}

Intestinal flora and lipid metabolism in colorectal cancer

Lipids include triglycerides, phospholipids, cholesterol, and glycolipid. Triglycerides provide energy for living organisms by emulsifying bile acid salts and catalyzing lipase in the small intestine.^{33,34} Phospholipids and sugar esters maintain biomembrane structure and function.³⁵ Cholesterol can transform into vitamins, bile acid, or steroid hormones.³⁶ Many studies indicate that a high-fat diet can induce colorectal cancer, and imply that intestinal flora play irreplaceable roles; however, their specific mechanisms remain unclear.^{37,38}

In this review, we searched for clues on tumorigenesis by summarizing the pertinent literature. High-fat diets can increase bile and bile acid secretion in the colorectum, and some clostridia can accelerate transformation of bile acid into secondary bile acid by participating in the synthesis of various enzymes during fatty acid metabolism.^{39,40} Secondary bile acid, as a carcinogenic substance, promotes colorectal cancer by multiple molecular mechanisms – synthesizing oxygen free radicals, fracturing DNA strands, making chromosomes unstable, and forming cancer stem cells.^{41,42} Interactions between fatty acids, bile acids, and intestinal flora can produce diacylglycerol, prostaglandin, and leukotriene, leading to tumorigenesis by activating immune or inflammatory responses.^{43–45}

Intestinal flora and amino acid metabolism in colorectal cancer

Amino acid metabolism involves two parts. Amino acids can be used to synthesize proteins, peptides, and other

nitrogenous substances and, moreover, they can be decomposed into α -ketonic acid, amines, and carbon dioxide through deamination, transamination, and decarboxylation. Many toxic substances such as sulfur, nitrates, hydrogen sulfide, ammonia, and amines are involved in the metabolic process, and these toxic substances can lead to colorectal cancer.⁴⁶ Food residue with high protein content can stimulate sulfate-reducing bacterial growth. Hydrogen sulfide is a product of sulfate-reducing bacteria as well as an intermediate product of amino acid metabolism.⁴⁷ Hydrogen sulfide elicits several pathogenic events, including cell proliferation, differentiation, apoptosis, and inflammation – ultimately leading to malignant enterocyte transformation.^{48,49} Nitrate is not toxic, but easily reduces to nitrite due to the intestinal flora. Nitrite combines with nitrogenous compounds such as amines, amino compounds, and methyl urea to form carcinogenic nitroso compounds.^{50,51} Furthermore, mucin as an intermediate product of amino acid metabolism is a mutagenic agent with cooperation from the intestinal flora.⁵² Many enzymes, peptides, and other nitrogenous substances secreted by the intestinal flora are involved in activating and regulating important signal molecules and signaling pathways in tumorigenesis.^{53,54}

Results and discussion

The intestinal flora and host maintain a dynamic balance under physiological conditions. When this balance is disrupted, the entire micro-ecological system is significantly altered.^{55,56} The synergistic effect among intestinal flora, metabolites, and the host plays a pivotal role in the occurrence and development of colorectal cancer. First, microbes are the initial factors in colorectal cancer. Changes to the intestinal flora distribution and abundance contributes to inflammatory and immunological responses and induces malignant transformation of the intestinal mucosal cells.⁵⁷ Second, epidemiological surveys have indicated that the balance of intestinal flora in patients with precancerous lesions, including inflammatory bowel disease (IBD) and intestinal polyps, were altered significantly.^{58,59} Third, various metabolic products of the intestinal flora can, directly or indirectly, promote development and progression of colorectal cancer.⁶⁰ Fourth, micro-ecology helps to prevent tumorigenesis by reestablishing the intestinal micro-ecological balance.^{61,62} In conclusion, colorectal cancer is a dysbacteriosis-induced disease, and the understanding of this disease has changed in the molecular age.

Researchers have increasingly focused on determining the specific bacteria or microbial community structural changes

in colorectal cancer by sequencing 16S rRNA and bioinformatics analysis in recent years. Many researchers support that *Streptococcus bovis*⁶³ and *Streptococcus gallolyticus*⁶⁴ are the specific bacteria involved in colorectal cancer; however, there are some lacunae in this research. Sequencing of the 16S rRNA variable region only identifies the bacterial species, and the intra-individual variability of the bacteria was not considered. In addition, a better scientific method for studying the intestinal flora in colorectal cancer is to explore its relationship with the intestinal micro-ecological system. The intestinal micro-ecological system is complex and integral, with individual differences. Establishing an association network for the intestinal micro-ecological system in colorectal cancer may offer an approach to solving this dilemma. As shown in Figure 2, the association network for the intestinal flora and microbial metabolites in colorectal cancer, from a metabolic perspective, was constructed by analyzing the previous literature. Although we tried to search all pertinent literature, mistakes of omission inevitably occurred because of the complexity of microbial metabolism and the many compounds involved in it. Research on the relationship between microbial metabolites and colorectal cancer were relatively insufficient.

Future directions

There appears to be a complex relationship between colorectal cancer and intestinal flora. Microbial metabolites may play vital roles in balancing the intestinal micro-ecology and in developing colorectal cancer. The intestinal flora is insufficiently understood, intestinal micro-ecology is complex, and intestinal flora show significant intra-individual variability; thus, evaluating all of these interactions is challenging. With the great progress of integrated systems, molecular biology, and bioinformatics, we urgently call for a synthesis of the existing research to establish a comprehensive database that focuses on individual relationships among the intestinal flora, microbial metabolites, and colorectal cancer.

It is plausible that the intestinal flora and microbial metabolites in colorectal cancer are related to the immune system and inflammatory abnormalities. Although much effort has been expended, many bottlenecks must be addressed before stepping from the imbalanced intestinal micro-ecological system to immune system and inflammatory abnormalities to genesis and development of colorectal cancer. The clinical correlation of the intestinal flora, microbial metabolites, and colorectal cancer remains unknown; thus, it is essential to conduct further functional assays on pathogenesis such as the microbiome, microbial metabolomics, and peptidome assays.

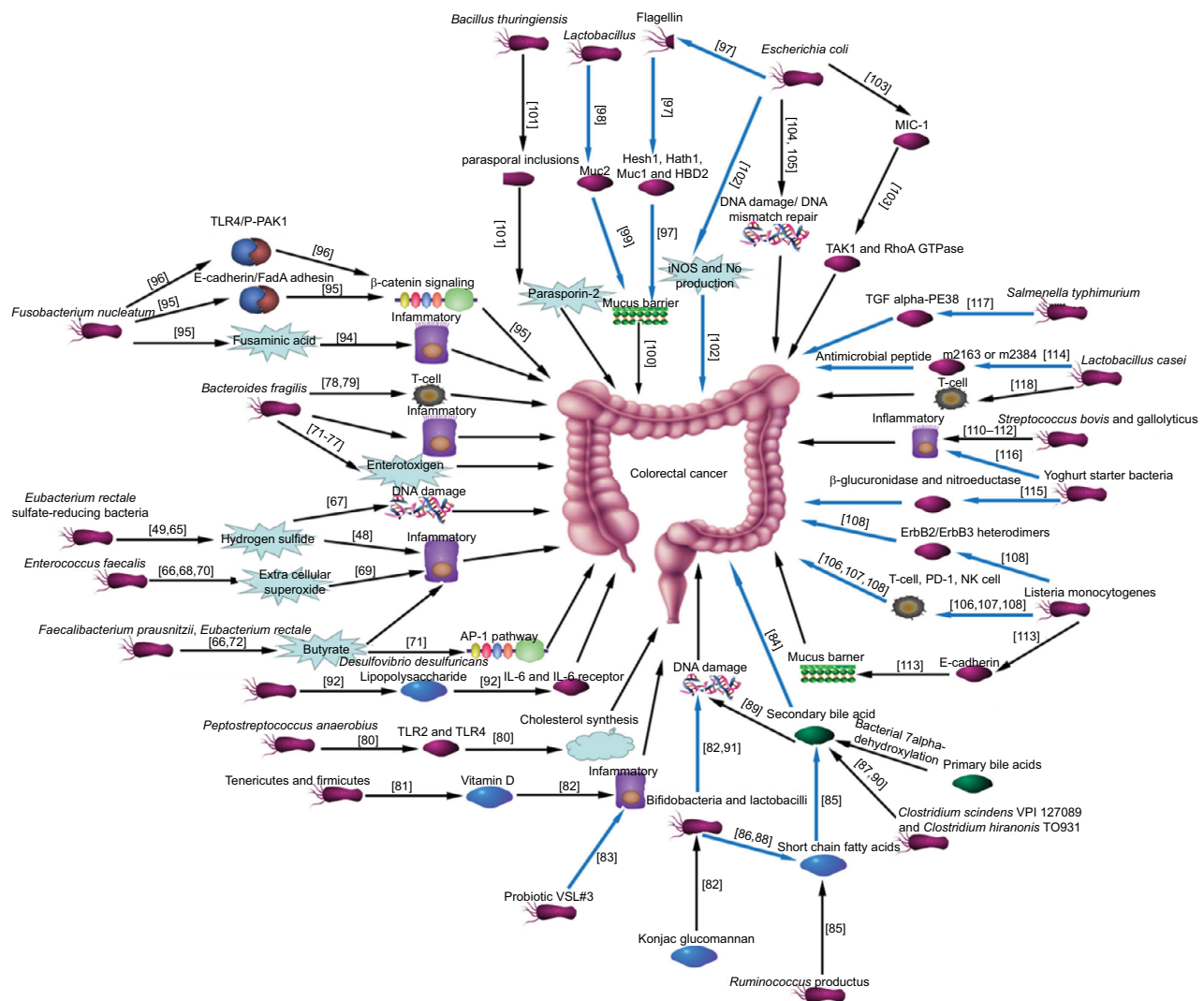


Figure 2 Network for the intestinal flora and microbial metabolites in colorectal cancer.

Notes: An association network of the intestinal flora and microbial metabolites in colorectal cancer from a metabolic perspective was constructed by analyzing the previous literature. The black and blue arrows represent pathogenic bacteria as well as probiotics, respectively. References are located within the square parentheses.

Multiple probiotics have been applied clinically for some time, and preclinical trials involving intestinal flora transfusion are also underway. Prospective and retrospective studies on the incidence of colorectal cancer after clinical interventions with microbial preparations should be scheduled.

Several avenues are available to pursue translational applications. First, microchip arrays or metabonomic technologies can assess the risk and monitor the curative effects of a bacterial species or specific microbial metabolite in colorectal cancer. Second, probiotics, microbial metabolites, and fecal microbial transfusions can all be used to recover the intestinal micro-ecological system to prevent colorectal cancer; however, this requires further clinical testing. Third, intestinal micro-ecology is influenced by many factors, including the endocrine system, diet, sleep, and stress. Testing

the intestinal flora and microbial metabolites in feces can guide the adjustment of dietary structure or living habits to prevent colorectal cancer.

Disclosure

The authors report no conflicts of interest in this work.

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