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How chronic inflammation fuels carcinogenesis as an environmental epimutagen

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Abstract
Chronic inflammation, induced by environmental and intrinsic factors, frequently leads to carcinogenesis. In inflammation-associated cancers, such as gastric, colon, and cervical cancers, an important role of epigenetic alterations has been implicated. Such epigenetic alterations include aberrant DNA methylation and histone modifications, some of which can permanently alter cellular characteristics and predispose cells to malignant transformation. Even in normal-appearing tissues, high levels of aberrant DNA methylation can be present, with these levels correlating to future cancer risk. The mechanisms of how chronic inflammation induces aberrant DNA methylation involve the repression of DNA methylation erasers, TET enzymes, and the increased activity of DNMTs. Aberrant DNA methylation in normal tissues can serve as a biomarker for cancer risk in the stomach and uterus. Beyond chronic inflammation, factors such as folate, vitamin B_{12}, and vitamin C deficiency can affect DNA methylation through metabolic pathways. Additionally, environmental chemicals, such as arsenic and NNK, and microbial metabolites, have been implicated in inducing epigenetic alterations. Further research is warranted on epigenetic alterations due to environmental factors, and the factors themselves, namely epimutagens.

Keywords Chronic inflammation, Carcinogenicity, DNA methylation, Epimutagen

1 Introduction

Chronic inflammation arises from environmental and intrinsic factors, such as persistent infections (e.g., *Helicobacter pylori* [*H. pylori*], human papilloma virus [HPV], and hepatitis viruses), autoimmune disorders, long-term exposure to environmental toxins (e.g., tobacco smoke), metabolic disorders, tissue damage, and chronic stress. Chronic inflammation is well known to be associated with cancer development, traditionally thought to be driven by inducing mutations [1–3]. However, growing evidence suggests a great impact of epigenetic alterations induced by chronic inflammation on carcinogenesis [4–7]. At a molecular level, chronic inflammation can induce aberrant DNA methylation, particularly genes pre-marked with specific histone modifications, via activation of the NF-κB pathway and production of nitric oxide [8–10]. Aberrant DNA methylation

can disrupt gene regulation without affecting the DNA sequence itself, leading to long-lasting cellular changes [11–13].

The causal role of epigenetic alterations in cancer development has been shown by multiple lines of evidence. First, global DNA hypomethylation promoted tumor formation in mice [14, 15], and suppression of aberrant DNA methylation by DNA demethylating agents repressed tumorigenesis in mouse models [16–19]. Second, tumor suppressor genes mutated in human cancers are also silenced by aberrant promoter DNA methylation during precancerous stages, with this silencing maintained in tumors [20–22]. Third, the therapeutic efficacy of DNA demethylating agents and histone modification inhibitors has been shown in human hematological tumors and multiple animal models of human solid and hematological tumors, providing strong support for the causal role of epigenetic alterations in the development of these tumors [23–29].

Notably, a substantial amount of epigenetic alterations can accumulate in non-cancer cells, enabling cells to bypass normal growth checkpoints and ultimately predisposing them to malignant transformation [30, 31]. For example, while *BRAF* mutations typically induce cellular senescence in normal cells, the accumulation of epigenetic alterations in non-cancer cells can circumvent this process, allowing continued cell proliferation despite the presence of a *BRAF* mutation, ultimately leading to colorectal tumor formation [32]. Additionally, global hypomethylation can also occur even in non-cancer tissues, and can lead to chromosomal instability [15].

This review examines the role of chronic inflammation as an epigenetic mutagen (epimutagen), with a particular focus on stomach, colon, and uterine cervical cancers where chronic inflammation is heavily involved, and discusses potential applications of the findings. We will also explore substances that act as epimutagens and modulators of epigenetic processes.

2 Mutations and epigenetic alterations in cancers

Some cancers are associated with defined mutagens, such as tobacco smoking for squamous cell lung cancers (SCCs) and ultraviolet radiation exposure for melanomas. These cancers often present with frequent driver gene mutations, such as *PIK3CA* mutations in SCCs and *BRAF* mutations in melanomas, along with high mutation burdens [33]. Other cancers, such as gastric and hepatocellular cancers, are associated with chronic inflammation and display less frequent driver gene mutations [34, 35], suggesting the importance of epigenetic alterations in these cancers. For example, although driver genes such as *TP53* and *CDH1* are identifiable in some gastric cancers, a substantial portion lack sufficient numbers of driver gene mutations [36]. These tumors often involve epigenetic alterations, such as the silencing of *CDKN2A*, *CDH1*, and *MLH1* through DNA hypermethylation. This shows that some cancer types are heavily influenced by mutations, while others are more by epigenetic alterations. Furthermore, it suggests that even within the same cancer type, the relative importance of mutations and epigenetic alterations depends on the individual.

3 Mutations and epigenetic alterations in normal-appearing tissues and their association with cancer risk

Both mutations and epigenetic alterations are now known to be present even in normal-appearing tissues, and are likely to play a crucial role in predisposing cells to malignancies. Regarding mutations, their presence in normal-appearing tissues was recently demonstrated in various tissues by the use of small amounts of samples, which increases the relative proportion of a clone, and/or high-accuracy sequencing [37]. In contrast with mutations, aberrant DNA methylation can be present at high levels even in normal-appearing tissues, and its accumulation in tissues exposed to chronic inflammation has been known for more than two decades [38–40]. The high levels of aberrant DNA methylation enabled us to show that its accumulation levels can be correlated with cancer risk [41, 42]. The predisposed status of a normal-appearing tissue due to accumulation of epigenetic alterations is termed as an epigenetic field for cancerization [30].

The relative importance of genetic and epigenetic alterations in cancer risk was estimated by measuring point mutations and aberrant DNA methylation in normal-appearing tissues of healthy individuals (low risk), individuals exposed to risk factors (intermediate risk), and patients with esophageal or gastric cancers (high risk) [43]. In esophageal mucosa, both point mutations and aberrant DNA methylation increased as cancer risk increased. In gastric mucosa, point mutations increased from low to intermediate risk, but not from intermediate to high risk. In contrast, aberrant DNA methylation increased along with cancer risk. This showed that epigenetic alterations in normal-appearing tissues play a more important role than genetic alterations in cancer risk assessment, depending on the cancer type and its etiology (Fig. 1).

4 Molecular mechanisms for induction of epigenetic alterations by chronic inflammation

In the stomach, *H. pylori* infection was strongly associated with high levels of aberrant DNA methylation [39]. In the stomach of Mongolian gerbils, even when *H. pylori* was present in large amounts, suppressing inflammatory responses with cyclosporin A almost completely inhibited methylation induction, highlighting the critical role of

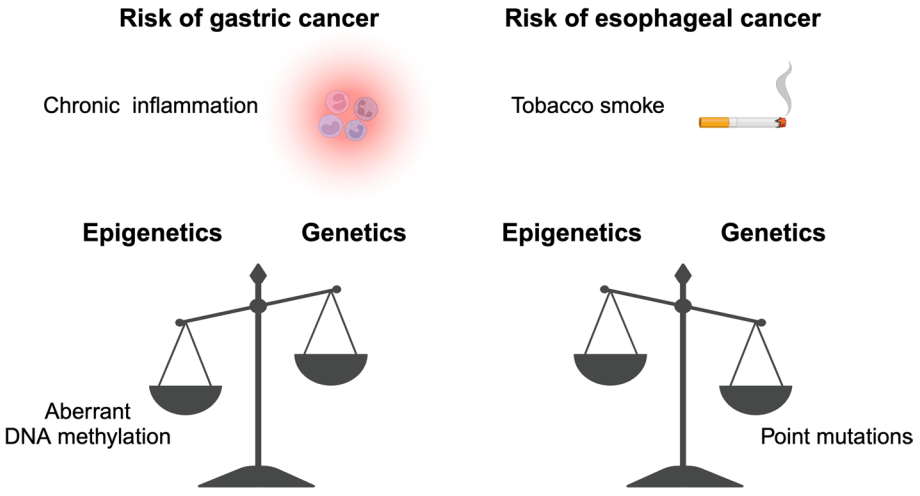

Fig. 1 Balance between genetic and epigenetic alterations in carcinogenesis. Certain types of cancer driven by chronic inflammation primarily involve epigenetic alterations, while other types of cancer driven by mutagens primarily involve mutations.

inflammation in driving epigenetic alterations [10]. In addition, while *H. pylori* infection potently induced severe DNA methylation, dietary salt and alcohol did not [44]. These agents caused repeated acute inflammation, which is characterized by prolonged neutrophil infiltration, while *H. pylori* infection caused chronic inflammation characterized by macrophage and lymphocyte infiltration. The lack of aberrant DNA methylation induction despite sustained cell proliferation in the repeated acute inflammation suggests that signals from macrophages or lymphocytes are required for induction of aberrant DNA methylation.

In *H. pylori* infection-induced chronic inflammation, the infiltration of macrophages stimulates the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [44–47]. TNF-α and IL-1β activate the NF-κB pathway, which turned out to be a major driver of inflammation-induced aberrant DNA methylation. NF-κB translocates to the nucleus upon activation, acting as a transcription factor that induces genes involved in cell survival, proliferation, and inflammation [48]. Importantly, activated NF-κB upregulates *MIR20A*, *MIR26B*, and *MIR29C* that target ten-eleven translocation (TET) enzymes, and down-regulates *TET* expression [8]. Since TET enzymes mediate DNA demethylation, their down-regulation can contribute to the induction of aberrant DNA methylation.

Another hint was massive production of reactive oxygen and nitrogen species (ROS/RNS) by immune cells to fight pathogens during inflammation [49, 50]. Particularly nitric oxide (NO), produced by nitric oxide synthase 2 (*NOS2*), was reported to enhance the activity of DNA methyltransferases (DNMTs) [51] and to inhibit the activity of TET enzymes [52]. Although the impact of NO only was minimal, a combination of NF-κB-mediated down-regulation of TET enzymes and NO-induced enhancement of DNMT activity synergistically drove widespread induction of aberrant DNA methylation across the genome [8] (Fig. 2).

Histone modifications are also altered by chronic inflammation, especially by NO. NO-mediated *S*-nitrosylation inhibits activity of histone deacetylases (HDACs), increasing histone or protein acetylation [53, 54]. In addition, NO is reported to inhibit the activity of lysine-specific histone demethylase KDM3A, and potentially other Jumonji-C demethylases, which in turn leads to an increase of KDM3A expression. NO also reduces the iron cofactor of demethylases, and thereby increases global levels of H3K9me2 [55].

5 Clinical applications of epigenetic alterations associated with chronic inflammation

In the stomach, aberrant DNA methylation is accumulated in *H. pylori*-infected gastric mucosa [56–58]. Importantly, the methylation level in gastric mucosa decreases after *H. pylori* eradication [56–58]. Since DNA methylation of a CpG island does not disappear without therapeutic drugs, this phenomenon suggests that the aberrant DNA methylation occurs mainly in differentiated epithelial cells. Most stem cells in gastric mucosa remain unmethylated, and the overall methylation level decreases when differentiated cells with aberrant DNA methylation are replaced by cells newly produced from unaffected stem cells after *H. pylori* eradication. Our recent organoid and single-cell analysis on gastric stem cells and differentiated cells supported this model (Takeuchi et al., manuscript in preparation).

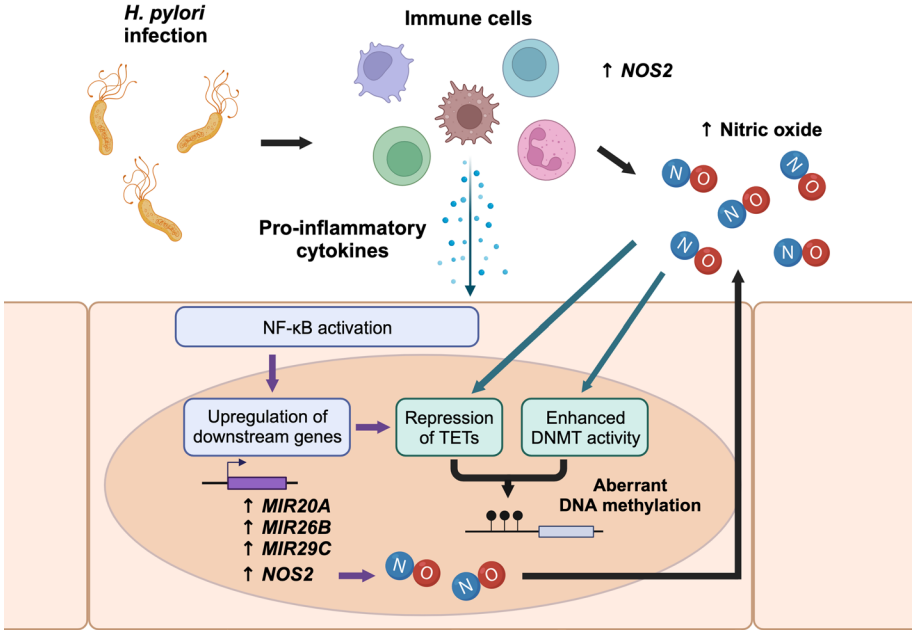

Fig. 2 Induction mechanism of aberrant DNA methylation by chronic inflammation triggered by *H. pylori* infection. Proinflammatory cytokines, such as IL-1β and TNF-α, activate the NF-κB pathway, repressing TETs and upregulating downstream genes, including *NOS2*. NO from inflammatory and epithelial cells increases DNMT activity and inhibits TET expression. Simultaneous occurrence of TET repression and increased DNMT activity potently drive aberrant DNA methylation induction in gastric epithelial cells.

The methylation is widespread and involves numerous genomic loci [59], including promoter CpG island hypermethylation that silences tumor suppressor genes such as *CDKN2A* [58], *RUNX3* [50], *CDH1* (E-cadherin) [60], and *MLH1* [61]. Additionally, global hypomethylation is observed and is considered to contribute to chromosomal instability [15, 62]. These hyper- and hypomethylations in gastric stem cells produce an epigenetic field for cancerization [30] and closely overlap with precancerous conditions such as atrophic gastritis and intestinal metaplasia [22, 63].

The severity of an epigenetic field can be measured by the DNA methylation level of a marker gene, and the methylation level is associated with cancer risk, namely with a pathway to cancer or that to longevity after *H. pylori* eradication [41]. To bring this finding into cancer risk diagnosis, a multi-center prospective study demonstrated that assessing the accumulation of aberrant DNA methylation at the *MIR124-3* gene in the gastric mucosa of gastric cancer patients cured by endoscopic treatment can predict the risk of metachronous gastric cancer, with a multivariate-adjusted hazard ratio of 2.3 [64]. The methylation level of *MIR124-3* reflects the genome-wide burden of epimutations, supporting its use as a surrogate marker for cancer risk [41]. Additionally, another multi-center prospective study demonstrated that measuring DNA methylation levels of *RIMS1* can stratify gastric cancer risk among healthy individuals after *H. pylori* eradication [65] (Fig. 3).

In colonic and intestinal mucosa, aberrant DNA methylation is accumulated in patients with inflammatory bowel diseases (IBD), namely ulcerative colitis (UC) and Crohn's disease (CD). Tumor suppressor genes including *CDKN2A* [66], *CDH1* [67], *RASSF1A* and *p14/ARF* [68] undergo hypermethylation, while global hypomethylation further contributes to genomic instability [15, 69]. These epigenetic alterations occur not

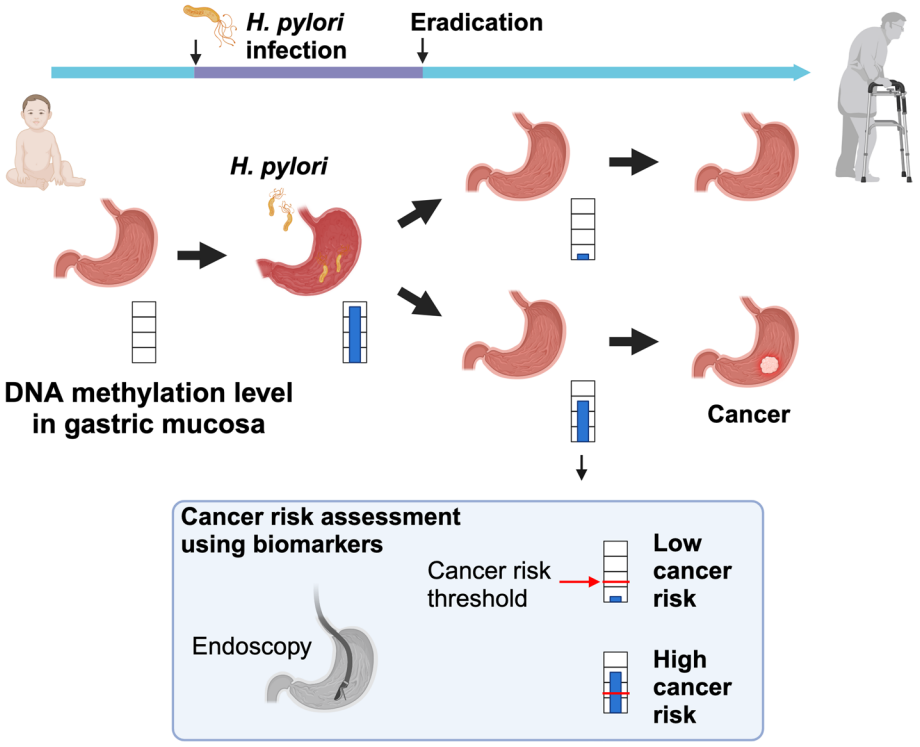

Fig. 3 Aberrant DNA methylation accumulates in the gastric mucosa following *H. pylori* infection during childhood and its eradication in adulthood. *H. pylori* infection potently induces aberrant DNA methylation of many genes. After eradication, these methylation changes can either decrease or persist. The decrease in methylation levels suggests that differentiated cells are more susceptible to methylation induction, and that the DNA methylation level after *H. pylori* eradication is correlated with epigenomic damage in stem cells and thus with gastric cancer risk (see the text).

only in epithelial cells but also in immune cells. For example, depletion of *UHRF1*, a key component of maintenance of DNA methylation, in mice with UC led to severe pathology due to excessive TNF-α production through its hypomethylation in macrophages [70]. Moreover, the histone methyltransferase G9a was found to mediate H3K9me2 deposition in T cells, which restricted Th17 and Treg differentiation by limiting chromatin accessibility and responsiveness to TGF-β, driving dysregulated immune responses and colitis progression [71].

Promising biomarkers for cancer risk in IBD have been identified, each with unique diagnostic and prognostic utility. For CD, *FHIT* hypermethylation was associated with the presence of CD and its progression [72]. Combined *TGFβ1* and *IL-6* hypermethylation in whole peripheral blood samples showed promise as a non-invasive diagnostic tool for pediatric CD [73]. For UC, *CXCL5* hypermethylation in whole peripheral blood was reported to serve as a less invasive diagnostic marker, helping to distinguish UC from other inflammatory conditions [74]. As a practical and non-invasive approach for early cancer detection, altered methylation levels of *BMP3* and *VAV3* in stool samples, relative to *ZDHHC1*, have also been reported [75]. Lastly, hypermethylation of *ITGA4* and *TFPI2* has been identified as risk markers for colitis-associated cancer, enabling cancer risk assessment and preventive strategies in high-risk individuals [76]. Collectively, these epigenetic biomarkers are likely to contribute to an advancement in the assessment of cancer risks.

In the uterine cervix, persistent infection with high-risk HPV types 16 and 18, along with its resultant chronic inflammation, is a major driver of cervical carcinogenesis. As in the stomach and colon, chronic inflammation due to HPV infection is known to alter cellular DNA methylation patterns [77]. Importantly the accumulation of aberrant DNA methylation in cervical epithelial cells has been associated with an increased risk of cervical cancer [78, 79]. A recent prospective study demonstrated the effectiveness of DNA methylation biomarkers, particularly those targeting HPV-associated and host genes, in cervical cancer screening, highlighting their potential as a cancer risk biomarker [42].

These findings in the stomach, colon, and uterine cervix confirm the broad utility of DNA methylation as a reliable tool for early detection and risk assessment in chronic inflammation-associated cancers.

6 Other environmental factors

Environmental factors such as nutritional deficiencies can significantly impact cancer risk through epigenetic alterations in tissues with or even without chronic inflammation. Folate and vitamin B_{12} are involved in the synthesis of S-adenosylmethionine (SAM), a universal methyl donor required for DNA methylation. Folate supplementation was found to reduce the expression of pro-inflammatory cytokines and inhibit NF-κB activation after liposaccharide (LPS) induction [80], showing the potential for correcting inflammation-induced epigenetic alterations. On the other hand, supplementation of vitamin C, a cofactor for oxidative DNA demethylation by TET enzymes, can boost TET activity [81]. Importantly, a clinical study in patients with TET2 germline mutations showed that vitamin C supplementation decreased aberrant DNA methylation in blood cells [82]. These findings emphasize the promising potential of dietary and pharmacological interventions to target epigenetic alterations for therapeutic and preventive purposes.

Other environmental chemicals, such as arsenic and NNK (a tobacco-specific nitrosamine), are also reported as epimutagens that can disrupt normal epigenetic regulation. Chronic and low-level arsenic exposure was associated with DNA hypomethylation and aberrant gene expressions [83]. These alterations are accompanied by reduced DNMT activity, attributed to arsenic's direct binding and its subsequent degradation of DNMT through the ubiquitin-proteasome pathway [84]. Such epigenetic alterations are reported to activate oncogenes and drive carcinogenesis in tissues, including the skin, bladder and lungs [85]. Similarly, NNK was reported to induce DNMT1 nuclear localization and hypermethylation of key genes involved in cell cycle regulation and DNA repair, thus further driving cancer development in smokers [86, 87]. These findings highlight the profound role of environmental factors in driving epigenetic alterations, emphasizing the need to understand their broader implications in carcinogenesis and potential strategies to mitigate their effects.

The microbiome is also an environmental factor influencing host cells, and plays a crucial role in shaping the epigenome and directing health and disease (Fig. 4), a topic that has gained significant attention in recent studies [88]. Its composition is profoundly shaped by environmental factors, mainly dietary components. In a healthy state, the gut microbiome produces short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which regulate host cell energy metabolism by serving as substrates for acetyl-CoA production and driving the tricarboxylic acid (TCA) cycle, which prevents

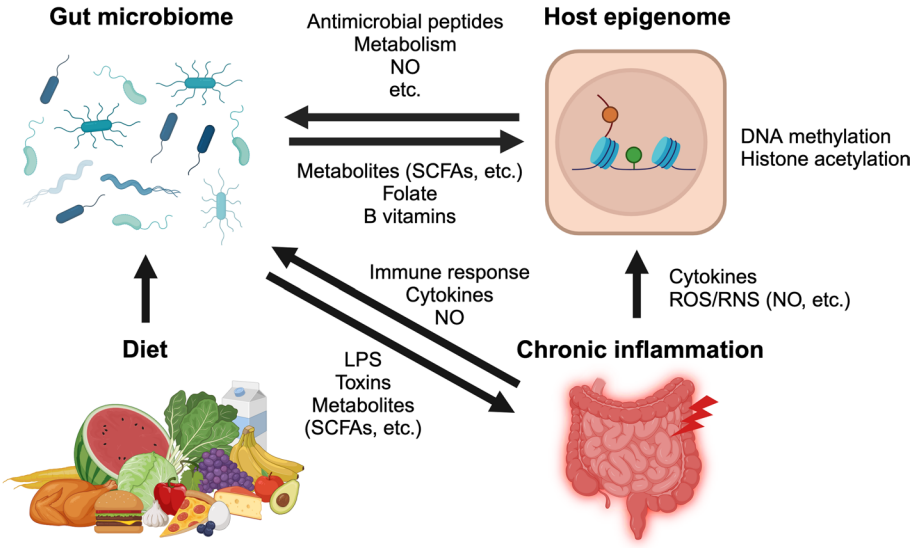

Fig. 4 The microbiome influences the host epigenomes through its metabolites and metabolism of vitamin B_{12} and folate. The gene expression changes, in turn, affect the microbiome composition through secreted factors such as NO. Additionally, chronic inflammation can further alter the gut microbiome composition and host epigenomes.

autophagy [89]. SCFAs also inhibit HDACs [90], modulate gene expression, supporting barrier function and reducing immune responses in the colon [89, 91]. Additionally, microbial metabolism of vitamin B_{12} and folate affects DNA methylation in host cells [90]. In contrast, under disease conditions, chronic inflammation significantly impacts microbial diversity and functionality, partly through NO overproduction [92], leading to widespread epigenetic alterations in host cells as discussed in previous sections. These mechanisms highlight the complex crosstalk between diet, the microbiome, and the host epigenome in healthy and diseased states, which can either enhance homeostasis or contribute to disease.

7 Outlook

Chronic inflammation, induced by environmental and intrinsic factors, clearly drives carcinogenesis by promoting epigenetic alterations, acting as an epimutagen. In addition, folate, vitamin B_{12}, and vitamin C are modulators of epigenetic processes with mechanistic support. Other chemicals, however, require more robust analysis to understand their underlying mechanisms. The interplay between the gut microbiome and epigenetic alterations is a growing field, with potential therapeutic implications for modulating microbiota to prevent or reverse harmful epigenetic alterations in inflammatory conditions. However, the extreme complexity of this field calls for further research. Moreover, factors such as age and genetic background are likely to influence epigenetic alterations induced by chronic inflammation and chemical substances, warranting more refined and larger scale studies.

Application of epigenetic alterations in normal tissues to cancer risk diagnosis is now approaching clinical use in the uterus and stomach [42, 64]. In other tissues, such as the liver and colon, similar approaches are likely to be successful [93, 94]. For therapeutic purposes, aberrant DNA methylation in tumors is now used as a target [95, 96]. To advance cancer prevention, early detection, and risk stratification, further investigation

is needed to clarify how specific environmental exposures drive epigenetic alterations in normal tissues.

8 Conclusions

Chronic inflammation driven by environmental factors such as infection plays a critical role in carcinogenesis, and induction of epigenetic alterations is the major mechanism involved. Such alterations are present even in normal tissues and are involved in field cancerization in certain cancer types. Emerging biomarkers derived from inflammation-induced aberrant DNA methylation offer promising avenues for cancer risk diagnosis. Targeting these epigenetic alterations, alongside preventive strategies such as *H. pylori* eradiation or vitamin supplementation, may help reduce cancer risks associated with chronic inflammation. Advancing this field will require further understanding of environmental and biological factors driving epigenetic alterations.

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Author contributions
YY Liu, Y Ohashi, and T Ushijima wrote the manuscript and created the figures. All authors gave final approval to the submitted and published versions.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
We declare a conflict of interest with Sysmex company, which is developing an epigenetic gastric cancer risk diagnosis.
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