Microbial carcinogenesis: lactic acid bacteria in gastric cancer

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Abstract

While *Helicobacter pylori* is a fundamental risk factor, gastric cancer (GC) aetiology involves combined effects of microbial (both *H. pylori* and non-*H. pylori*), host and environmental factors. Significant differences exist between the gastric microbiome of those with gastritis, intestinal metaplasia and GC, suggesting that dysbiosis in the stomach is dynamic and correlates with progression to GC. Most notably, a consistent increase in abundance of lactic acid bacteria (LAB) has been observed in GC patients including *Streptococcus*, *Lactobacillus*, *Bifidobacterium* and *Lactococcus*. This review summarises how LAB can influence GC by a number of mechanisms that include supply of exogenous lactate —a fuel source for cancer cells that promotes inflammation, angiogenesis, metastasis, epithelial-mesenchymal transition and immune evasion—, production of reactive oxygen species and N-nitroso compounds, as well as anti-*H. pylori* properties that enable colonization by other non-*H. pylori* carcinogenic pathobionts.

Abbreviations

A, antrum; AG, atrophic gastritis; ARG1, Arginase 1; B, body; C, cardia; CAF; cancer-associated fibroblast; Cav-1, caveolin-1; CD147, chaperone protein cluster of differentiation 147; CFU; colony-forming units; CIN, chromosomal instability; DLD, dihydrolipoamide dehydrogenase; EBV, Epstein-Barr virus; ECM, extracellular matrix; EMMPRIN, extracellular matrix metalloproteinase inducer; ENO1, enolase 1; FD, functional dyspepsia; GC, gastric cancer; GAC, gastric adenocarcinomas; GIT, gastrointestinal; GLO, glyoxalase; GLUT, glucose transporter; GS, genomically stable; HP, *Helicobacter pylori*; HP+, HP-positive; HP-, HP-negative; HCAR, hydrocarboxylic acid receptor; HIF-1, hypoxia-inducible factor 1; HK2, hexokinase 2; INS-GAS, Insulin-Gastrin; IM, intestinal metaplasia; LAB, lactic acid bacteria; LDH, lactate dehydrogenase; MAG, multifocal atrophic gastritis without

intestinal metaplasia; MAG-IM, multifocal atrophic gastritis with intestinal metaplasia; MCT, monocarboxylate transporters; MDSC, myeloid-derived suppressor cell; MG, methylglyoxal; MSI, microsatellite instability; NAG, non-atrophic gastritis; NK, natural killer; PDK1, pyruvate dehydrogenase kinase 1; PKM2, pyruvate kinase; qPCR, quantitative PCR; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SLC16A, solute carrier 16A family; TAM, tumor-associated macrophages; TCGA, The Cancer Genome Atlas; TME, tumor microenvironment; T-RFLP, terminal restriction fragment length polymorphism; VEGF, vascular endothelial growth factor.

1. Microbes and carcinogenesis

Microbial carcinogenesis is most commonly explained through the simplistic model of dysregulated inflammation. More recently, the role of microbes in cancer development has expanded to include the potential capacity to modulate several cancer hallmarks, including tumor-promoting inflammation [1], altered immune response [2], tumor growth [3-5], angiogenesis [6], pro-carcinogenic metabolite production [7, 8], as well as DNA damage and induction of genomic instability [9] (Fig. 1).

A good example of this is the metabolite butyrate, which is produced by bacterial species through the anaerobic fermentation of carbohydrates and provides an important energy source for host cells such as colonocytes. While butyrate has been shown in a range of studies to have beneficial anti-cancer effects [10], in the right genetic background, butyrate promotes carcinogenesis through the increased proliferation of aberrant epithelial cells [10, 11]. Here, we summarise how lactate, a metabolite that is related to butyrate, and can be produced by both host and microbial cells, has similar properties. We highlight the importance of lactate in gastric carcinogenesis, and we present evidence towards a “lactate paradox” in the form of microbiome-produced lactate that acts as fuel for gastric tumor cells and shapes the tumor microenvironment (TME).

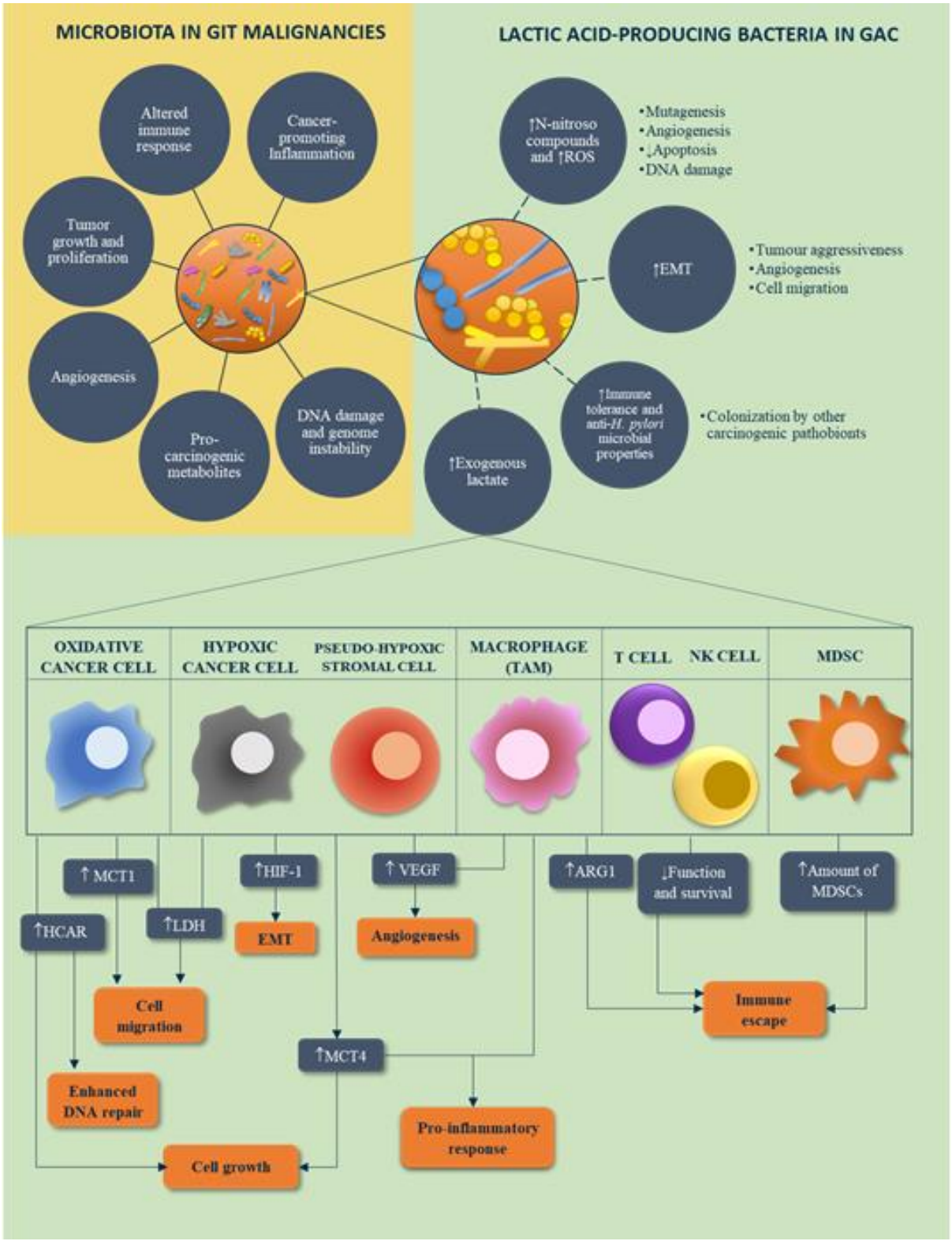
MICROBIOTA IN GIT MALIGNANCIES
Altered immune response
Cancer-promoting Inflammation
Tumor growth and proliferation
Angiogenesis
Pro-carcinogenic metabolites
DNA damage and genome instability
LACTIC ACID-PRODUCING BACTERIA IN GAC
↑N-nitroso compounds and ↑ROS
•Mutagenesis
•Angiogenesis
•↓Apoptosis
•DNA damage
↑EMT
•Tumour aggressiveness
•Angiogenesis
•Cell migration
↑Immune tolerance and anti-H. pylori microbial properties
•Colonization by other carcinogenic pathobionts
↑Exogenous lactate
OXIDATIVE CANCER CELL
HYPOXIC CANCER CELL
PSEUDO-HYPOXIC STROMAL CELL
MACROPHAGE (TAM)
T CELL
NK CELL
MDSC
↑ MCT1
↑HCAR
↑LDH
Cell migration
Enhanced DNA repair
Cell growth
↑HIF-1
EMT
↑ VEGF
Angiogenesis
↑MCT4
Pro-inflammatory response
↑ARG1
↓Function and survival
↑Amount of MDSCs
Immune escape

Fig 1. Role of the gastrointestinal microbiome in cancer. The GIT microbiome is involved in major steps of carcinogenesis including tumor-promoting inflammation, altered immune response, tumor growth, angiogenesis, pro-carcinogenic metabolite production, DNA damage and induction of genomic instability. In GAC, lactic acid bacteria are enriched. Four main mechanisms by which these bacteria may influence the outcome of gastric disease include: 1) increased N-nitroso compounds and reactive oxygen species (ROS). N-nitroso compounds have been shown to promote mutagenesis, angiogenesis, protooncogene expression, and to inhibit apoptosis [12-14] while ROS have been shown to induce DNA damage [15]. 2) Increased EMT by induced multipotency [16], contributing to tumor progression [17]. 3) Promote colonisation by non-*H. pylori* carcinogenic pathobionts by induced immune tolerance [18] and their anti-*H. pylori* microbial properties [19-21]. 4) Augmented production of exogenous lactate. Lactate is involved in several hallmarks of cancer [22] and regulates the expression of important key players. Lactate can serve as a fuel source for oxidative cancer cells, upregulating MCT1 [23] and subsequently contributing to cell migration [24]. Cell migration and metastasis are also correlated with high LDH [25] and VEGF expression [26, 27], the latter being an important angiogenic factor in cancer [28]. EMT can be induced by HIF-1 [29], which can be activated by lactate in an oxygen-independent manner [30-32]. Lactate can also regulate the HCAR1/MCTs axis and enhance DNA repair capacity in tumor cells contributing to chemoresistance [33]. Tumor growth can be potentiated by lactate-mediated expression of HCAR1 [34] and MCT4 [35]. MCT4 is also indispensable for the activation of the inflammatory response of TAMs [36]. Lactate mediates M2-like polarization of TAMs, which is believed to be tumor supportive [37], and increases VEGF and ARG1 expression [30] in these cells, contributing to immune escape [38]. Lactate also inhibits T and NK cells function and survival [39], and increases the amount of MDSCs, which can further supress NK cell cytotoxicity [40].

GIT, gastrointestinal; GAC, gastric adenocarcinoma; EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species; TAM, tumor-associated macrophage; NK, natural killer; MDSC, myeloid-derived suppressor cell; MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4; HCAR1, hydrocarboxylic acid receptor 1; HIF-1, hypoxia-inducible factor-1; LDH, lactate dehydrogenase; VEGF, vascular endothelial growth factor; ARG1, Arginase 1; CAFs, cancer-associated fibroblasts; Cav-1, caveolin-1.

2. Gastric cancer

Gastric cancer (GC) is the 5th most common cancer worldwide [41, 42] and is considered a leading cause of cancer death globally [43, 44] despite declining incidence and prevalence rates. In fact, in 2013, GC was the third most common cause of cancer-related deaths in developed countries, accounting for 984,000 new cases and 841,000 deaths worldwide [43]. Recent studies suggest that most GC cases are frequently diagnosed in the final stages of the disease, resulting in generally poor survival rates. Almost two thirds of GC cases occur in East Asia, Eastern Europe and Central and South America, these regions being classified as high GC risk populations [43].

The majority of GCs are adenocarcinomas (GAC) which have been conventionally classified into a number of histological subtypes based on Lauren's classification (i.e. intestinal, diffuse, mixed and non-classifiable) [45]. More recently, the World Health Organization categorized GAC into four subtypes including papillary, mucinous, tubular, and signet ring cell [46]. Importantly, recent advanced genome technologies have led to a novel GC classification scheme. This classification, known as The Cancer Genome Atlas (TCGA) classification, comprises four GC subtypes: (1) Epstein-Barr virus (EBV)-positive, (2) microsatellite instability (MSI), (3) genomically stable (GS), and (4) chromosomal instability (CIN) [47].

GAC is a multifactorial and multistep inflammatory disease. Correa's cascade, a widely accepted model for GAC, illustrates the stages of gastric carcinogenesis from precancerous lesions—superficial gastritis, chronic atrophic gastritis, intestinal metaplasia and dysplasia—to adenocarcinoma [48]. A number of factors play a significant role in GAC, including host genetics [49-52], environmental factors (e.g. smoking, alcohol consumption, high salt and meat intake, and low vegetable/fruit intake), and microbial factors (i.e. *Helicobacter pylori* infection

and the gastric microbiota) [53-55]. *H. pylori*, a Gram-negative curved rod has been associated with 89% of new GAC cases around the world [56, 57]. *H. pylori* chronic infection plays an important role in the early stages of the disease including chronic gastritis, atrophic gastritis and intestinal metaplasia [58-62], however, its colonization in atrophy and intestinal metaplasia is scarce [63, 64], leading to the hypothesis that other bacteria within the gastric microbiome are also involved in GAC development. Importantly, the latest clinical guidelines on the management of gastric epithelial precancerous conditions reiterated the need to identify patients with advanced stages of gastritis (i.e. atrophy and/or intestinal metaplasia affecting both antral and corpus mucosa) given that they are considered to be at higher risk for GAC [65].

3. Role of lactate in gastric carcinogenesis

Once a tissue has turned malignant, it exhibits limitless replicative potential, which requires changes and adaptations in energy metabolism to sustain the increased rate of cell division and anabolic tumor growth [66]. Malignant cells are mostly programmed to rely on aerobic glycolysis instead of oxidative phosphorylation, which is less efficient in terms of adenosine triphosphate production but provides tumor cells with an appropriate fuel supply to support their accelerated growth rate. This provokes an increase in glucose uptake and high amounts of lactate in an oxygen-independent manner [67, 68], a well-established phenomenon known as the Warburg effect [69, 70]. Given that lactate is crucial for major processes during carcinogenesis including angiogenesis, immune evasion, cell migration, metastasis, and cell sufficiency, it has been recently proposed that upregulated lactagenesis is the ultimate purpose of the Warburg effect in cancer cells [22]. Indeed, basal lactate production in an average human is of the order of 0.8 mmol/kg body weight/h while lactate can be found at concentrations ranging from 10-12.9 mmol/kg in glycolytic tumors [71-74]. This increased lactate

concentration will in turn impact on lactate transport and metabolism, oxygen levels, and the TME.

3.1 Lactate transport

Lactate transport is mainly carried out by four members of the solute carrier 16A family (SLC16A) known as the monocarboxylate transporters (MCT) 1, 2, 3 and 4, which are also involved in the proton-linked transport of acetate, pyruvate, butyrate, and ketone bodies [75-77]. MCTs are involved in the regulation of important physiological and pathological processes in diverse tissues, however, they appear to be particularly important for the brain and malignant tumors (for a comprehensive review on this topic, please see [78]).

The data on MCT regulation in GAC is somewhat conflicting. Pinheiro *et al* [79] reported that MCT1 expression was associated with advanced GAC while Lee *et al* [80] reported MCT4 overexpression to be mainly found in GAC cell lines derived from metastasis or ascites. Furthermore, previous observations in patients with GAC have shown that high MCT4 expression is found in stromal but not tumor cells and is correlated with a worse prognosis and increased tumor progression [81]. Importantly, inhibition of MCTs has been shown to result in reduced tumor cell proliferation and lactate uptake in GAC cell lines that overexpressed MCTs [80]. This is in line with several reports in diverse types of cancer where MCT inhibition resulted in delayed tumor growth [32, 82-85]. However, significant decreased expression of MCT4 has also been reported in advanced GAC and metastasis as compared to normal gastric mucosa and early GC, suggesting a progressive loss of this isoform with disease progression [79].

The expression of the chaperone protein cluster of differentiation 147 (CD147) (aka basigin or extracellular matrix metalloproteinase inducer, EMMPRIN) is required for MCT1 and MCT4 proper expression at the cell surface and functioning [86-89]. CD147 is considered a key element in oncogenesis, being widely correlated with poor prognosis and progression of several malignancies (for further information on this topic, please see the comprehensive review and meta-analysis by [90]). CD147 interaction with MCT1 and MCT4 has been shown to be crucial for their regulation in gastric tumor cells [79]. Moreover, upregulation of CD147 in GAC has been reported [79, 91] and has been associated with local invasion and poor prognosis via tumor growth and angiogenesis [92]. Importantly, a recent meta-analysis, comprising 1993 subjects, showed that CD147 expression is correlated with poor prognosis in GAC [93].

3.2 Lactate metabolism in tumor cells

There are two stereoisomeric forms of lactate, D- and L-lactate. D-lactate can be produced in small amounts in cancer cells through the ubiquitous methylglyoxal (MG) pathway. MG is produced from carbohydrate, fat and protein metabolism [94]. Interestingly, MG has been suggested to modify heat shock proteins, which can alter and/or enhance their chaperone functions and stress response activities in cancer cells [95]. Due to its reactive and toxic nature, MG is then converted to D-lactate via the intermediate S-D-lactoylglutathione by the enzymes glyoxalase (GLO)-1 and GLO-2, the former being recently reported to be an important metabolic oncogene in GAC that could be used as a prognostic factor [96, 97]. Thus, an interesting take would be that cancer cells, in an attempt to detoxify MG, increase their D-lactate production, which in turn feeds the Warburg effect.

L-lactate, on the other hand, is abundantly produced by tumour and stromal cells. The metabolic imbalance in glycolytic cells is promoted by the continuous conversion of pyruvate

to lactate through lactate dehydrogenase (LDH) [98], which is induced by oncogenes [99]. Increased levels of LDH has been correlated with poor prognosis in cancer and is a hallmark of highly glycolytic tumors [25, 100]. In the later stages of gastric carcinogenesis, lactate and LDH seem to play an important role. Using oxamate, an inhibitor of LDH-A, Liu *et al* [101] demonstrated that lower levels of LDH-A decreased aerobic glycolysis, subsequently reducing the production of lactic acid in GAC cells. Altered cell morphology, impaired migration and proliferation, and increased apoptosis were also observed with the inhibition of LDH-A in GAC [101]. Additionally, the isoenzyme LDH-5 has been correlated with increased tumor and stromal vascular endothelial growth factor (VEGF) and is also a marker for poor prognosis in GAC [102]. Of note, the expression of one of the main LDH subunits, LDH-A, is also increased in cardia GC [103]. Further, increased expression of both LDH and dihydrolipoamide dehydrogenase (DLD) has been suggested to influence the development and progression of GAC [104].

3.3 Hypoxia

The rapid growth of cancer cells leads to the formation of new blood vessels; however, these new vessels are insufficient to sustain their accelerated growth. This leads to limited blood supply and hypoxia, which is a critical switch point for tumor cell metabolism. Consequently, tumors are heterogeneous tissues containing both oxygenated and hypoxic/glycolytic cell populations.

Hypoxic conditions induce the expression of Hypoxia-inducible factor 1 (HIF-1) [105], a critical transcription factor involved in the cellular responses to oxygen levels that increase tumor cell survival during hypoxia. HIF-1 promotes the expression of important glycolytic enzymes and transporters including the M2 isoform of pyruvate kinase (PKM2), pyruvate

dehydrogenase kinase 1 (PDK1), glucose transporters (GLUTs), enolase 1 (ENO1), hexokinase 2 (HK2), and LDH [106-110]. Importantly, HIF-1 can also be activated by lactate in an oxygen-independent manner [30-32].

HIF-1α is involved in angiogenesis, proliferation and metastasis [111]. HIF-1α expression is frequently found in several human solid tumors and its over-expression has been associated with poor prognosis in GAC [111, 112]. Further, a meta-analysis conducted by Lin *et al* [113] showed that HIF-1α positive expression was present in 50% of patients with GAC, and it was correlated with poor patient outcome. This appears to be mediated by HIF-1α contribution to chemoresistance and metastasis in GAC [114, 115].

3.4 Tumor microenvironment

The TME not only consists of tumor cells but also cancer-associated fibroblasts (CAFs) pericytes/endothelial cells, the extracellular matrix (ECM), and immune cells including tumor-associated macrophages (TAMs), neutrophils, eosinophils, natural killer cells, and lymphocytes. These heterogeneous cells have different metabolic profiles depending on oxygen, glucose and lactate availability. Epithelial cancer cells can induce a metabolic shift towards aerobic glycolysis of neighbouring stromal cells, for example CAFs, which produce and export lactate [116]. Lactate is later taken up by oxidative cancer cells through MCT1 [117]. This metabolic setting provides a fuel-supportive microenvironment that feeds epithelial tumor cells and supports tumor growth and angiogenesis. This model of lactate shuttling is termed “the reverse Warburg effect” and plays an important role in tumor growth and angiogenesis, increasing lactate production and secretion [118-120].

TAMs are among the most frequent inflammatory tumor infiltrating immune cells of the TME and play an essential role in tumor progression by promoting cell migration, invasion, and metastasis [121, 122]. Once released by cancer cells, lactate can be taken up by TAMs via MCT1 [30, 123]. Lactate has been shown to induce M2-like polarization of TAMs, which is mediated by HIF-α [30]. Interestingly, TAM infiltration has been associated with epithelial-mesenchymal transition (EMT) in GAC [124], which has been demonstrated to occur through the activation of the Wnt/β-catenin pathway [125]. Indeed, increased levels of TAMs and M2 infiltration in patients with GAC is associated with poor prognosis [125, 126].

4. Microbially-derived lactate in gastric carcinogenesis

4.1. Lactic acid bacteria in gastric carcinogenesis

The gastrointestinal microbiome plays an important role for the maintenance of energy metabolism, absorption of nutrients, shaping of the immune system, and protection against pathogenic microbes [127, 128]. It can influence health by the production of metabolites (e.g. butyrate) and pro-inflammatory compounds, dysregulation of cell proliferation and stem cells physiology, and alteration of the metabolism of chemotherapeutic agents [129-131].

The colonization density within the stomach ranges from 10^2 to 10^4 colony-forming units (CFU)/ml, being significantly lower than that in the healthy colon, which ranges from 10^{10} to 10^{12} CFU/ml [132]. This is partly due to the low pH of the stomach and other mucosa-associated mechanisms including peristaltic movement. *H. pylori* is currently considered the most abundant microbial species of the stomach [133-135]. Despite this, other microorganisms are also capable of colonizing the gastric mucosa.

1 **Table 1**. Summarised main findings of recent gastric microbiota studies.

Author/year	Ethnicity	Disease status (n)	Total Sample size	Biological samples	Microbiome	Main findings
Dicksved et al 2009	Swedish	GAC (10) FD (5)	15	Gastric biopsies (A and B)	16S rRNA gene amplification, T-RFLP and 16S rRNA gene sequencing (from six GAC samples)	No significant differences in microbiota composition between GAC and control group. Enriched genera in GAC: *Streptococcus*, *Lactobacillus*, *Veillonella* and *Prevotella*
Avilés-Jiménez et al 2014	Mexican	NAG (5) IM (5) GAC (5)	15	Gastric biopsies (A and B)	16S rRNA microarray G3 phylochip	Gradual change in the gastric microbiota profile from NAG to IM to GAC. Increased trend of *Lactobacillus colehominis* and Lachnospiraceae with carcinogenesis progression.
Wang et al 2016	Chinese	NAG (212) GAC (103)	315	Gastric biopsies (A)	qPCR (bacterial load in 315 patients) and 16S rRNA gene sequencing (in 12 subjects)	*Lactobacillus* and Lachnospiraceae uncultured are enriched in GAC. The gastric microbiota is altered in patients with GAC and is correlated with bacterial overgrowth and diversification. Enrichment of microbiota potentially associated with cancer-promoting activities.
Yang et al 2016	Colombian (Tumaco and Tuquerres)	Tuquerres NAG (10) Tuquerres MAG (8) Tuquerres MAG-IM (2) Tumaco NAG (12) Tumaco MAG (7) Tumaco MAG-IM (1)	40	Gastric biopsies (A, B, incisura angularis)	16S rRNA gene sequencing	Individuals from Tuquerres (town with 25-fold higher risk of GAC compared to Tumaco), had increased abundance of *Leptotrichia wadei*. *Veillonella*, *Actinomyces*, *Prevotella* and *Streptococcus* were correlated with the presence of MAG-IM.

Tseng et al 2016	Taiwanese	GAC (6, before and after tumour resection)	6	Gastric biopsies from tumour and non-tumour tissue	16S rRNA gene sequencing	Changes in the gastric microbiota composition, diversity and gene functions were found before and after surgical removal of GAC. Top genera before tumour resection: *Ralstonia*, *Helicobacter*, *Lactobacillus*, *Stenotrophomonas*, *Burkholderia*, *Bacillus*, *Curvibacter*, *Bdellovibrio*, *Sulfuritalea*, and *Legionella*.
Jo et al 2016	Korean	Healthy (16 HP+ and 13 HP-) GAC (15 HP+ and 19 HP-)	63	Gastric biopsies (A, B) and blood samples	16S rRNA gene 454-pyrosequencing	The gastric microbiota composition was not significantly different between cancer and control subgroups. Nitrate-reducing bacteria were increased in the cancer subgroup. Top genera in GAC and HP- subjects: *Stenotrophomonas*, *Streptococcus*, *Propionibacterium*, *Ralstonia* and *Citrobacter*.
Li et al 2017	Chinese	NAG (9, HP+) IM (9) GAC (7, tumour and non-tumour) HP- controls (8)	33	Gastric biopsies (A, B)	16S rRNA gene sequencing	HP reduces bacterial diversity in HP-infected patients and its eradication restores microbial composition. GAC samples have reduced bacterial diversity. Top genera in HP- individuals: *Haemophilus*, *Serratia*, *Neisseria*, and *Stenotrophomonas.*
Coker et al 2018	Chinese (Xi'an, 81)*	Superficial gastritis (21) AG (23) IM (17) GAC (20, tumour and non-tumour)	81	Gastric biopsies (A, B, fundus)	16S rRNA gene sequencing	Higher abundance and strong co-occurrence of oral bacteria in GAC. Top genera enriched in GAC: *Streptococcus*, *Lactobacillus*, *Peptostreptococcus*, *Gemella*, and *Fusobacterium.*
Yu et al 2017b	Chinese (80), Mexican (80)	Chinese cardia GAC (80) Mexican non-cardia GAC (80, tumour and non-tumour)	160	Gastric biopsies (Mexican: A, B; Chinese: C)	16S rRNA gene sequencing	HP and oral microbiota dominate the stomach of most patients with GAC. Top genera in non-malignant tissue: *Helicobacter*, Enterobacteriaceae (Chinese subgroup), and *Streptococcus* and *Lactobacillus* (Mexican subgroup).

Castaño-Rodriguez et al 2017	Ethnic Chinese (Malaysia and Singapore)	FD (20) GAC (12)	32	Gastric biopsies (A) and blood samples	16S rRNA transcript sequencing	HP infection status affects overall constitution of the gastric microbiota. Increased bacterial diversity in GAC. Enrichment of proinflammatory oral bacterial species in GAC. Increased abundance of LAB and upregulated SCFAs production metabolism. Top genera in GAC: *Lactococcus*, *Lactobacillus*, *Veillonella*, *Fusobacterium*, and *Leptotrichia.*
Sohn et al. 2017	Korean	FD (2 HP- and 3 HP+) GAC (2 HP- and 5 HP+)	12	Gastric biopsies (B) and blood samples	16S rRNA gene 454-pyrosequencing	Higher proportion of *Streptococcus mitis* group, including *S. pseudopneumoniae*, *S. mitis*, *S. infantis*, *S. oralis*, and *S. tigurinus* in HP- cancer subjects. Also, urease-producing and nitrate-reducing bacteria are enriched in this subgroup.
Ferreira et al 2018	Portuguese (135)**	Chronic gastritis (81) GAC (54)	135	Gastric biopsies (A, B)	16S rRNA gene sequencing and real-time qPCR	Higher dysbiosis and reduced bacterial diversity in GAC. Increased nitrate reductase and nitrite reductase functions in GAC. *Lactobacillus*, *Clostridium* and *Rhodococcus* are significantly enriched in GAC.
Hsieh et al 2018	Taiwanese	Gastritis (9) IM (7) GAC (11)	27	Gastric biopsies (A, B, C, fundus, and angle)	16S rRNA gene sequencing	Patients with GAC have an increased abundance of *Clostridium*, *Fusobacterium* and *Lactobacillus*. HP-infected patients exhibit a less diverse microbiota. Top species in GAC: *Clostridium colicans*, *Fusobacterium canifelinum*, *Fusobacterium nucleatum*, *Lactobacillus gasseri*, *Lactobacillus reuteri*, *Prevotella intermedia*, and *Prevotella oris*.
Hu et al. 2018	Chinese	Superficial gastritis (5) GAC (6)	11	Gastric mucosal washes	Shotgun metagenomics	Composition and function of the gastric microbiota differs between superficial gastritis and GAC individuals. HP prevalence was not significantly different between these two subgroups. Enrichment of 13 bacterial taxa and reduced species richness in GAC. Increased relative abundance of oral proinflammatory bacteria in GAC: strain *Porphyromonas_endodontalis*.t_GCF_000174815, species

						Streptococcus_mitis_oralis_pneumoniae and genus *Alloprevotella*.
Liu et al. 2019	Chinese	GAC (276)	276	Gastric biopsies (normal, peritumour and tumour)	16S rRNA gene sequencing	Gastric microbiota composition is altered in GAC and is determined by the stomach microenvironment but not by GAC stage or subtype. HP is decreased in the tumoral microhabitat and has a negative co-occurrence with *Prevotella, Bacteroides, Faecalibacterium, Phascolarctobacterium* and *Roseburia. Streptococcus, Selenomonas, Prevotella melaninogenica, Streptococcus anginosus* and *Propionibacterium acnes* were enriched in the tumoral microhabitat.

HP, *Helicobacter pylori*; HP+, HP-positive; HP-, HP-negative; A, antrum; B, body; C, cardia; GAC, gastric adenocarcinoma; IM, intestinal metaplasia; AG, atrophic gastritis; FD, functional dyspepsia; MAG, multifocal atrophic gastritis (without intestinal metaplasia); MAG-IM, multifocal atrophic gastritis with intestinal metaplasia; NAG, non-atrophic gastritis; qPCR, quantitative PCR; T-RFLP, terminal restriction fragment length polymorphism; LAB, lactic acid bacteria; SCFAs, short-chain fatty acids. * These results were validated in 126 Inner Mongolians (56 superficial gastritis, 51 AG and 19 GAC) **These results were validated in 38 Portuguese (15 chronic gastritis and 23 GAC), 53 Chinese (GAC) and 53 Mexican (GAC) subjects.

Using conventional culture methods, species belonging to the genera *Lactobacillus*, *Clostridium*, and *Veillonella*, were reported to be the most representative microbes in the healthy stomach [136]. Given that most of the microbes in the stomach are non-cultivable (approximately 80%), the development of new molecular methods, such as 16S rRNA gene sequencing, has led to a better characterization of the bacterial composition of the gastric environment. Several studies have reported consistent results in terms of the healthy gastric microbiota composition at the phyla level, although significant variability exists in relation to both abundance and dominance of lower taxonomic levels (Table 1). The most predominant phyla in the stomach are Proteobacteria (which includes *H. pylori*), Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria [133, 134, 137-141].

A number of studies have shown that *H. pylori* infection is associated with significant changes in the gastric mucosa [133, 138, 141-143] (Table 1). In fact, it has been suggested that in addition to being a direct promoter of GAC, *H. pylori* potentiates the transformation of the gastric mucosa into a hypochlorhidric environment [144-146], which would allow other microbes to colonize [135, 147, 148].

More recently, bacterial overgrowth that resulted in a significant alteration of the gastric microbiota, has been shown in patients with GAC [142]. To date, bacterial genera most consistently reported to be enriched in patients with GAC include *Lactobacillus*, *Streptococcus*, *Veillonella*, *Prevotella*, *Fusobacterium*, *Lachnospiraceae*, *Leptotrichia*, and *Clostridium* (Table 1). Interestingly, some of these bacteria are known to have detrimental effects in the stomach, despite being present in the normal intestinal flora [149, 150].

Most notably, recent reports show a consistent increase in abundance of lactic acid bacteria (LAB) in patients with GAC including *Streptococcus [140, 143, 151, 152]*, *Lactobacillus* [140-143, 153, 154], *Bifidobacterium* and *Lactococcus* [143] (Table 2). Importantly, this increase in abundance in LAB in GAC was found in the active gastric microbiota (RNA profiling) [143] and across different stages of the GAC cascade [141]. This suggests that this increase is not the result of non-viable bacteria or contaminating DNA. In support, *Lactobacillus, Bifidobacterium,* and *Streptococcus* have been found to be higher in GAC subjects using culture-based methods [155, 156]. These findings would suggest that microbially-derived lactate increases in the GAC cascade.

Supporting this, early work by Armstrong *et al* [157] showed increased levels of L-lactate, D-lactate and LDH in GC patients compared to patients presenting with gastric ulcers and healthy individuals, a highly relevant finding given that the D- stereoisomeric form is mostly produced by bacteria. More recently, Parsons *et al* [158] reported D-LDH to be overexpressed in gastric samples from *H. pylori*-induced atrophic gastritis patients as compared to samples from autoimmune atrophic gastritis patients. Given that D-LDH is required for the metabolism of D-lactate, these findings suggest that *H. pylori* infection results in modulation of microbial lactate metabolism in gastric precancerous lesions.

4.2 Mechanisms involved in gastric carcinogenesis

There is overwhelming evidence supporting the recent notion that the microbiome can influence cancer development and treatment [159]. In this context, it is plausible that microbial lactate can shape the TEM in a similar manner to host lactate considering LAB can produce up to 188 mM of D-lactate and 182 mM of L-lactate in just 48 hours [160]. There is limited evidence on the direct effect of LAB and their lactate on eukaryotic cells, however, Ohta *et al*

Table 2. Studies reporting enrichment of gastric microbial taxa of interest during gastric carcinogenesis.

Disease status	Lactobacillus	Streptococcus	Lachnospiraceae	Prevotella	Clostridium	Fusobacterium	Leptotrichia
IM		Yang *et al* 2016 Jo *et al* 2016		Yang *et al* 2016		Li *et al* 2017	Li *et al* 2017
GAC	Dicksved *et al* 2009 Avilés-Jiménez *et al* 2014 Tseng *et al* 2016 Wang *et al* 2016 Yu *et al* 2017b Castaño-Rodriguez *et al* 2017 Coker *et al* 2017 Ferreira *et al* 2018 Hsieh *et al* 2018	Dicksved *et al* 2009 Coker *et al* 2017 Yu *et al* 2017b Castaño-Rodriguez *et al* 2017 Hsieh *et al* 2018 Hu et al. 2018 Liu et al. 2019 Sohn et al. 2017	Avilés-Jiménez *et al* 2014 Wang *et al* 2016 Castaño-Rodriguez *et al* 2017 Coker *et al* 2017	Dicksved *et al* 2009 Coker *et al* 2017 Castaño-Rodriguez *et al* 2017 Hsieh *et al* 2018 Liu et al. 2019	Castaño-Rodriguez *et al* 2017 Ferreira *et al* 2018 Hsieh *et al* 2018	Castaño-Rodriguez *et al* 2017 Coker *et al* 2017 Hsieh *et al* 2018 Liu et al. 2019	Castaño-Rodriguez *et al* 2017

IM, intestinal metaplasia; GAC, gastric adenocarcinoma.

[16] have showed that LAB can turn human adult fibroblasts into multipotent cells resulting in cell clusters that incorporate LAB into their cytoplasm and show increased expression of *NANOG*, a known multipotency marker.

LAB have been widely shown to enhance gastrointestinal homeostasis, immunomodulation, availability of essential micronutrients and protection against cancer [161]. However, it has also been established that LAB are especially potent inducers of reactive oxygen species (ROS) generation in cultured cells and *in vivo* [162], which has been shown to induce DNA damage in colonic cells, suggesting contrasting impacts of LAB on the gastrointestinal tract [15]. Similarly, LAB have been shown to reduce nitrate to nitrite, which leads to the formation of large amounts of N-nitroso compounds [163, 164]. N-nitroso compounds promote mutagenesis, angiogenesis, protooncogene expression, and inhibit apoptosis [12-14]. In line with these observations, Ferreira *et al* [153] demonstrated that there is an increased functional activity of nitrate and nitrite reductases in the GAC microbiota as compared to the chronic gastritis microbiota.

The strongest *in vivo* evidence for a role of LAB in gastric carcinogenesis is based on studies using the Insulin-Gastrin (INS-GAS) transgenic mouse model, which overexpress human gastrin and spontaneously develop gastric atrophy [146, 165, 166]. Lertpiriyapong *et al* [146] reported that colonization of male INS-GAS mice with restricted microbiota consisting of *Lactobacillus murinus* ASF361, *Clostridium* ASF356, and *Bacteroides* ASF519, was sufficient to promote gastrointestinal intraepithelial neoplasias, which correlated with robust upregulation of pro-inflammatory and cancer-associated genes. These findings suggest that the stomach of subjects presenting with gastric atrophy may be more susceptible to the detrimental effects of colonization by opportunistic microbiota, including *Lactobacillus* spp. that are

present in the human oral cavity and esophagus [167]. Once LAB colonize the gastric atrophic mucosa, their capacity to induce immune tolerance [18] and their known anti-*H. pylori* microbial properties [19-21, 168, 169] could favor the establishment of other important carcinogenic pathobionts including *Veillonella*, *Prevotella*, *Fusobacterium*, and *Leptotrichia* [170-174], all of which are shown to be enriched in patients with GAC [140, 143, 152, 154, 175, 176]. This would be in accordance with a less simplistic scenario, in which gastric carcinogenesis is the result of early colonization with *H. pylori* followed by atrophic gastritis and subsequent colonization by pathobionts with synergistic effects, in a genetically susceptible individual.

5. Conclusions

Lactate not only acts as a fuel source for cancer cells but is also capable of promoting inflammation, angiogenesis, metastasis, and altering immune responses and key glycolytic enzymes, which could all result in poor disease outcome [22, 32, 177, 178]. The enrichment of LAB members, particularly in the later stages of gastric carcinogenesis, could have detrimental effects given that lactate is involved in all major steps of carcinogenesis (Fig. 1). LAB could influence GAC by a number of mechanisms that include increased production of exogenous lactate, ROS and N-nitroso compounds as well as increased EMT, immune tolerance and colonisation by other carcinogenic pathobionts (Fig. 1). Although *Lactobacillus* strains have been used as probiotics to control colonization of pathogens like *H. pylori* [20, 21, 169], and are suggested to have anti-proliferative and pro-apoptotic effects in cell-lines derived from GAC [179], the findings from human microbiome studies as well as animal models would caution against their use in patients with GAC. In fact, it may be worthwhile replacing LAB from the gastric environment of these patients through microbiome manipulation therapies. The mechanisms we highlight in this review may also be important in the context of other

gastrointestinal (e.g. esophagus) and female reproductive cancers, where LAB constitute a large proportion of the resident microbiomes.

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