DOI:10.31557/APJEC.2811.20260628

REVIEW

The Gut Microbiome in Environmentally-Induced Oncogenesis: From Sentimental Biomarkers to Precision Therapeutics- A Comprehensive Review

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Abstract

The gut microbiome serves a primary interface between host physiology and harmful environmental xenobiotics like microplastics, heavy metal and pesticides. The persistent exposure to these pollutants is the primary cause of profound dysbiosis, characterized by a sharp reduction in commensal bacteria, such as lactobacillus species along with the proliferation of proinflammatory cytokines. This typical microbial imbalance translocates endotoxins to trigger the activation of TLR4 and NLRP3 inflammasome pathways by compromising the integrity of barrier. This results in the initiation of chronic inflammation and along with chronic stress inside the gut, in order to activate the sequence known as inflammation induced carcinoma. Advancements in metabolomics and metagenomics have highlighted several metabolic and microbial signatures, like alteration of tryptophan and short chain fatty acids, that serve as a signature for the exposure of these pollutants. To assess the long-term risk of carcinogenesis, the integration of machine learning algorithms with these datasets will surely enable the researchers to develop exposure scores. Furthermore, a great deal of advancements has been observed in the development of therapeutic strategies, and they have evolved from the traditional restoration of microbiota by giving prebiotics, FMT and probiotics to other high precision interventions like synthetic biology, phage therapy and CRISP-Cas9, offering a more efficient surgical and programmable engineering of gut associated commensal microbiota to neutralize oncogenes at the site of dysplasia. Despite the potential of techniques like non-invasive biomarkers identification and precision-based therapeutics, there is a dire need to overcome methodological standardization along with successful clinical translation of complex and integrated muti-omics data across the globe. This review highlights how the concepts of personalized health interventions can be practiced if the environment and health related gaps are fulfilled, eventually transforming the toxic nature of microbes into a programmable shield that actively regulates the immune components and protects environmentally induced oncogenes.

Keywords: Environmental Xenobiotics, Microbial Dysbiosis. Oncogenesis, Metabolomics, Metagnemic Signatures

Asian Pac Environ Cancer, 23-34

Submission Date: 03/18/2026 Acceptance Date: 05/01/2026

1. Introduction

Gut-Microbiome Interaction

Mankind has always been curious about the traits and characteristics that make us stand out from all other living beings. A great deal of research has uncovered a lot of fascinating abilities of the environmental factors that directly or indirectly impact human health, but among those factors, microbes caught the attention. Till today microbiota are not only concerned with the development of dairy products through fermentation, but in fact these microbiota (including bacteria, phages, viruses and archaea) are also involved in maintaining the overall gut

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health [1, 2]. A great deal of research has already been done to understand the complex physiology of microbiotas because they directly affect gut health. These microbes are thought to establish their interaction with the human beings, starting from the birth and evolves with the passage of time [3].

One notable thing is the increasing concentration of these microbes as we descend from stomach to large intestine. The actual quantity and diversified nature of gut microbiota surprises a lot as there cumulative unique genes (almost 3.3 millions) are estimated to greatly outweighs human genome by a factor of 150 [4, 5]. These microbes are not only responsible for degrading the complex substances inside the gut but also maintain an integral role in the development and maintenance of immune system. Apart from their benefits, several studies have also highlighted the adverse impacts of theses microbes on the gut health, if there concentration is altered [6, 7]. Recent studies have unveiled the complex pathways through which these microbes are causing a lot of diseases including, inflammatory bowel diseases, inflammation, weight gain, blood pressure, depression, perturbed immune and endocrine system, obesity, allergic responses, Alzheimer's & Parkinson's diseases, hypertension, atherosclerosis and various gut associated cancers [8, 9].

Deregulation of energy consumption and microbiota-gut axis are the two widely associated factors that contributes towards the progression of the said diseases [4, 10]. The key culprits that are involved in all these diseases are the metabolites (primary and secondary) secreted by these gut residing microbes including bile acid, tryptophan, short chain fatty acids (SCAFs). Much clinical evidence has been generated that supports the above statement of how these metabolites affects the composition of microbes in gut health. By far, the most studied alterations are the one that involves modulation of immune system, either by the hyperactivity or underactivity of these metabolites [11]. Lately, the interaction of human gut- microbiomes has extensively been studied in the context of epithelial cells as it is also involved in protecting the skin against invading microbes along with the fortifications of luminal components that are also acting as a barrier. But, the extensive use of antibiotics is thought to disrupt the microbial consortium ultimately leading towards the start of inflammation and associated anomalies [12, 13]. Researchers have also discovered that the absence of gut-bacteria makes gram-free mice susceptible towards microbial invasion by impairing the intestinal barrier.

Pollutants as Cancer Drivers

Environmental pollution can arise either by natural or artificial sources, while the most studied one in context of pollution is artificial pollution mainly concerned with industrialization. Combustion of fossil fuels is by far the greatest contributor towards the air pollution as it is involved in conversion of Sulphur and phosphorous both of which are strong carcinogen [14, 15]. On contrast, the pollutants associated with solid substances are categorized as carbon monoxide, particulate matter, heavy metals, volatile organic compounds, oxides of nitrogen and Sulphur along with polycyclic aromatic hydrocarbons (PAHs). Aberrant genetic alterations, oxidative stress and methylation of DNA (gene-off) are some of the few health risks imposed by these pollutants [16-18]. With regards to air pollution, the burning of fossil fuels, including power generation, soil, air and water, burning of forest (savanna fires), and combustion of agricultural waste in the urban areas, are by far the most studied source of air pollution [19].

The main reason behind the emission of these pollutants is the incomplete combustion of the solid fuel mass and according to a survey, the concentration of these pollutants is almost 2-5 times higher in indoors than outdoors, where the combustion of these solid fuel is the main source of energy [20]. While majority of the pollutants associated with these solid fuels have adverse effects on humans but still benzene, gasoline gas, asbestos and food contaminated with various inorganic compounds mainly arsenic and zinc, are the most persistent ones and they are directly linked with the alteration of cells genetic make-up. In fact, pollution associate with the combustion of these solid fuels is categorized as the 11th major risk factor contributing to a lot of anomalies including cardiovascular diseases, thyroid and lung cancer, obstructive pulmonary disease, lower respiratory tract infections and cardiovascular diseases [21].

In fact, the carcinogenic potential of pollutants is solely based on regional topography, climatic conditions and the source that is responsible for spreading pollution. According to the data presented by a report of WHO, back in 2021, air pollution is responsible for the death of almost 7 million people regardless of age and gender. Strict measures should be taken to reduce the burden of the diseases, that may arises due to the spread of these pollutants, mainly respiratory disorders and various types of lungs and breast cancer [16, 22]. Another study concludes in the United States of America put light on the fact that, higher the pollution – lower will be the rate of survival and most of the time, the affected ones are children (that were already diagnosed with cancers). Moreover, it was considered a necessity to conduct carcinogenic and genotoxic studies along with epigenetic modifications. Furthermore, several pre-clinical studies have also highlighted the effects of harmful pollutants on the initiation, progression and transformation of lungs, breast and thyroid cancer [16, 17, 23].

These studies directly target the use of pharmaceutical and exogenous estrogen (act as breast carcinogen) in the progression of early-stage cancer. Although the exact mechanism through which breast cancer progresses is still under debate but one that is confirmed is, the mimicry of breast cancer in human and mice models alike [24, 25]. Recent studies have also revealed the role of pollutants either as, initiator or disruptors in the downstream signaling that ultimately disrupts the normal physiological processes as some of these are involved in maintaining the overall growth patterns by directly affecting cell cycle while some of these works by preventing apoptosis (programmed cell death) by interacting with the gene p53 and its subtypes [26]. Another study conducted by Charles

Baudouin and team highlighted various environmental factors that are responsible for skin cancer initiation and progression alike. Benzo-pyrene, heavy metals, benzene, ozone and polycyclic aromatic hydrocarbons were some of the pollutants reported by the team that reacts with skin cells and initiate tumor formation but still, ultraviolet radiations has been categorized as the primary source for basal cell carcinoma in males as per the reports of several pre-clinical studies [27].

Gut Microbiota: Key Mediator in Toxicity

The relation of xenobiotics with gut microbiota has been explored for decades, in order to understand how pollutants and other compounds are metabolized and what their by-products are and if those by-products are beneficial or harmful for the body. According to a study conducted by scheline in 1973, the potential of gut microbiota to metabolize xenobiotic was at least 7-10 times greater than that of liver itself. More than 40 different kind of drug substrates have been identified to take part in in the chemical transformation of various drugs by promoting hydrolysis, oxidation and reduction, removal of succinate, thiazole ring transformation, protein degradation, acetylation, methylation, de-glycosylation, de-conjugation and most importantly, the cleavage of N-oxide bounds [28, 29]. Furthermore, studies on bioremediation profile were also conducted by Haiser and Turnbaugh to explore the metabolization of these harmful pollutants and they reported a total of 529 microbes that are affecting some 1369 compounds [30]. Although the gut microbiota is far less in relative concentration inside the body, than in the soil environments, but there role as a degrader of chemicals inside the GI tract is significant. But still the rate, at which these bacteria convert these harmful pollutants depends entirely on the amount of chemicals reaching the distal end of the GI tract, where the population of bacteria is maximum [31].

Environmental chemicals are poorly absorbed by the small intestine and they are sometimes transported by the blood across membrane but most of the time they are excreted through bile. As these compounds are non-polar in nature, so they are to be transported to liver to be detoxified into either sulfate, glucuronic acid or sometimes glutathione conjugates [32]. Still, there are some compounds that are not affected by stomach and small intestine, but once they fall into large intestine, they are hydrolyzed by commensal bacteria sticking to the walls. This conversion causes the pollutants to be degraded into low molecular weight, non-polar compounds that are to be re-absorbed by the body through the process of enterohepatic circulation, where these small compounds return back to liver where they are re-used in some other reaction wherever needed [33]. This degradation of pollutants is in fact carried out some major families of enzymes including, nitroreductases, azoreductases, B-lysase and sulfatase present in commensal gut-residing bacteria [34, 35, 26]. Enzyme azoreductases are categorized into flavin-dependent and flavin-free NADPH and these are responsible for the cleavage of azo (N=N) bonds while nitroreductases, classified into type-1 and type-2 (based on their sensitivity towards oxygen), are involved in the conversion of nitro (- NO2) groups. While on the other hand, sulfatases are linked with the conversion of sulfate esters present in some xenobiotic [32]. The main goal of this review is to analyze the correlation between gut-microbiome, environmental pollutants, exploration of inflammation and DNA damage, that ultimately drives oncogenesis. This article will also explore the diagnostic as well as therapeutic role of gut-microbiome. Ultimately, this will give new insights into the personalized medicine approach for the treatment of various types of pollutants induced cancer and their progression.

2. Environmental Driven Dysbiosis and Cancer

Plastic Pollutants and the Gut Microbiome

Since the invention of plastic, its unwavering production and low conversion rate has been posing a serious threat to society. Although biodegradable plastics have been introduced lately but still the incomplete degradation of these plastics convert it into microplastics that are in fact, for more dangerous than their precursor as there traces are found in normal human cells [36]. These microplastics are typically less than 5 mm in diameter and they have this capacity to be transported to long-range communities as they are persistent enough to remain accumulated inside human tissues. Surprisingly, further degradation of these microplastics produces Nano plastics (NP), that shows distinct physiochemical behavior due to their large surface area and low relative size [37]. Lately, traces of these micro and Nano-plastics have been found in various organs such as, blood, placenta and lungs, raising a serious concern regarding the adverse effects of these plastics [38]. In addition to this, their widespread exposure has been linked with increased risk of inflammatory bowel disease, diabetes mellitus, neurodegenerative disorders and infertility (rare cases). As they are ingested through the body, they are absorbed by the gut-residing microbiota, ultimately disrupting their ability to hydrolyze various food components [39, 40].

Human microbiome is a complex microbial community that is already present inside various parts of the body like skin, GI tract, mouth and reproductive system where they support digestion and various other functions. As this microbiome is directly involved in maintaining gut health and regulation of diseases, it draws attention towards understanding its complex working mechanism through which they maintain the overall health and homeostatic regulation. Some of the key functions of this microbiome is to regulate immune response (to fight against diseases) along with developmental physiology and integrity of intestine (small and large intestine alike). Another fascinating role of gut microbiota, is the fermentation of specific compounds that secrete various primary and secondary metabolites, mainly short-chain fatty acids and hydrocarbon receptors (involved in developmental processes). As discussed previously, these microbiota supports overall gut health suggesting conflicting theories in this regard and their ingestion is also linked with destruction of intestinal walls. These

evidence are supported by the data given by Schwabl and colleagues [41], when they observed the presence of traces of microplastics in human feces, suggesting a lack in the analysis and presentation of these MPs towards the disruption of microbial diversity along with their composition, which ultimately affects the intestinal environment in a negative manner.

Mechanism of Carcinogenesis

The transition of healthy GI tract to a state of dysbiosis is by far the most dominant factor that drives pollution induced carcinogenesis inside the body. Heavy metals, particulate matter, pesticides and microplastics are the key environmental pollutants that play a significant role in altering the metabolic activity and composition of healthy gut microbiota. This perturbation directly affects the beneficial bacteria that produces short chain fatty acids (SCFA) accompanied by the excessive growth of pro-inflammatory pathogenic species. As a result of this imbalance, the ability of bacteria to produce the SCFA is diminished by removing the key regulator of immune response and reduce production of butyrate, the main energy source for colonocytes [42]. In addition to this, pollutants are also studied to induce disruption in intestinal barrier by promoting the condition, "leaky gut" by downregulating the occludin and claudin (tight junction proteins) [43, 44]. This breach allows the translocation of bacterial endotoxins, notably lipopolysaccharides (LPS), from the gut lumen to body's systemic circulation thus promoting a low-grade inflammation, linked with the initiation of carcinogenesis [45]. This prolonged systemic inflammation initiates the formation of tumor microenvironment that is essential for cell survival and replication along with the sustained release of ROS and RNS, due to continuous activation of neutrophils and macrophages to the damage's sites. This causes the suppression of body's natural surveillance system, comprises of cytotoxic T lymphocytes and natural killers, against these emerging cell malignancies. Meanwhile, the combination of established chronic inflammation, gut barrier dysfunction and microbial imbalance establishes a feed-forward loop that causes the initiation and acceleration of carcinogenesis, by-passing immune checkpoints [46].

A lot of other studies have also highlighted the role of oxidative stress in promoting inflammation, after its initiation by the LPS inside due to the production of reactive oxygen species (ROS) by particulate matter and heavy metals [3]. This further amplifies the gut dysbiosis by negatively affecting the antioxidant producing bacteria (Lactobacillus and Bifidobacterium) inside the GI tract along with sharp increase in the production of Enterobacteria, a ROS generating pathogenic strain. This results in the initiation of a vicious chronic cycle in which DNA, proteins and lipid molecules are attacked by the reactive oxygen species (ROS) species while the inflammation further activates the pro-inflammatory pathways that upregulate cytokine production. A lot of researchers have stated that the exposure of pollutants to already occured gut dysbiosis is further worsened by the activation of Toll-Like Receptor-4 (TLR4)/NF-kB pathways of inflammation by persistently promoting the transcription of Interleukins (IL-1β, IL-6) and Tumor Necrosis Factor-alpha (TNF-α) like cytokines [47, 48]. This activation of cytokines is further worsened by the up regulation of anti-apoptotic genes like Bcl-xL and Bcl-2, enabling the damaged cells to proliferate, evade and survive ultimately converting them to proto-oncogenes. In addition to this, caspases dependent pyroptosis (pro-inflammatory form of cell death accompanied by recruitment of immune cells to the damaged site) is also induced by the activation of NOD-like Receptor Pyrin domain-containing 3 (NLRP3) inflammasomes that further upregulate the carcinogenic milieu [49]. This condition of continuous inflammation, caused by the altered microbiota and gut dysbiosis, enables the tissues to be transformed into tumors, thus creating a tumor-permissive environment characterized by reduced anti-tumor activity, instability in genomic composition and enhanced angiogenesis.

The integration of sustained oxidative stress and chronic inflammation along with irreparable genomic damage inside host is the final hallmark of cancer initiation inside the gut. The generation of inflammatory cytokines, reactive nitrogen species, and reactive oxygen species in combination with the excessive accumulation of pollutants (heavy metals, microplastics) are the main events that triggers the progression of carcinogenesis. For instance, several studies have highlighted the transversion of Guanine to thiamine mutations when the hydroxyl radicals, produced during excessive chronic stress, induce 8-oxodeG lesions that if left unrepaired are linked to the oncogenic transversion of KRAS and TP53 (a classical tumor suppressor gene) [50]. Moreover, Rio and colleagues also studied a pattern in pollutants induced cancer and they highlighted a sequential pathway known as "inflammation-dysplasia-carcinoma sequence", mediated by the pollutants themselves, that is basically a cascade where the precursor for the progression of invasive cancer is chronic inflammation itself [51, 52]. This toxic behavioral change extends from the genetic code to the complete epigenome, initiating further abrupt negative changes that are linked with extensive damage of various adjacent genes. Another study reveals the linking of this toxic pattern with the alteration of epigenetics like histone modifications (methylation, acetylation), dysregulation of non-coding RNA and global hypo and hyper-methylation of DNA itself [18]. These epigenetic alterations are of greater concern as they are linked with prolong exposure to cancer even after the cessation of primary pollutants, serving as an epigenetic memory rendering the individuals to other fatal malignancies [53]. Collectively, induction of gut dysbiosis by pollutants and increased oxidative stress, permeability and chronic inflammation culminates in the genome wise instability along with DNA damage to further aids colorectal cancer, pancreatic, and hepatobiliary cancer (Table 1).

3. Microbiome: A Biomarker for Environmental Exposure

The gut microbiome can be translated into distinct

Table 1. Pollutant Induced Gut Dysbiosis: Summary of Microbiota Alterations, Mechanistic Pathways and Inflammation

Pollutant Category	Examples	Effects on Gut Microbiome	Key Mechanism & Associated Cancers
Microplastics and Nanoplastics	Polystyrene, Polyethylene, Polythenene Terephthalate (PET), Polypropylene	· Causes a sharp reduction in SCFA producers (Bacteroidetes, Firmicutes species) [91] · Promotes opportunistic pathogens [52, 92]	· Disruption of intestinal barrier (gastric cancer) [91, 92] · Translocation of LPS to induce damage to intestinal walls · Activation of inflammatory pathways modulating colorectal cancer (TLR4/NF-kB) [52]
Heavy Metals	Cadmium, Mercury, Arsenic, Lead	· Causes reduction in Bifidobacterium, lactobacillus species · Promote production of proinflammatory bacteria (proteobacteria) [93, 94]	· Generation of reactive oxygen species (affects liver and colorectal cancer) [94] · Induces DNA damage · Activation of metal efflux pumps (negatively regulating lungs cancer) [94]
Particulate Matter (PM)	PM10 (coarse particles), PM2.5 (fine particles)	· Causes reduction in microbial biodiversity inside gut (commensal bacteria) [95] · Further promotes dysbiosis, exceeding inflammation [92, 93]	· Induces systemic inflammation in lungs cancer [92] · Involved in the enterohepatic circulation of toxins [95]
Persistent organic pollutants (POPs)	Dioxins, Pesticides, Polychlorinated biphenyls, Polycyclic aromatic hydrocarbons (PAHs)	· Causes reduction in anti-inflammatory microbiota including Faecalibacterium prausnitzii · Alters the bile producing bacterial community [93]	· Disruption of AhR signaling pathway · Alters epigenetic modifications (DNA methylation and acetylation in breast cancer) [93] · Initiates chronic oxidative stress involved in progression of pancreatic cancer [96]
Endocrine Disrupting Chemicals (EDCs)	Phthalates, Bisphenol A	· Causes alterations in bacterial concentration (reduction in Firmicutes/ Bacteroidetes) [92] · Negatively affects the production of SCFA [93]	· Mimics estrogen hormone, affecting breast cancer (produces false alarms) [92] · Interfere with receptors responsible for hormonal regulation in prostate and thyroid cancer [97]

taxonomic, metabolic and functional signatures as it studied to be a recorder of environmental signature while living inside the host. This section will detail how techniques like machine learning, bacterial metagenomic profiling and metabolomics of gut microbiota can be collectively accessed to have a clear picture of how the microbiome itself can be transformed into a prognostic biomarker for inflammation and environ emend induced cancer.

Metagenomic Profiling

Till today, there are a lot of advanced techniques utilized for the efficient identification of microbial communities-linked to pollutant exposures as there identification is quite complex. Unlike the traditional 16S rRNA technique, metagenomic sequencing has emerged as the new gold standard for the microbial profiling (strain and specie level resolution of microbial communities) as the previous one is based on amplicon sequencing and providing information only on the genus level [54, 55]. This advance approach is helping the researchers to detect the alteration in metabolic pathways like metabolism of bile acid, xenobiotic degradation and biosynthesis of SCFA, characterized by pollutant induced shifts inside the gut [54]. As can be evident from the previously cited literature, metagenomic analysis has been extensively utilized in detecting genes altered by heavy metals as these genes show upregulated chronic stress and residence against the metal efflux pumps along-with the reduction of butyrate producing genes [56]. In addition to this, a study conducted by Zhang and colleagues highlighted the potential impact of chronic exposure to cadmium as this modulates genes in such a way that they showed resistance towards the metal enrichment within the gut metagenome along with a sharp decline in the gene, butyrate kinase [57]. Furthermore, these functional signatures are also studied to serve as the early warning indicators of exposure to toxic micropollutants, ultimately preceding histopathological and clinical changes.

Metabolomic Biomarkers of Exposure

Apart from taxonomic shifts in microbial genus, the integration of metagenomic with metabolomic has also proven beneficial as it provides a direct guideline for reading microbial alteration in real time. A lot of specific secondary microbial metabolites have been identified as non-invasive biomarkers that are currently being utilized in the assessment of pollutant-induced carcinogenesis, and these include lipopolysaccharide variants, trimethylamine N-oxide and deoxycholic acid. For instance, production of continuous deoxycholic acid by dysbiotic clostridium species is linked with the transversion of inflammation induced colorectal cancer along with irreparable DNA damage, after the cells are exposed by pesticide [57, 58]. Moreover, tryptophan metabolites (involved in the modulation of hydrocarbon receptor signaling (AhR)) are also altered because of these pollutants reflecting impaired immune modulation inside the gut [59]. One of the key findings on the aberrant production of deoxycholic acid was reported by Mesnage and colleagues when they utilize untargeted metabolomics on fecal sample from males, who were chronically exposed to organophosphates. They observed a sharp reduction in indole-3-propionate with a sharp increase in the quantity of deoxycholic acid, suggesting a strong correlation of these triggers with high levels of urinary pesticide with

increased DNA damage [60]. Hence, early detection of such metabolic signatures offers a better understanding of pollutant-induced carcinogenesis by bridging the gap between neoplastic transformation of cells and exposure to environmental toxins.

Utilization of Machine Learning: Exposure Scores

Apart from metabolomic profiling, recent studies have also demonstrated the effectiveness of machine learning algorithms in effective differentiation between normal individual variations and microbial related variations of the genome. Researchers have developed microbial, "exposure scores" by training machine learning algorithms, on larger dataset having known exposure to pollutants that can easily predict the time and duration of toxins, encountered by the host genome [61, 62]. Till today, a lot of different bacterial taxa have been identified using these models such as, increase in concentration of Escherichia coli and a decrease in Faecalibacterium prausnitzii across a diverse population of humans exposed to heavy metal and microplastics [63]. Moreover, some of these signatures are classified as early indicators for the developmental changes that occur in adenocarcinoma over the course of time, long before its clinical diagnosis [64]. But still these tools are to be validated on diverse population comprising of larger datasets before thay can be clinically used for the screening of microbial biomarkers in environment induced carcinogenesis. As can be evident from the results published by Cheng and colleagues in 2023, when they obtained metagenomic dataset of 1200 individuals along 3 different geographical regions. All the samples were exposed to heavy metals and after applying the random forest classifier, their model obtained an AUC of 0.89, as they not only predicted high levels of arsenic exposure but also identified a 12 taxa signature associated with all the samples in the experimental cohort [65].

4. Microbiome Based Therapeutic Regimens

The main goal of microbial based therapeutic intervention is to interrupt the cascade of pollutant induced inflammation and dysplasia carcinoma sequence. To mitigate the systemic damage caused by environmental xenobiotics, transitions have been made from the traditional prebiotics towards more precise gene editing techniques such as CRISPR-Cas 9.

Traditional Therapeutics: Prebiotics, Probiotics and FMT

The main goal of traditional therapeutic regimens is to modulate the microbial community in such a way that it would be able to restore the ecological balance of the GI tract in context of pollutant induced carcinogenesis. The first line of defense is the prebiotics and probiotics themselves which aim at replenishing the diminished bacterial composition (affected by microplastics and pesticides) inside the gut, comprising Bifidobacterium and Lactobacillus species [66]. These microbes are best known for strengthening the intestinal barrier by providing resistance against translocation of lipopolysaccharides and the aberrant activation of TLR4 pathway [67]. Apart from prebiotics and probiotics, fecal microbiota transplantation (FMT) is another therapeutic regimen that is also being administered to treat microbial dysbiosis as it has been studied to have beneficial effects on the gut by transferring a healthy microbial culture to ensure proper functioning of the gut [68, 69]. But still, the main advantage of FMT is its ability to suppress inflammation and oxidative stress and thus ensure the suppression of inflammation induced carcinoma inside the GI tract [70].

Targeted Microbial Control: Phage Therapy

Phage therapy is another therapeutic regimen that surpasses the traditional restoration of diverse microbial communities and is linked with providing researchers with targeted surgical precision so that they can easily modulate pathogenic bacteria without harming the beneficial flora [71]. As can be evident by the recently published data, bacteriophages were able to eliminate bacteria that were actively involved either in the metabolization of pollutants into carcinogenic metabolites or the activation of inflammasomes, in environmentally induced carcinomas [72, 73]. The best advantage offered by this technique is that it avoids collateral damage, primarily linked with the use of broad-spectrum antibiotics as these antibiotics have the potential to further worsen dysbiosis [74]. In addition to this, phage therapy restricts the cytokine signaling (promoting tumor initiation and progression) by selectively reducing the pro-inflammatory molecules, offering a better prophylactic strategy for treating carcinogenesis [75].

Next Generation Precision

Next generation precision techniques have been developed and modified to better cope with the pollutant induced carcinogenesis and two of the most important techniques that have been used in this context are synthetic biology and CRISPR-Cas9. One of the most predominant advantages of the techniques is their ability to do site specific editing of genomes of microbiota to either neutralize the oncogenes or to enhance the degradation of xenobiotics associated with dysbiosis and carcinogenesis [76]. For instance, studies have been conducted on the anti-toxic effect of engineered bacterial strains [77], and the results were good as these strains were not only involved in detection of toxicity related triggers but also in the secretion of anti-inflammatory as well as anti-oxidant molecules at the site of dysplasia [78]. This new and enhanced programable approach is enabling the researchers to create a unique therapeutic response that can be adopted according to the exposures faced by the host, thus transforming the passive gut microbiome into a programable active shield against the instability caused by pollutants [79] (Table 2).

5. Challenges and Opportunities

Lack of Standardization

Although there exists a lot of hurdles in making good use of these microbiomes as signatures for the better understanding of carcinogenesis, the main one is the lack of uniformity (standardization) of methodology

Table 2. Microbiome Based Therapeutic Strategies for Environmentally Induced Carcinogens

Therapeutic Strategy	Description	Mechanism of Action	Advantages and Limitations	References
Prebiotics	Contains non-digestible fibers that benefits growth of bacteria	Stimulate the production of butyrate, propionate and acetate	Advantages: Relatively safe and cost effective. Limitations: Variation among individual responses along with delayed effects.	[1, 2, 4]
Probiotics	Contains live commensal bacterial strains (Bifidobacterium and Lactobacillus)	Helps in restoration of ecological balance by restricting LPS translocation	Advantages: Widely available and well-tolerated by host. Limitations: Poor GI tract survival by bacteria with strain specificity.	[6, 7, 10, 11]
Fecal Microbiota Transplantation (FMT)	Involves transfer of healthy donor bacteria strains inside gut	Helps in modulation of immune response and complete microbial restoration	Advantages: Highly competent technique for treating dysbiosis. Limitations: Involved procedural risks, requirement for donor screening, and no published results on long term safety.	[68, 69, 71]
CRISPR-Cas9 Engineering	Involved editing of microbial genome for disease treatment and yield enhancement	Helps in enhancing xenobiotic degradation, oncogenic neutralization, and secretion of anti-inflammatory cytokines	Advantages: Technique is programmable, adaptive and promise long-lasting effects. Limitations: Have several off-target effects along with delivery challenges.	[76, 77, 79, 98]
Phage Therapy	Consists of target specific bacteriophages (bacteria-eater)	Helps in selective eradication of toxin producing bacterial strains from gut	Advantages: Highly precise technique offering no collateral damage. Limitations: Phages show resistance and it offers limited host range.	[71, 74, 75, 99]
Synthetic Biology (Programmable Probiotics)	Comprises genetically engineered bacteria for therapeutic applications	Helps in detection of toxins and is actively involved in production of anti-inflammatory cytokines at site of dysbiosis.	Advantages: Shows real-time response of bacteria and serves as an active shield. Limitations: Regulatory complications and biosafety concerns are the main hurdles.	[71, 72, 78]

applied across the scientific landscape [80]. Various discrepancies in whole genome shotgun sequencing and the traditionally liked 16S rRNA technique renders the researchers to get a complete and viable picture of gene abundance, abundance and its activity along with resolution of species that are actively involved in the phenomenon [81, 82]. At present batch effects, variations in methods for DNA extraction, storage, variations in collection of samples from cells and the sequencing platforms used [83], are being introduced into the testing procedure that obstructs the true nature of captured signals and adds further complications in the efficient identification of microbial communities that are linked with the initiation of carcinogenesis [84]. To overcome this effect, there is a need to introduce gold standard universal protocols for the effective creation of meta-analysis of large datasets which in turn will enable the researchers to differentiate between the true pathological shifts induced by microplastics and heavy metal pollutants and the standard variation among the microbiota in people across the globe. In fact, this standardization is pre-requisite for the efficient conversion of key laboratory findings into reliable modes for clinical diagnosis across the international communities.

Leveraging Machine Learning: Identifying Exposure Scores

As the genomic dataset generated by multi-omic studies is quite vast in terms of storage and understanding, it requires advanced computational algorithms to detect and highlight meaningful patterns of the disease under observation. Although it has a lot of advantages, the primary challenge faced by these bioinformatics integrated algorithms and tools is the generation of noise from the datasets under evaluation. This noise usually arises from, rate of exposure, age, diet and geographical location from which the samples are taken over the course of duration, rendering the tools ineffective in isolating the real cause and impact of environment related toxins on samples [85]. To overcome this, the machine learning algorithm, random forest classifier, was introduced as it was found to effectively differentiate between normal individuals and those that are exposed to microbial dysbiosis after exposure to harmful pollutants [86]. This model of machine learning was studied to be able to generate exposure scores that not only predict the time and duration of exposure but also was responsible for identification of bacterial taxa that was responsible for the dysbiosis, offering a highly reliable, accurate and easy to use method for handling complex environmental health related data [87].

Personalized Medicine: Environmental Footprint Screening

One of the ultimate goals of identification of metabolic and microbial signatures is to to further move towards advanced approaches that facilitate personalized medicine and precision oncology. But the major challenge that lies

in between is the epigenetic alterations (DNA methylation and acetylation) that are studied to exist as an epigenetic memory, just like the B-cells of immune system, as these alterations persist long after the primary exposure has been ceased [88, 89]. So, by analyzing a person's environmental signature and collection of metabolic biomarkers, microbial dysbiosis accompanied by the activation of inflammatory pathways, makes it easier for the clinicians to better predict the genetic alterations and to go beyond genetic screenings [90]. This approach will allow the researchers to detect early signs of various sorts of carcinomas long before the clinical diagnosis, allowing for better individual assessment for risks that can account for the exposure that a person has been imposed on or will have to for the cancer to develop properly.

In conclusion, the complex interplay between gut microbiota and environmental dysbiosis is the key factor that determines the initiation, progression and transformation of inflammation dysplasia carcinoma sequence inside the gut. As established throughout the manuscript, heavy metals and microplastics not only serve as passive toxins but are also involved in disruption of microbial ecology, thus triggering chronic inflammation pathways such as TLR4 and NLRP3 pathways. However, the advancements in high resolution genomic profiling and the induction of machine learning algorithms offer the best opportunity for the non-invasive early detection of pollutant induced cancer inside the gut. While natural way of restoration is offered by traditional therapeutic regimens like probiotics, prebiotics and FMT, strategic evolution in CRISPR-based synthetic biology and phage therapy is enabling the researchers to create a more programable mode of precision medicine. To get a clearer picture, the scientific community must move towards the standardization of protocols currently being used in metagenomics and metabolomics to further validate microbial signatures across diverse groups of populations. Lastly, the transformation of gut microbiome forms a target of microbial-induced stress towards an advanced, programable diagnostic and therapeutic intervention will have to be considered to further minimize the burden of cancer in the international community.

Conflict of Interest

The authors show no competing interest in preparation of this manuscript.

Acknowledgments

Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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