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Microbial Genotoxins as Emerging Drivers of Cancer: Mechanisms, Detection, and Therapeutic Opportunities

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ABSTRACT

Through DNA damage, disruption of repair pathways, and chronic inflammation, microbial genotoxins found in bacteria, viruses, fungi, and parasites are important causes of cancer. Their taxonomic diversity, molecular mechanisms, and functions in forming mutational signatures linked to cancer are summarized in this review. Fungal aflatoxins, viral proteins like HPV E6/E7, and bacterial genotoxins like colibactin and cytolethal distending toxin cause unique DNA lesions, such as double-strand breaks and adducts, that lead to oncogenic changes. These genotoxins create pro-carcinogenic microenvironments by enhancing oxidative stress, disrupting DNA repair, and dysregulating cell cycle checkpoints. Genotoxin signatures can be precisely identified thanks to advanced detection techniques like proteomics, whole-genome sequencing, and genotoxicity assays. Promising interventions include DNA repair enhancement therapies and preventive measures like vaccination, microbiome modification, and toxin inhibitors. The review promotes public health measures to lower genotoxin exposure and emphasizes translational implications for precision oncology, such as early detection and risk stratification. To mitigate genotoxin-driven cancers, interdisciplinary research is necessary to bridge knowledge gaps, such as establishing causation in human cohorts and developing long-term infection models.

INTRODUCTION

Our knowledge of microbial roles in oncogenesis was revolutionized in 1984 when *Helicobacter pylori* was discovered to be a risk factor for gastric cancer. Intricate relationships between microbes, host genetics, and environmental factors were revealed by this discovery, which sparked studies connecting the microbiome to cancers of the liver, colon, cervix, and other locations (1). It is now known that microbial genotoxins, which harm host DNA either directly or indirectly, are important factors in the development and spread of cancer (2). These substances create pro-carcinogenic microenvironments by causing DNA lesions, disrupting repair pathways, and encouraging persistent inflammation. For example, viral proteins like HPV E6/E7 cause cervical cancer through specific mutational signatures, whereas bacterial genotoxins like colibactin contribute to colorectal cancer (3). Despite their importance, little is known about microbial genotoxins in comparison to carcinogenesis caused by chemicals or radiation. According to this review, genotoxins are important but underappreciated causes of cancer that have the power to change paradigms in diagnosis and treatment. It synthesizes genotoxin diversity, molecular mechanisms, detection techniques, and therapeutic approaches and is intended for use by microbiologists, oncologists, and genomicists. Through the integration of genomics, oncology, and microbiology, we emphasize new approaches to cancer prevention and treatment, highlight translational opportunities, and promote interdisciplinary research to address this developing field (4).

Taxonomy and Diversity of Microbial Genotoxins

Through a variety of methods, microbial genotoxins, which

include bacteria, viruses, fungi, and parasites, damage the genomic integrity of their hosts. Chronic infections are made possible by their evolutionary adaptations, which put hosts at risk for cancer (5). Determining their oncogenic roles and creating focused interventions requires an understanding of their taxonomy. The main genotoxins are categorized in this section along with information on their origins, mechanisms, and links to cancer, all of which are backed by genomic and biochemical research (6).

Bacterial Genotoxins: Strong DNA-damaging agents are bacterial genotoxins, such as colibactin (*Escherichia coli*), cytolethal distending toxin (CDT, produced by *Campylobacter jejuni, Salmonella enterica*), typhoid toxin (*Salmonella Typhi*), and mycolactone (*Mycobacterium ulcerans*) (7). In colorectal cancer models, colibactin, a polyketide-nonribosomal peptide encoded by the pks island, alkylates adenine residues, causing interstrand crosslinks (ICLs) and double-strand breaks (DSBs). Its oncogenic potential is highlighted by the fact that it is common in *E. coli* strains linked to inflammatory bowel disease, a risk factor for cancer (8). A tripartite toxin with DNase activity, CDT contributes to colorectal and gastric cancers by causing chromatin fragmentation and G2/M arrest. Typhoid toxin, which is associated with gallbladder cancer, targets DNA through its nuclease component and is composed of the CdtB, PltA, and PltB subunits. In cancers linked to Buruli ulcers, mycolactone suppresses Sec61, upsetting cellular homeostasis and indirectly encouraging DNA damage through stress reactions (9) (10). By taking advantage of host repair flaws, these toxins increase the rate of mutations. It is more difficult to detect and control them because their production is controlled by environmental cues and quorum sensing. According to recent research, they play a part in gut microbiome dysbiosis, which is a major risk factor for cancer. One promising approach is the development of inhibitors that target the pathways involved in toxin biosynthesis (11).

Viral Genotoxin-Associated Proteins: Through indirect mechanisms, viral proteins like HBx (hepatitis B virus, HBV), LMP1 (Epstein-Barr virus, EBV), and E6/E7 (human papillomavirus, HPV) undermine genomic integrity (12). While HPV E7 inactivates retinoblastoma protein (Rb), upsetting cell cycle checkpoints and causing cervical and oropharyngeal cancers, HPV E6 uses ubiquitin-mediated proteolysis to break down p53, compromising DNA damage responses. In hepatocellular carcinoma, HBx promotes chromosomal abnormalities and epigenetic instability by inhibiting histone deacetylases (13). In nasopharyngeal carcinoma and lymphomas, LMP1 increases inflammation and DNA damage by activating NF-κB signaling. These proteins frequently increase genotoxic stress by working in concert with bacterial co-infections(14). Through insertional mutagenesis, their incorporation into host genomes activates oncogenes such as MYC, thereby promoting oncogenesis. According to recent research, viral proteins may help to promote chronic infections by modifying host immune responses (15). Developing targeted treatments, like immune checkpoint inhibitors, requires an understanding of how they interact with cellular signaling pathways. Novel viral protein interactions have been discovered thanks to advances in proteomics, which has created opportunities for the development of therapeutics (16).

Fungal and Parasitic Toxins: In certain geographical areas, genotoxins from fungi and parasites are linked to cancer. Aspergillus flavus and Aspergillus parasiticus produce aflatoxin B1, which causes hepatocellular carcinoma in sub-Saharan Africa and Southeast Asia by forming mutagenic DNA adducts (such as 8,9-dihydro-8-(N7-guanyl)-9-hydroxy-aflatoxin B1) (17). Reactive epoxides are produced during its metabolism by cytochrome P450, which intensifies DNA damage. DNA breaks and oxidative stress are caused by parasitic genotoxins from Schistosoma haematobium (*schistosomiasis*) and Trypanosoma cruzi (chagas disease) (18). In endemic areas, schistosome eggs release genotoxic factors that promote bladder cancer and urothelial dysplasia. These toxins increase the risk of cancer by interacting with environmental carcinogens like hepatitis viruses. Portable assays are necessary because detection in resource-constrained environments is difficult due to inadequate diagnostic infrastructure (18). According to recent research, parasitic toxins can enhance genotoxic effects by modifying host immune responses. Preventive measures that lower exposure, like better food storage and antiparasitic medications, are essential (19).

Molecular Pathways of Genotoxin-Induced Carcinogenesis

By causing DNA damage, disrupting repair pathways, and dysregulating cellular homeostasis, microbial genotoxins promote carcinogenesis. Together, these pathways produce mutagenic environments that encourage the development and spread of tumors (20). The molecular mechanisms behind genotoxin-induced oncogenesis are examined in this section, with a focus on how they affect cellular signaling and genomic stability. These pathways have been clarified by developments in proteomics and genomics, which have identified potential treatment targets (21).

Table 1

Summary of Major Microbial Genotoxins and Their Associated Cancers

Genotoxin	Source	Cancer Type	Mechanism
Colibactin	E. coli	Colorectal cancer	DSBs, ICLs
Aflatoxin B1	Aspergillus flavus	Hepatocellular carcinoma	DNA adducts
E6/E7	HPV	Cervical cancer	p53/Rb inactivation
CDT	Campylobacter jejuni	Colorectal cancer	Chromatin fragmentation
Typhoid toxin	Salmonella Typhi	Gallbladder cancer	Nuclease activity

DNA Damage Mechanisms: Genotoxins cause a variety of DNA damage, such as base modifications (e.g., 8-oxoG from reactive oxygen species, ROS), interstrand crosslinks (ICLs, e.g., aflatoxins), and double-strand breaks (DSBs, e.g., colibactin) (23). The cyclopropane warhead of Colibactin alkylates DNA, which stops replication forks and results in colorectal cancer mutations. Guanine adducts created by aflatoxins result in G>T transversions,

especially in TP53, a major cause of liver cancer (10). Chromatin is broken up by CDT's DNase activity, which causes chromosomal instability and replication stress. If left untreated, these lesions increase the rate of mutations by interfering with transcription and replication (23). The concentration of the toxin, the length of exposure, and the host's ability to repair itself all affect how much damage is done. These effects are exacerbated, particularly in inflammatory tissues, by chronic exposure, which is typical in persistent infections. Heterogeneity in DNA damage responses is revealed by single-cell genomics, underscoring the necessity of tailored interventions (14). Developing treatments to lessen the harm caused by genotoxin requires an understanding of these mechanisms. Treatment results may be improved by focusing on DNA damage checkpoints (24).

Interference with DNA Repair: Genotoxins exacerbate genomic instability by interfering with important DNA repair pathways. By creating replication stress, colibactin prevents homologous recombination (HR), whereas CDT interferes with nucleotide excision repair (NER) by directly binding to DNA (25). By suppressing enzymes such as APE1, HPV E6/E7 raises the rate of mutations and inhibits base excision repair (BER) (8). Hepatocellular carcinoma is caused by TP53 mutations as a result of aflatoxins' inhibition of mismatch repair (MMR) (10). Tumorigenesis is fueled by these disruptions, which result in a buildup of mutations in tumor suppressors and oncogenes. The susceptibility to damage caused by genotoxins is modulated by host genetic polymorphisms in repair genes like BRCA1. Novel repair pathway interactions have been found through CRISPR screening, providing possible targets for treatment (26). Although specificity and delivery issues still exist, the development of medications to restore repair function is encouraging. In cancers caused by genotoxins, the combination of repair activators and checkpoint inhibitors may increase effectiveness (27).

Cell Cycle and Apoptosis Modulation: Genotoxins promote the survival of damaged cells by inhibiting apoptosis and dysregulating cell cycle checkpoints. While HPV E6 inactivates p53, preventing apoptosis in cervical cancer, CDT uses ATM/ATR signaling to induce G2/M arrest (8). In liver cancer, HBx promotes the growth of damaged hepatocytes by upregulating anti-apoptotic Bcl-2. By upsetting cellular homeostasis, mycolactone suppresses apoptosis indirectly by triggering stress reactions. These processes facilitate the accumulation of mutations, which propel the growth of tumors (28). According to recent research, genotoxins alter checkpoint kinases, providing checkpoint inhibitor targets. Although clinical trials are required to validate this approach, combining these inhibitors with DNA repair therapies may improve treatment efficacy. For cancers linked to genotoxins, research is also being done on apoptosis pathway targeting, such as Bcl-2 inhibitors (29).

Oxidative and Nitrosative Stress in Genotoxin Action

Reactive oxygen species, or ROS, and reactive nitrogen species, or RNS, are produced by persistent microbial infections, which intensify DNA damage and encourage the development of cancer. 8-oxoG and etheno adducts are highly mutagenic lesions associated with gastric cancer that are produced by *H. pylori*-induced gastritis. ROS from Schistosoma haematobium infections cause oxidative DNA lesions, which in turn promote urothelial carcinoma. Peroxynitrite and other RNS compounds create nitro-adducts, which exacerbate genomic instability in inflammatory tissues (30). A pro-carcinogenic microenvironment is produced by these oxidative products, especially in chronic infection settings such as colitis and hepatitis. Although clinical trials have produced conflicting results because of non-specific effects, reducing oxidative stress with antioxidants or anti-inflammatory drugs may lessen the effects of genotoxin (31). Risk assessment has been aided by the discovery of oxidative stress biomarkers through metabolomic research. Genotoxin-induced oncogenesis may be further inhibited by focusing on inflammatory pathways like NF-κB (32). To break this cycle, new anti-inflammatory medications are being investigated (32).

Mutational Signatures and Genomic Landscapes

Different mutational patterns produced by microbial genotoxins provide information about their carcinogenic contributions. Based on genomic sequencing data, this section looks at how they affect genomic landscapes, including point mutations, chromosomal abnormalities, and viral integration (33).

COSMIC Signature Correlations: Typical COSMIC mutational signatures are produced by genotoxins. Aflatoxin is linked to SBS24 (G>T transversions), colibactin to SBS18 (C>A mutations), and HPV to APOBEC-related signatures (SBS2, SBS13) (10). These signatures help epidemiological studies by allowing the retrospective identification of microbial contributions to cancer. In colorectal cancers from patients with pks+ *E. coli* colonization, SBS18 is enriched (3). By improving signature detection, computational tools such as SigProfiler increase the accuracy of diagnosis. Because these signatures differ depending on the type of tissue, organ-specific analyses are required (34).

Chromosomal Aberrations and Structural Variations: Genotoxins result in translocations, deletions, and aneuploidy. Aflatoxin causes large-scale TP53 deletions, while CDT causes chromosomal instability through centrosome amplification. By inducing cellular stress responses, mycolactone encourages abnormalities. Tumorigenesis is accelerated by these structural alterations that interfere with oncogenes and tumor suppressors. Whole-genome sequencing (WGS) and high-resolution cytogenetics are essential for mapping these changes and directing targeted treatments (35), (36).

Integration with Host Genome: HBV and HPV E6/E7 are examples of viral genotoxins that integrate into the host genome, resulting in oncogene activation (e.g., MYC, TERT) and insertional mutagenesis. Cervical and oropharyngeal cancers frequently integrate HPV, whereas hepatocellular carcinomas disrupt tumor suppressors due to HBV (37). Because these occurrences intensify genomic instability, next-generation sequencing is required for targeted detection strategies (38).

Host–Microbe Interactions Modulating Genotoxin Impact

Genotoxin effects are modulated by host factors, such as immune status, microbiome diversity, and genetic polymorphisms. Genotoxin potency is increased by chronic inflammation caused by H. pylori or HBV, which increases ROS/RNS. In colorectal cancer models, synergistic interactions, like co-exposure to colibactin and CDT, increase DNA damage. Oncogenesis is exacerbated by EBV's LMP1, which encourages immune evasion (39). Cancer risk is increased by microbiome dysbiosis, which is defined by an overabundance of bacteria that produce genotoxin. Susceptibility is influenced by host genetics, specifically DNA repair gene variants, underscoring the necessity of individualized risk assessments (40). According to recent research, the composition of the gut microbiota influences the production of toxins, providing targets for interventions based on the microbiome. To restore microbiome balance and lessen the effects of genotoxin, probiotics and dietary interventions are being investigated (41).

Co-Factors and Environmental Modulators

Genotoxin potency is increased by environmental factors such as co-infections (e.g., HIV-HPV), smoking, alcohol, and diet (e.g., aflatoxin-contaminated grains). Chronic infections caused by antibiotic-resistant pks+ *E. coli* increase the risk of cancer (42). Genotoxin exposure in the stomach mucosa is prolonged by H. pylori antibiotic resistance. The significance of integrated risk reduction strategies, such as dietary interventions, enhanced food safety, and antibiotic stewardship, is highlighted by these modulators. In high-risk areas, the incidence of liver cancer has decreased as a result of public health initiatives aimed at reducing aflatoxin exposure (25). Genotoxin-driven cancers are also lessened by international initiatives to decrease parasitic infections and enhance sanitation (43).

Detection and Analytical Tools

To detect genotoxin exposure and its carcinogenic effects, sophisticated detection techniques are essential. The role of proteomic, genomic, and genotoxicity assays in precision diagnostics is reviewed in this section (44).

Table 2

Current and Emerging Therapeutic Approaches Targeting Genotoxin Effects

Strategy	Example	Status
Microbiome modulation	Probiotics, FMT	Clinical trials
Vaccination	HPV, HBV vaccines	Approved
Toxin inhibitors	Colibactin synthesis block	Preclinical
DNA repair enhancement	BER/HR activators	Experimental

Genotoxicity Assays: The comet assay measures single- and double-strand DNA breaks, the Ames test finds mutagenicity in microbial extracts, and γ-H2AX foci detect DSBs (46). By confirming genotoxin activity both in vitro and in vivo, these tests aid in risk assessment. High-throughput variants improve early detection by increasing scalability for population studies. The sensitivity of these tests has increased due to recent developments in automated imaging (47).

Molecular Genomics: Genotoxin-induced mutational signatures are revealed by whole-genome sequencing (WGS) and exome sequencing. Accurate toxin attribution is made possible by tools such as SigProfiler and MutSigCV, which detect COSMIC patterns (48). In tissues exposed to genotoxins, single-cell sequencing eliminates cellular heterogeneity and provides information on the development of tumors. These methods are essential for creating diagnostic panels for cancers caused by genotoxins (25).

Proteomic and Metabolomic Approaches: Toxin-specific adducts (like colibactin-DNA) and metabolites, such as ROS-induced lipid peroxidation products, are detected by mass spectrometry. These methods make it easier to find biomarkers for exposure and cancer risk assessment. Metabolomics helps develop diagnostics by identifying microbial metabolic pathways associated with the production of genotoxins (29). The accuracy of exposure detection is improved by combining proteomics and genomics (49).

Therapeutic and Preventive Strategies

There is a great deal of promise for cancer mitigation through preventive and therapeutic approaches that target genotoxins. The translational potential of microbiome modulation, vaccination, toxin inhibition, and DNA repair enhancement is highlighted in this section (21).

Microbiome Modulation: Genotoxin-producing bacteria such as pks+ *E. coli* are decreased by probiotics, prebiotics, and fecal microbiota transplantation (FMT). CRISPR-based editing provides precision microbiome engineering by targeting genes involved in toxin biosynthesis, such as colibactin's pks island. The effectiveness of FMT in preventing colorectal cancer is being assessed in clinical trials, with encouraging preliminary findings. By restoring the balance of the microbiome, these strategies hope to lower the risk of cancer (31).

Vaccination Against Genotoxin-Producing Pathogens: Vaccines against H. pylori, HPV, and HBV reduce exposure to genotoxins and can be used as models for targeting bacteria that produce CDT, including *C. jejuni*. HPV vaccinations effectively prevent E6/E7-caused cervical cancer. Novel vaccines against *C. jejuni* that target the production of CDT are being developed in preclinical research (50). Expanding immunization programs could significantly reduce the number of cancers linked to genotoxins (25).

Blocking Genotoxin Production or Activity: Preclinical promise is demonstrated by CRISPR-based pks island disruption and small molecule inhibitors of colibactin synthase. Research is being done on neutralizing antibodies against CDT, which could provide targeted intervention. For clinical safety and effectiveness, these methods need to be optimized. Toxin inhibitors and microbiome modification together may improve preventative measures (51).

Targeted DNA Repair Enhancement: Genotoxin-induced

damage is lessened by pharmacologically activating BER or HR. Although there are still issues with specificity, APE1 agonists increase BER in hepatocytes exposed to aflatoxin. Early research indicates that HR activators may be useful in the treatment of HPV-related cancers. These treatments may enhance current ones and improve the prognosis of cancers caused by genotoxin 82, 83.

Translational and Clinical Implications

Early identification of at-risk individuals is made possible by WGS screening for genotoxin signatures. Precision oncology techniques, including targeted therapies for HPV-driven cancers, are informed by risk stratification based on host genetics and microbial exposure. Public health initiatives are improved when genotoxin data is incorporated into prevention recommendations, such as dietary changes and antibiotic stewardship (38). The impact of focused interventions is demonstrated by the decreased incidence of liver cancer in high-risk areas due to aflatoxin control in food supplies. These methods hold the potential to revolutionize the diagnosis and treatment of cancer, especially in high-risk groups (25).

Knowledge Gaps and Future Perspectives

Confounding variables like diet and co-infections make it difficult to distinguish between causation and association in human cohorts. Chronic genotoxin exposure requires long-term infection models, such as humanized mice or 3D organoids (52). Predictive modeling of cancer risk will be enhanced by the integration of multiple omics, including proteomics, metabolomics, and genomics. A new area of oncology is the development of genotoxin-targeted treatments, such as small molecule inhibitors or toxin-neutralizing antibodies. An emerging field that needs more research is the role of the fungal and virome microbiomes in the production of genotoxin (31).

CONCLUSION

Microbial genotoxins, which cause inflammation, repair flaws, and DNA damage, are important causes of cancer. Genotoxin signatures can be precisely identified thanks to advanced detection techniques like WGS, proteomics, and metabolomics. DNA repair treatments combined with preventive measures like vaccinations, microbiome modification, and toxin inhibitors have a great deal of promise to lower the incidence of cancers linked to genotoxin. These findings must be translated into clinical practice through interdisciplinary research that spans microbiology, oncology, and genomics. This will open the door to new diagnostic and treatment paradigms that will lessen the worldwide burden of cancers caused by genotoxin.

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