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Review

DNA Damage and the Gut Microbiome: From Mechanisms to Disease Outcomes

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Abstract: Both the number of cells and the collective genome of the gut microbiota outnumber their mammalian hosts, and the metabolic and physiological interactions of the gut microbiota with the host have not yet been fully characterized. Cancer remains one of the leading causes of death, and more research into the critical events that can lead to cancer and the importance of the gut microbiota remains to be determined. The gut microbiota can release microbial molecules that simulate host endogenous processes, such as inflammatory responses, or can alter host metabolism of ingested substances. Both of these reactions can be beneficial or deleterious to the host, and some can be genotoxic, thus contributing to cancer progression. This review focused on the molecular evidence currently available on the mechanistic understanding of how the gut microbiota are involved in human carcinogenesis. We first reviewed the key events of carcinogenesis, especially how DNA damage proceeds to tumor formulation. Then, the current knowledge on host DNA damage attributed to the gut microbiota was summarized, followed by the genotoxic endogenous processes the gut microbiota can induce. Finally, we touched base on the association between specific gut microbiota dysbiosis and different types of cancer and concluded with the up-to-date knowledge as well as future research direction for advancing our understanding of the relationship between the gut microbiota and cancer development.

Keywords: DNA damage; gut microbiome; cancer; DNA adduct; biotransformation; biomarker

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1. Introduction

Cancer remains the second most frequent cause of death in the human population worldwide and is still increasing the medical and public health burdens [1,2]. Efforts from the biological, medical, and public health research have been made to understand the mechanisms and reasons for cancer and to create preventative measures or treatments to reduce the progression to cancer. To date, we have understood that cancer progression is initiated by failure to repair abnormal DNA sequences caused by replicating errors or DNA damage. DNA damaging agents can be endogenous, such as formaldehyde, which is involved in cellular metabolism [3,4], and they can be exogenous, such as aflatoxin in ingested grain [5]. As the key events of cancer, DNA damage and its formulating mechanisms are informative for developing therapeutic measures, designing public health interventions, and identifying the risk factors. As cancer research progresses, we have characterized the important mechanisms of DNA damage, which can subsequently induce cancer progression. For instance, ionizing radiation can release electrons from the molecules of a DNA sequence, causing breaks of covalent bonds; and polycyclic aromatic hydrocarbons (PAHs) have very electrophilic functional groups, which can attach to nucleophilic sites in DNA to create bulky DNA adducts. However, we are still far from understanding the repertoire of the causes and mechanisms of DNA damage, as some identified risk factors of cancer still lack mechanistic information. For example, the profiles and alterations of our gut microbiome have long been associated with various malignancies, such as colorectal and liver cancers; yet, the underlying mechanisms are only partially revealed.

The collection of bacteria, fungi, archaea, bacteriophages, and other microbes residing in the gastrointestinal tract (GI) of a host is termed the "gut microbiota," whose number of micro-organisms has been estimated to exceed 10^{14}. Among them, more than 99.9% of the cells are bacteria. In a human body, the number of gut bacterial cells is ~1–10 times the number of human cells, and the gut bacteria are mainly represented by two predominant phyla, namely Bacteroidetes and Firmicutes [6–8]. The collection of genomes from the gut microbiota is defined as the "gut microbiome," the size of which exceeds the human genome by over 100 times. The gut microbiome encompasses essential, important, or currently ambiguous biochemical and metabolic functions that help maintain the homeostasis of its host [6,9]. Many human illnesses are associated with an imbalance in the gut microbiota, termed dysbiosis. Dysbiosis is commonly defined as a dwindled microbial diversity, the presence of potentially harmful micro-organisms, or the absence of benignant species [9,10]. Recent studies have proposed a more host-centric definition of dysbiosis, which suggests that dysbiosis is a state of weakened host control over the microbial environment, such as an increased availability of host-derived oxygen and nitrate in the colon [9,11]. To summarize, dysbiosis features an imbalanced community profile of the microbiota and can impair the physiological functions related to host-microbiota homeostasis. Together, animal and epidemiological studies have provided mounting evidence associating dysbiosis with maladies, such as cardiovascular diseases [12–14], Alzheimer's disease [15,16], and the topic of this review, cancer.

The development of cancer starts with key events, such as DNA damage. Recent evidence suggested that the levels of DNA damage differ between germ-free (GF) and conventionally-raised (CONV-R) mice [17]. To date, there is limited summary on the current comprehensions of how the gut microbiome can affect cancer progression, especially from the mechanistic standpoint. The objective of this review is to summarize the available research on gut-microbiota-attributed carcinogenesis, including how the gut microbiota can synthesize DNA damaging agents, produce or elevate DNA damage, and eventually induce or initiate cancer.

2. DNA Damage and Cancer Development

To understand how gut microbiome can be involved in the different stages of cancer development and progression, it would be essential to firstly review how molecular reactions in a DNA sequence can eventually progress to a cancer incidence. Gene mutation is defined as a change in a DNA sequence and is a key step in the progression to cancer. Mutations occurring in genes that control cell growth (e.g., *RAS*) or DNA repair (e.g., *p53*), thus resulting in impaired functions, can consequently lead to cancer, as these impairments can cause cells to multiply uncontrollably and become cancerous. Somatic gene mutation can be caused by repair errors in damaged or miscoded DNA (e.g., during mitosis). The progression of DNA damage to mutation and to the initiation of cancer is illustrated in Figure 1.

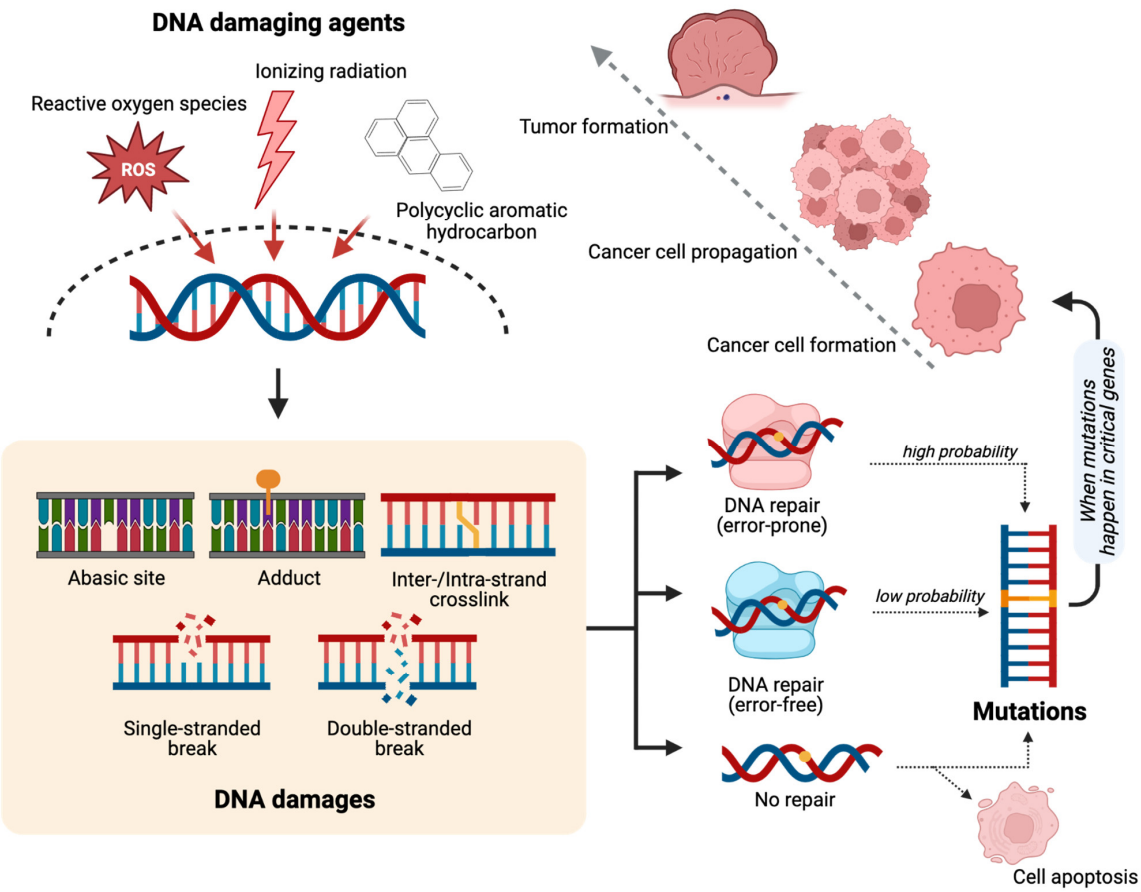

Figure 1. From DNA damage to cancer progression. The DNA macromolecule is vulnerable to endogenous and exogenous DNA damaging agents; thus, different types of DNA damage are formed. If not repaired or repaired incorrectly, DNA damage can result in mutations, and when mutations occur in critical genes (e.g., genes that regulate cell growth), a normal cell can be transformed into a cancerous cell, which, after propagations, can grow into tumor and cause cancer.

DNA damage is defined as any modification of DNA that changes its coding properties or regular functions in transcription or replication [18], which can occur in several mechanisms, resulting in different forms. In a molecular reaction that formulates DNA damage, the molecule that impairs the DNA is termed the DNA damaging agent (DDA). DDAs can be endogenous or exogenous and with their diverse chemical properties and structures can induce different types of DNA damage. Table 1 summarizes the common types of DNA damage, their possible DDAs, and the encountering DNA's repair methods. Lesioned DNA in the body can trigger a collective counteraction termed the DNA damage response, which includes the detection of the DNA damage, signaling of the impaired location, and promotion of the repair reaction. The signaling pathways involved in DDRs are well reviewed by Jackson and Bartek [19]. Due to the wide diversity of DNA lesion types, multiple distinctive DNA repair mechanisms are needed, including mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), single-strand break repair (SSBR), and double-strand break repair (DSBR). Generally, simple DNA damage, such as abasic sites, alkylated or oxidated DNA adducts, and deaminated nucleotides, can be accurately repaired in a relatively error-free manner by DNA polymerases. In contrast, complicated DNA damage, such as bulky DNA adducts (e.g., PAH-attached nucleotides), DNA inter-/intra-strand crosslinks, and strand breaks, introduces severe challenges to the integrity of the DNA's double helix; thus, it is difficult to repair. To address these serious lesions more quickly, more erroneous repair mechanisms by error-prone DNA polymerases have been used to efficiently restore nucleotides to the lesions, although inaccurately.

Table 1. DNA damage type, repair pathway, and accuracy.

Type	Definition	Example DDAs		Mechanism	Repair Pathway	Repair Error	Reference
		Exogenous	Endogenous				
Abasic site	Loss of a purine or pyrimidine base in a DNA sequence.	Ionizing radiation	ROS, DNA glycosy-lases	DDAs attack and break the glycosidic linkages between the deoxyribose and the nitrogenous base of a nucleotide.	BER (major) and NER (minor)	More error free	
Adduct	DNA nucleotides covalently bound to substances that add a functional group to the DNA's primary structure.	PAHs, formaldehyde, aflatoxin	ROS, en-dogenous alkylating agents (e.g., formalde-hyde)	Generally, the electrophilic sites of DDA attack the nucleophilic sites of the nucleotide and form the covalent bond.	Structurally dependent, including DR, BER, NER, MMR.	Structurally dependent bulky adducts generally lead to error-prone repairs.	
Deamination	Removal of an amino group from a nucleotide.	NA *	MT, nitric oxide	(1) DDAs cause deamination, such as deaminating dC to dU. (2) Misincorporation of dUMP instead of dTMP during replication.	BER	More error free	
Single-strand break	Discontinuities in one strand of the DNA's double helix.	Ionizing radiation	ROS	DDAs cause cleavage, thus discontinuity, in one strand of the DNA duplex.	SSBR, HR, BER	More error prone	[20]
Double-strand break	Discontinuities in both strands of the DNA's double helix.	Ionizing radiation, bleomycin, neocarzinostatin	Colibactin, hydrogen peroxide	DDAs cause cleavage, thus discontinuity, in both strands of the DNA duplex.	DSBR, NHEJ, HR	Majorly error prone	[21,22]
Intra- and inter-strand crosslink	Two nucleotides in the same (intra-) or different (inter-) strands of DNA were reacted to form a covalent bond.	Nitrogen mustards, cisplatin, psoralens	Nitrous acid, aldehydes (e.g., malon-dialdehyde)	DDAs often have two independently reactive groups that bind with two nucleotide residues of DNA to form a crosslink.	NER, HR, BER	Majorly error prone	[23]

* There has been little research on characterizing potential exogenous DNA damaging agents that attack the DNA molecules by deamination. BER: base excision repair, dA: deoxyadenosine, dT: deoxythymidine, dC: deoxycytidine, dG: deoxyguanosine, dTMP: deoxythymidine monophosphate, dUMP: deoxyuridine monophosphate, DDA: DNA damaging agent, DNA: deoxyribonucleic acid, DR: direct repair, DSBR: double-strand break repair, HR: homologous recombination, MER: mismatch excision repair, MMR: mismatch repair; MT: (cytosine-5)-methyltransferase, NER: nucleotide excision repair, NHEJ: non-homologous end joining, ROS: reactive oxygen species, SSBR: single-strand break repair.

3. DNA Damage Attributed to the Gut Microbiome

In the previous section, we established that different DDAs, due to their distinctive chemical and structural properties, can introduce various types of DNA damage. The in vivo gut microbiome is capable of inducing a broad spectrum of metabolisms and biochemical reactions and can synthesize different DDAs, which can attack the hosts' DNA. Herein, we review the investigations that monitored DNA damage induced by the gut microbiome (Table 2).

Table 2. Local DNA damage attributed to the gut microbiome.

DNA Damage	Specific Gut Microbiome Species	Mechanism	Reference
DNA adduct	*pks*$^+$ *Enterobacteriaceae* spp.	Some specific bacteria that harbor the *pks* genomic island (*pks*$^+$) synthesize various colibactins, which can conjugate to DNA and form a colibactin–DNA adduct.	[24]
	H. pylori	*H. pylori* disrupts intracellular processes in the gut epithelium that cause inflammation, and the host responds by involving immune cells through their release of cytokines, forming reactive oxygen/nitrogen species (ROS and RNS), which can eventually attack DNA to form adducts, such as 8-oxo-dG.	[25,26]
	(Not applicable)	DNA adducts related to oxidative stress (i.e., 8-oxo-dG) are lower in the small intestine of SPF mice than in GF mice. 5-Cl-dC, a DNA adduct attributed to neutrophil activity, is higher in colon and small intestine of GF mice than SPF mice. Lipid-peroxidation-induced DNA adduct, N2-ε-dG, is higher in the liver of SPF mice than in GF mice.	[17]
DNA crosslinking	*pks*$^+$ *Enterobacteriaceae* spp.	*pks*$^+$ bacteria induce colibactin–DNA adduct and can then form DNA inter-strand crosslinks.	[27–29]
DNA single-strand break	*pks*$^+$ *Enterobacteriaceae* spp.	DNA inter-strand crosslinks formed by colibactin can be depurinated, subsequently leading to single-strand breaks.	
	E. coli, *C. jejuni*, and others	CDT is produced by some pathogenic Gram-negative bacteria. Most members of CDTs hold similar structures, sequence homology, and endonuclease activities of DNase I, which can induce single-strand breaks (nicks) in DNA.	[30–33]
	S. typhi, *S. enterica*, and other *Salmonella species*	TT have been identified in several *Salmonella* spp. TT released from bacteria possess endonuclease activities similar to CDT, which can introduce single-strand breaks.	[30,34]

Table 2. *Cont.*

DNA Damage	Specific Gut Microbiome Species	Mechanism	Reference
DNA double-strand break	*pks*$^{+}$ *Enterobacteriaceae* spp.	When colibactins introduce accumulating single-strand breaks, and two closed nicks face each other on opposite strands, a DSB can be created.	[29]
		Some species of colibactins (e.g., colibactin-645) from *pks*$^{+}$ bacteria, under certain situations (e.g., presence of Cu (II)), induce DNA double-strand breaks.	[27,35]
	E. coli, *C. jejuni*, and others	Highly concentrated CDT accumulates single-strand breaks, and when two closed nicks face each other on opposite strands, a DSB can be created.	[30,31,36]

E. coli: *Escherichia coli*; *B. fragilis*: *Bacteroides fragilis*; *C. jejuni*: *Campylobacter jejuni*; *H. hepaticus*: *Helicobacter hepaticus*; *H. pylori*: *Helicobacter pylori*; *S. enterica*: *Salmonella enterica*; *S. typhi*: *Salmonella typhi*; 8-oxo-dG: 8-hydroxyguanine; CDT: cytolethal distending toxin; pks: polyketide synthase; RNS: reactive nitrogen species; GF: germ free; SPF: specific pathogen-free; TT: typhoid toxin.

3.1. Colibactin-Derived DNA Damage

Among the dedicated research works, the *pks* genomic island found in the genome of some *Enterobacteriaceae* spp., such as *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter koseri*, and *Enterobacter aerogenes*, is the most well-characterized gene that codes for the enzymes necessary for the synthesis of colibactin—a genotoxic metabolite that can attack DNA in different mechanisms [27,37,38]. In *pks*$^{+}$ bacteria, colibactin is firstly synthesized as a prodrug, precolibactin, which is then cleaved in the bacterial periplasm to release the active, genotoxic colibactin. How colibactin can attack DNA and generate DNA damage is illustrated in Figure 2. In brief, the cyclopropane ring embedded in colibactins is a reactive structural motif, which is highly electrophilic for binding DNA and forms bulky DNA adducts [24,39]. Several studies have characterized the complicated structures of colibactin–DNA adducts [24,39–41]. Many colibactins have multiple electrophilic sites (e.g., a second cyclopropane ring); thus, the secondary electrophilic site can bind to an additional nucleotide, which can result in DNA crosslinks [28,39]. The most current study monitored inter-strand crosslinks generated by colibactin, and although intra-strand crosslinks are possible, the steric effect of the large colibactin–DNA adduct may favor the formation of inter-strand crosslinks [28]. Xue et al. investigated how depurination and subsequent reactions of the inter-strand crosslinks formed by colibactin can result in single-strand breaks (SSBs); then, the accumulation of SSBs can further lead to double-strand breaks (DSBs). Some specific species of colibactin, e.g., colibactin-645, demonstrate the power of directly and seriously attacking the DNA to form DSBs; yet, a clear molecular mechanism still requires investigation [27,35]. Together, the lesions caused by colibactin are bulky and difficult to repair, leading to a high probability of subsequent mutations.

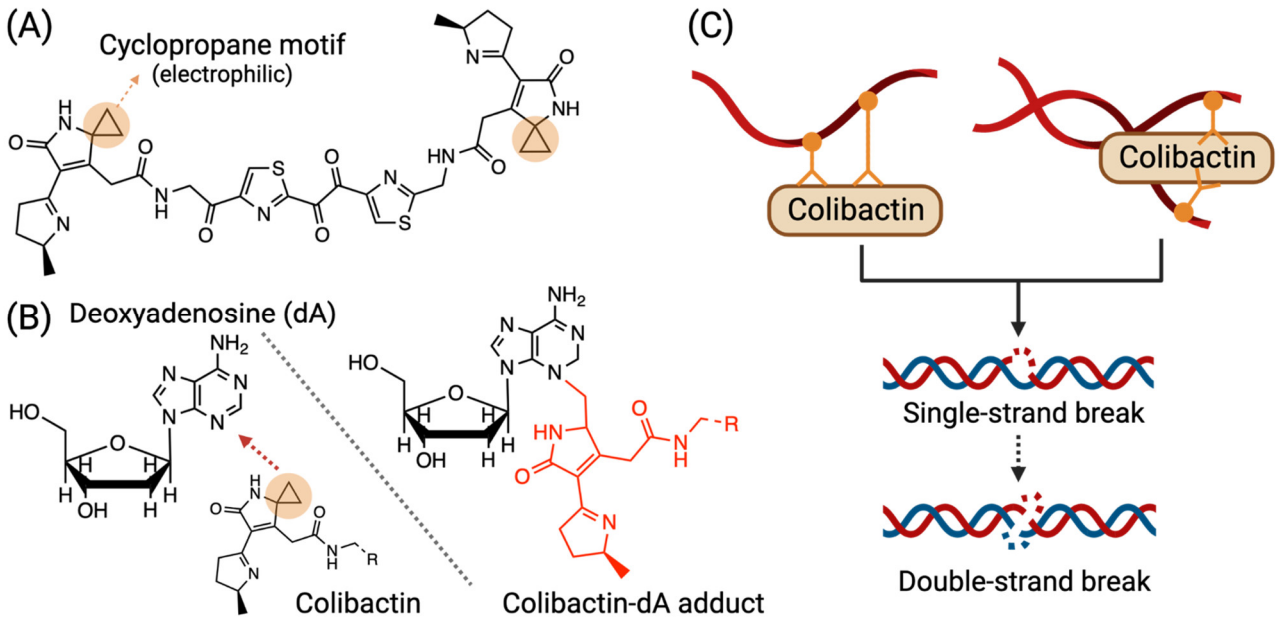

Figure 2. Mechanisms of colibactin in formulation of DNA damage. (**A**) Chemical structure of a representative colibactin species that contains one or more electrophilic cyclopropane motif with high DNA attacking potential. (**B**) The cyclopropane motif of the colibactin can attack DNA nucleotides (deoxyadenosine (dA) is used as example) to form colibactin–DNA adducts. (**C**) Colibactins with two electrophilic sites (i.e., cyclopropane motif) can form intra- (left) and inter-strand (right) crosslinks in the DNA; after depurination and subsequent reactions of the colibactin inter-strand crosslink, single-strand breaks can be introduced, and the accumulation of single-strand breaks can lead to double-strand breaks.

3.2. Other Toxins: Cytolethal Distending Toxins and Typhoid Toxin

While colibactin poses great harm and has attracted great research attention with its strong genotoxicity, there are other gut bacterial toxins being revealed as DDAs. Cytolethal distending toxins (CDTs) include a family of bacterial toxins produced by some pathogenic Gram-negative bacteria, such as *E. coli*, *Shigella dysenteriae*, and *Campylobacter jejuni* [42]. The canonical nomenclature of CDTs uses the initials of the producing bacterium followed by "CDT" (e.g., *E. coli* CDT as EcCDT) [43]. CDTs are AB_2 dimers, with one of the subunits (CdtB) possessing DNA-cleaving properties similar to DNase I and the other subunits (CdtA and CdtC) as binding components [30]. With the endonuclease activity similar to DNAse I, CDTs primarily and directly induce SSBs. Under optimal conditions, where two SSBs face each other, a DSB can be created [31,36]. Another example of genotoxic bacterial toxin that can appear in the gut is the typhoid toxin (TT), which is identified in *Salmonella typhi*, *Salmonella paratyphi*, and other *S. enterica* subspecies (e.g., *arizonae*, *javiana*) [30,44–46]. The structure of TT is an A_2B_5 organization, and it contains a CdtB subunit that exhibits endonuclease activities similar to CDTs and DNAse I [30,45,47]. The most current research work observed direct SSBs introduced by TT [34]. Although TT can theoretically result in DSBs indirectly, similar to CDTs, future investigation is needed to conclude this with evidence.

3.3. Indirect Pathways and Systemic Effects

Gut bacterial toxins, such as colibactins, CDTs, and TTs, as aforementioned, exhibit direct or indirect pathways by locally attacking host DNA. Toxin-related DNA damage has been observed in the GI epithelial cells both in vivo and in vitro [48–51]. The gut microbiota and their metabolites can also impair the host DNA on a wider and systemic scale, which is still a pioneering field with limited research. *Helicobacter pylori*, due to its high correlation with colorectal cancer, has been investigated deeply in terms of its systemic effect on the host [52]. One of the indirect effects of *H. pylori* infection is the creation of a pro-inflammatory environment in the host through several mechanisms, such as the release of peptidoglycans, which can eventually activate NF-κB and AP-1, as well as the release of outer membrane proteins, which induce cytokine synthesis [52–57]. There may remain uncharacterized processes of how *H. pylori* stimulates pro-inflammatory responses. Research has shown concomitance between high levels of pro-inflammatory markers and reactive oxygen/nitrogen species (ROS or RNS), as the respiratory burst of inflammatory cells during inflammation increases the production and accumulation of ROS [58]. ROS are the typical and powerful endogenous DDA with strong electrophilicity, which can oxidize the DNA and form DNA adducts, such as 8-hydroxyguanine (8-oxo-dG) and N7-hydroxyethyl-2′-deoxyguanine (N7-HE-dG) [59,60]. Together, if the gut microbiota can stimulate proinflammation, the level of DNA damage can be subsequently elevated, thus increasing the mutation rate and cancer incidence.

A recent study examined the total effect of the existence of gut microbiota on the levels of DNA adducts attributed to the gut microbiome [17]. The various structures of DNA adducts can imply that they originate from different endogenous processes; for instance, 8-oxo-dG is attributed to oxidative stress, and O6-methyl-deoxyguanosine represents the level of alkylating agents (e.g., *S*-adenosylmethionine) [61]. This study quantified (1) a higher level of 8-oxo-dG in the small intestine and (2) a lower level of 5-chloro-2′-deoxycytidine (5-Cl-dC) in the colon and small intestine of CONV-R mice than GF mice [17]. 5-Cl-dC results in DNA chlorinated by hypochlorous acid, which is released by neutrophils as an immune response. The lower 5-Cl-dC in CONV-R mice indicates the tolerance of the host immune system to the gut micro-organisms to maintain the commensal relationship, assure immunological homeostasis, and avoid autoimmunity [62,63]. The authors also believe that oxidative stress is lowered by the gut microbiome through pathways, including the synthesis of antioxidants or up-regulation of antioxidase activities, although further mechanistic investigation is needed. Interestingly, the authors not only quantitated DNA adduct levels in local GI tissues but also in more distant tissues, which can represent the systemic effects of the gut microbiota; they also observed higher N^2-ε-deoxyguanosine in the liver of CONV-R mice, which represents a higher activity of lipid peroxidation [17]. This study showed the potential of gut microbiota in influencing DNA damage in the host systemically.

4. Genotoxic Endogenous Processes Modulated by the Gut Microbiome

We summarized the efforts made in characterizing DNA damage caused by the gut bacterial toxins and instanced the possible systemic effects induced by the gut microbiota, which can indirectly induce cancer. Herein, we expand the topic to include the genotoxic endogenous processes that can be modulated by the gut microbiome, which will cover three mechanisms: bile acid and lipid metabolism; proinflammation and inflammation; and xenobiotic biotransformation. It is noted that while there are countable observational studies, clinical trials, and systemic reviews on the beneficial effects of probiotics in these mechanisms [64–68], our review focuses on genotoxic adverse effects.

4.1. Bile Acids and Lipid Metabolism

The involvement of the gut microbiota in metabolizing bile acids has been thoroughly investigated, as multiple in vivo, in vitro, and epidemiological studies have linked microbial-related (i.e., secondary) bile acids to adverse health events, especially colorectal cancer [69,70]. On the other hand, short-chain fatty acids (SCFAs), derived from bacterial fermentation of dietary fibers and resistant starch, are believed to be beneficial and essential in multiple ways, including the promotion of anti-inflammatory cytokines and the stimulation of expression in epithelial-barrier-forming molecules [71,72]. Together, a consensus with exemptions has been reached, namely that there is a department of bacteria (e.g., *Clostridium* spp.) that efficiently biotransform primary bile acids into secondary bile acids—which may induce pro-inflammatory effects through multiple mechanisms—and that there is another department of bacteria (e.g., *Roseburia* spp.), which productively synthesize SCFAs that may promote the anti-inflammatory system. The dynamic between these two departments of gut bacteria determines colonic inflammation, which is one of the prodromes of tumorigenesis. Herein, we focus on the different mechanisms of some secondary bile acids that can promote genotoxic pathways, such as proinflammation.

Zeng et al. had thoroughly reviewed the current understanding on secondary bile acids' potential in inducing cell proliferation, inflammation, and cancer [70]. In brief, primary bile acids are synthesized in the liver and stored in the gall bladder in glycine- or taurine-conjugated forms, which are ready for digestion and absorption of lipids, cholesterol, and fat-soluble vitamin when released to the duodenum. The excessive primary bile acids are reabsorbed in the distal ileum via enterohepatic circulation; however, 5 to 10% of primary bile acids are metabolized to secondary bile acids by the gut microbiota rather than reabsorbed. The major biotransformations include: deconjugation of primary bile acids into free bile acids (and glycine or taurine) by bile salt hydrolase (BSH); 7α-dehydroxylation of cholic acid (CA) and chenodeoxycholic acid (CDCA) to deoxycholic acid (DCA) and lithocholic acid (LCA), respectively; and 7β-dehydroxylation of ursodeoxycholic acid (UDCA) to LCA [70,73]. While some studies have shown that at a lower, balanced physiological level, secondary bile acids (DCA and LCA) have exhibited inhibiting properties in colonic cell proliferation and epithelial apoptosis [74–76], most research works focused on how higher concentrations of DCA and LCA lead to adverse health effects, which were dedicatedly reviewed in previous literature [77,78]. For instance, high secondary bile acid concentrations stimulate cell proliferation by activating epidermal growth factor receptors (EGRFs) and post-extracellular-signal-regulated kinase (EGRF/ERK) signaling [69,79]. Another genotoxic effect of secondary bile acids is their influence on ROS and RNS. Secondary bile acids are stimulators of several plasma membrane enzymes that produce ROS, including NAD(P)H oxidases and phospholipase A2. Secondary bile acids can also activate the innate and adaptive immune-related NF-κB, which can subsequently increase the systemic levels of proinflammation, ROS, and RNS. There are other mechanisms through which members of the gut microbiota can induce proinflammation and even inflammation, which we will discuss in the next section. In addition, observations were made that secondary bile acids induce DNA damage (SSBs) and apoptosis, whereas the specific mechanisms are yet to be fully elucidated [78,80]. In summary, secondary bile acids trigger a complicated concentration-dependent network, which can impact (pro)inflammation, cytotoxicity, and genotoxicity, and research is still ongoing to decipher the complex.

4.2. Proinflammation and Inflammation

In the previous section, we summarized how secondary bile acids can contribute to proinflammation through NF-κB dependent or independent induction of ROS/RNS synthesis. There are other pathways through which members of the gut microbiota can stimulate inflammation, thus increasing the cancer potential of a host.

4.2.1. *Helicobacter Pylori*

Infection with *H. pylori* and the resulting chronic inflammation are well-researched and understood risk factors of malignancies in the GI tract, including colorectal and gastric cancers; thus, *H. pylori* has been classified as a Group I carcinogen by the International Agency for Research on Cancer (IARS) [54]. Lamb and Chen, as well as other researchers, have thoroughly reviewed the pathogenicity, carcinogenicity, and host inflammatory responses to *H. pylori* [52,54,81–84]. In brief, after the colonization of *H. pylori* in the host stomach, their various virulence components contribute to the induction of host cell proliferation and inflammation, such as the flagella, lipopolysaccharide (LPS), vacuolating toxin VacA, and cytotoxin-associated gene pathogenicity island (*cag*PAI) [54]. Among the virulence factors, the *cag*PAI gene that encodes CagA is the most potent and investigated component [54,84,85], as CagA-positive *H. pylori* resulted in significantly higher incidence of gastric carcinoma than CagA-negative *H. pylori* in both animal and epidemiological studies [86,87]. CagA initiates or induces chronic inflammation via multiple pathways, which include direct binding, interaction, or phosphorylation of vital signaling proteins and methylation of tumor suppressor genes; moreover, new mechanisms are being proposed and investigated [84].

4.2.2. Bacterial Lipopolysaccharides and Other Microbial Products

LPS is the most abundant component within the cell walls of Gram-negative bacteria, and it can stimulate the release of interleukin 8 (IL-8, CXCL8, CXC ligand 8) and other inflammatory cytokines in various cell types (e.g., colonic and intestinal epithelial cells), leading to acute or chronic inflammation [88–91]. Observations have been made on elevated Gram-negative bacteria, LPS, and inflammatory cytokines in subjects with gut or systemic inflammations [92,93]. Some species of the gut microbiota can release other toxins, which can stimulate proinflammation. For example, Goodwin et al. showed in their study that the enterotoxin of *Bacteroides fragilis* is an upregulating ligand of spermine oxidase, which subsequently increases ROS, thus elevating oxidative stress and inflammation level [94].

4.3. Xenobiotic Biotransformation

The gut microbiome contains a repertoire of genes, with their functions incompletely characterized, and many of these genes encode metabolic enzymes essential for the catabolism and biotransformation of ingested macronutrients, trace elements, and xenobiotics. The chemical modifications of xenobiotics induced by our gut microbiome can lead to altered disease risk, bioavailability, toxicity, or efficacy, the topic of which started to attract high attention when many drugs were found with varying pharmacokinetics and pharmacodynamics, which resulted in inconsistent medication among the population [95]. It was later established that the different metabolic activities, due to varying gut microbiomes among individuals, contributed to such therapeutic variation, as the administrated drug underwent microbial metabolism to different degrees and structures [95,96].

Host xenobiotic metabolism can be generally classified into Phase I and Phase II metabolism, with Phase I involving enzymatic oxidation, reduction, or hydrolysis, and Phase II involving enzymatic conjugations of charged species, such as glucuronic acid and glutathione. Both phases increase the polarity of the substrate in order to facilitate detoxification. The metabolisms induced by the gut microbiota, on the other hand, have yet to be fully understood, but some common reactions are thoroughly described in the review by Koppel et al., which include hydrolytic transformations, lyase reactions, reductive transformations, functional group transfer reactions, and transformations mediated by radical enzymes [97]. Compared to the host metabolism, the capability of the gut microbiota to modify xenobiotics is more diverse and can result in varying and sometimes unexpected structures. Table 3 lists existing studies focusing on some possible but undesired dietary ingested compounds and the environmental contaminants possibly ingested by humans, whose biotransformation may have been altered by the gut microbiota. There has been much research focusing on the effect of the gut microbiota on specific drug metabolisms (e.g., gemcitabine and other chemotherapeutics) [95], but our review focuses more on the environmental and exposomic perspectives that the general population may encounter.

The most well-understood and representative biotransformation our gut microbiota facilitate is β-glucuronidation, which falls in the category of lyase reactions. Glucuronidation is a major Phase II metabolism in mammalian liver, where the substrates, including ingested xenobiotics, are catalytically conjugated to glucuronic acid, thereby adding their solubilities for excretion [98,99]. Once the conjugated glucuronides enter the intestine, the microbiome-encoded β-glucuronidases can remove the glucuronic acid, thus releasing the original molecules into the gut lumen. The activities of microbial β-glucuronidases affect the kinetics and toxicities of various xenobiotics [99], and many investigations have been conducted into how microbial β-glucuronidases affect drug efficacy or toxicity (e.g., CPT-11 [100,101]). From a non-drug and environmental contaminant perspective, there is less research on evaluating the metabolism altered by our gut microbiota. Of note, most studies monitored the overall effect of the gut microbiota in animal models, and it is still ambiguous as to what reactions or mechanisms are involved specifically. For example, the administration of several nitrated PAHs (nitro-PAHs) resulted in higher total DNA adduct levels in CONV-R mice compared to GF mice, which included 2-nitrofluorene, 2-acetylaminoflurorene, 1-nitropyrene (1-NP), and 3-methyl-3H-imidazo[4,5-f]quinoline-2-amine (Table 3). In these research works, the effect of the gut microbiota was observed as a gap to prove the role of gut microbes in involving xenobiotic biotransformation; however, which species and what mechanisms were responsible remained unknown. Other research works pointed out the species or pathways involved in gut-microbiota-related xenobiotic metabolism. For instance, the gut microbiota can reduce 6-nitrobenzo[*a*]pyrene to 6-nitrosobenzo[*a*]pyrene and 6-aminobenzo[*a*]pyrene to increase mutagenicity [102,103]. In another study, Kataoka et al. revealed that *Peptostreptococcus magnus* increased the toxicity of 1-NP by deconjugating the detoxified 1-NP (1-NP oxide-cysteine) by its β-lyase activity [104]. Some bacterial species demonstrated beneficial interactions with the host xenobiotic metabolism. For example, *Lactobacillus rossiae* protected the colon tissues of mice fed with 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), as fewer DNA adducts were observed [105].

Table 3. List of ingested dietary compounds and environmental pollutants, with studies supporting the view that biotransformation by the gut microbiome increases genotoxicity.

Class	Name	PubChem CID	Use	Specific Gut Microbiome Species	Mechanism	Reference
Nitro-PAHs	2-nitrofluorene	11831	By-product of combustion	NA	CONV-R mice experienced higher total DNA adduct levels than GF mice in all tissues collected.	[106]
				NA	SPF mice and HFA mice had higher total DNA adduct levels in local (e.g., colon epithelium) and distant (e.g., liver) tissues.	[107]
	2-acetylaminofluorene		By-product of combustion	NA	CONV-R mice experienced higher total DNA adduct levels than GF mice in all tissues collected.	[106]
	6-nitrobenzo[*a*]pyrene	44374	Engine emission	NA	Microbiome reduced 6-Nitrobenzo[*a*] pyrene to 6-nitrosobenzo[*a*]pyrene (PCID 119358) and 6-aminobenzo[*a*]pyrene (PCID 23911), whereby 6-nitrosobenzo[*a*]pyrene showed direct mutagenicity.	[102,103]
	1-nitropyrene	21694	By-product of combustion	NA	Specific DNA adducts were detected only in CONV-R but not in ABT mice.	[108]
				P. magnus	*P. magnus* metabolized sample had higher genotoxicity.	[104]
	2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine	1530	Known mutagen found in cooked foods and in cigarette smoke.	*L. rhamnosus*	CONV-R mice additionally fed with *L. rhanmosus* had lower total DNA adduct levels in the colon tissues compared to control CONV-R mice.	[105]
	3-methyl-3H-imidazo[4,5-f]quinolin-2-amine	53462	Known mutagen found in cooked foods and in cigarette smoke.	NA	SPF mice and HFA mice had higher total DNA adduct levels in local (e.g., colon epithelium) and distant (e.g., liver) tissues.	[107]
	2-Amino-9H-pyrido[2,3-b]indole	62805	Known mutagen found in cooked foods and in cigarette smoke.	*S. faecalis*, *C. butyricum*, *B. mesentericus*	HFA mice additionally administered with the probiotic mixture (Sf, Cb, Bm) had lower total DNA adduct level than the control HFA mice.	[109]
	MelQx	62275	Known mutagen found in cooked foods and in cigarette smoke.	*E. hallii*, *L. reuteri*, *L. rossiae*	The three bacteria tested were able to convert MelQx to a new microbial metabolite (MelQx-M1) with lower mutagenicity.	[110,111]
Dinitrotoluenes	2-nitrotoluene	6944	Production of dyes, pesticides, and rubber chemicals.	NA	DNA repair response was only observed in inoculated animal rather than GF animal.	[112]
Toxin	Aflatoxin B_1	186907	Mutagen produced by specific molds, particularly *Aspergillus* spp.	*L. rhamnosus*, *P. freudenreichii*	Healthy young men (n = 90) with potential exposure to Aflatoxin B_1 were assigned to the control group or probiotic-administered group. The probiotic-administered group had lower Aflatoxin B_1-induced DNA adduct.	[113]

B. mesentericu: *Bacillus mesentericus*; *C. butyricum*: *Clostridium butyricum*; *E. hallii*: *Eubacterium hallii*; *L. reuteri*: *Lactobacillus reuteri*; *L. rhamnosus*: *Lactobacillus rhamnosus*; *L. rossiae*: *Lactobacillus rossiae*; *P. freudenreichii*: *Propionibacterium freudenreichii*; *P. magnus*: *Peptostreptococcus magnus*; *S. faecalis*: *Streptococcus faecalis*; ABT: antibiotic treated; CONV-R: conventionally raised; GF: germ-free; HFA: human-flora-associated.

Together, ingested xenobiotics not only undergo host metabolism but also encounter the gut microbiota, whereby a diverse and complex series of microbial-related biotransformations can occur, thus altering the potency, bioavailability, and toxicity of xenobiotics. The involvement of the gut microbiota can be beneficial or deleterious, which is dependent on the community, metabolic capability, and specific reaction induced by the gut microbiota.

5. Gut Microbiome and Cancer Development: From Disease Associations to Mechanistic Understanding

We reviewed how the gut microbiota can formulate or induce DNA damage at the molecular levels through mechanisms such as bacterial toxins, elevation of oxidative stress, and stimulation of pro-inflammatory conditions. At an organism or population level, many animal and epidemiological efforts have been made in correlating gut microbiota and cancer. Malignancies that occur in the GI tract have been investigated the most, including colorectal cancer and gastric cancer. Other studies pointed out the associations between dysbiosis and extra-GI neoplasms, including liver and breast carcinoma. The most current research works used animal models and epidemiological approaches to gain relevance, with some touching base on possible mechanisms. Herein, we briefly review the current understanding on how our gut microbiota can be involved in different types of carcinomas.

5.1. Colorectal Cancer

Gut microbiota is most dense in the host colon; therefore, colorectal cancer, among all carcinomas, is the first and most researched cancer due to its relationship with the gut microbiota. Animal and human/epidemiological studies have observed altered microbial composition in precancerous colorectal lesions and in colorectal cancer. In addition, dysbiosis of the gut microbiota has been characterized in colorectal cancer patients compared to healthy controls, with increase in pro-inflammatory opportunistic pathogens and decrease in SCFA-producing bacteria [114–116]. The enrichment or depletion of many gut bacterial species have been associated with colorectal cancer incidence, such as members of the *Bacteroides* spp. (e.g., *B. stercoris*, *B. vulgatus*), *Bifidobacterium* spp. (e.g., *Bifidobacterium angulatum*, *Bifidobacterium longun*), and *Ruminococus* spp. (e.g., *Ruminococus gnavus*, *Ruminococus albus*) [117,118]. Several possible mechanisms of the gut microbiota were considered to respectively and collectively induce colorectal cancer, with support of in vitro and in vivo evidence, which includes the impairment of the intestinal epithelial barrier function [119], the induction of pro-inflammatory responses [120,121], the production of toxic metabolites by pathogenic bacteria [94], and the release of genotoxins [24,27,39].

5.2. Gastric Cancer

H. pylori is one of the most studied gut microbiota species, as it is associated with multiple adverse health events, including cancer. In fact, infection with *H. pylori* in an acidic stomach is the strongest known risk factor for gastric cancer [82], concluded in multiple epidemiological studies [122–124]. We summarized how the multiple virulent factors of *H. pylori* contribute to the induction of proinflammation, thus initiating or inducing cancer. How *H. pylori* is involved in the different stages of gastric cancer development is well reviewed by Wroblewski et al. [82]. Although the bacterial density in the host stomach is far lower than in the latter parts of the GI tract, the discovery of *H. pylori* and its adverse impact attracted more research on characterizing other gastric-residing bacteria involved in gastric cancer development. For instance, *Propionibacterium acnes* and *Prevotella copri* were considered strong risk factors along with *H. pylori* in a gastric cancer case–control study conducted by Gunathilake et al. [125]. How the gut microbiota profile interacts with gastric cancer incidence was thoroughly reviewed by Yang et al. [126]. So far, except for infection with *H. pylori*, the mechanisms through which other species of gut bacteria contribute to gastric cancer have remained ambiguous.

5.3. Extra-Gastrointestinal Cancer

The gut microbiota constantly interact with the host, and their metabolic activities as well as microbial–host communications bring systemic effect. As a result, it is not surprising that the gut microbiota can be involved in carcinoma outside the GI tract, although the mechanisms of carcinogenesis can be even harder to identify. The associations between gut dysbiosis and hepatocellular and breast carcinoma have been supported by experimental alterations of the animal gut microbiota and in human epidemiological studies [127–130]. Understanding how bacteria in the gut demonstrate carcinogenic effects in distant tissues is difficult, since the host and microbial processes can barely be differentiated with systemic circulation. New approaches and dedicated investigations in the future are needed to further our knowledge of extra-GI cancer induced by our gut microbiota.

6. Missing Pieces and Future Direction

Since the publication of primary results from the Human Microbiome Project in 2012, the realization that our human genome is outnumbered by the diverse and kaleidoscopic gut microbiome soon attracted the attention of the scientific community to recognize the physiological role, pharmaceutical application, and host–microbial interactions of the gut microbiota. In the 1980s, Marshall et al. provided solid epidemiological evidence on *H. pylori* being a strong risk factor for gastric cancer, and *H. pylori* has become the gut bacterial species with the most pathological evidence of its causality to cancer [82,84,126,131,132]. Increasing research has been conducted to understand the interplay between gut microbiota activities and host carcinogenesis. Different profiles as well as multiple specific species of the gut microbiota have been associated with carcinoma in colorectal, gastric, liver, and other organs. However, it is challenging to elucidate the specific pathways of how the gut microbiota interacts with the host and subsequently promotes or inhibits cancer progression due to reasons including the complete profile of the gut microbiota being continuously characterized and updated; the metabolic activities of the host and the gut being difficult to differentiate; and many effects of the gut microbiota being indirect and buffered by systemic circulation.

To date, mechanisms have been revealed of how the gut microbiota contribute to cancer progression, which include the release of genotoxins that can attack the DNA, elevation of oxidative stress, stimulation of proinflammation and inflammation, and alteration of xenobiotic metabolism. Some species were discovered to be responsible for these mechanisms—for instance, the *pks*$^{+}$ *Enterobacteriaceae* spp., *H. pylori*, and *B. fragilis*. However, we are far from recognizing the complete arsenal of how dysbiosis of the gut microbiota induces cancer. For example, epidemiological studies have shown dysbiosis of the gut microbiota associated with breast cancer, and biomarkers such as some antibacterial response genes showed significantly dysregulated gut microbiota [129,130,133]. However, how the dynamic in the gut can systemically affect and eventually lead to tumor formation in the breast remains ambiguous. As more novel biotechnological tools are introduced and applied, we may be only some steps away from deciphering the complicated gut microbiota activities in carcinogenesis. For example, the advancement of high-resolution mass spectrometry makes the global profiling of metabolic activities feasible (through methods such as non-targeted metabolomics); the integration of multi-omics data may also help holistically inspect the effects of gut microbiota at different molecular levels.

It is also noted that although bacteria majorly comprise our gut microbiota, other microorganisms, such as fungus, can play essential roles in interacting with the host [134–136], and little is known on their potential contribution to cancer development.

7. Conclusions

The gut microbiota, under symbiosis, is essential and beneficial to our health; in contrast, under a dysbiosis ecology, the gut microbiota can be insalubrious and contribute to adverse health outcomes, including cancer. The associations between dysbiosis and infection of specific bacteria have been well demonstrated in epidemiological studies, and some of the associations are even supported with proposed or evidenced mechanisms, such as how *H. pylori* induces genotoxic inflammation, how colibactin from *pks*$^+$ *Enterobacteriaceae* spp. alkylates DNA, etc. Our review summarized the currently characterized direct and indirect pathways of how our gut microbiota are involved in host cancer progression. However, the mystery of how microbes in the gut can participate in host cancer events both locally and systemically is only partially solved, as there are unidentified mechanisms that require future research. The field of gut microbiota research is continuously nourishing, and more understanding on the role of our gut bugs in carcinogenesis can have public health, pharmaceutical, toxicological, and clinical implications for preventing or curing cancer.

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