

REVIEW

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# Gut microbes involvement in gastrointestinal cancers through redox regulation

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## Abstract

Gastrointestinal (GI) cancers are among the most common and lethal cancers worldwide. GI microbes play an important role in the occurrence and development of GI cancers. The common mechanisms by which GI microbes may lead to the occurrence and development of cancer include the instability of the microbial internal environment, secretion of cancer-related metabolites, and destabilization of the GI mucosal barrier. In recent years, many studies have found that the relationship between GI microbes and the development of cancer is closely associated with the GI redox level. Redox instability associated with GI microbes may induce oxidative stress, DNA damage, cumulative gene mutation, protein dysfunction and abnormal lipid metabolism in GI cells. Redox-related metabolites of GI microbes, such as short-chain fatty acids, hydrogen sulfide and nitric oxide, which are involved in cancer, may also influence GI redox levels. This paper reviews the redox reactions of GI cells regulated by microorganisms and their metabolites, as well as redox reactions in the cancer-related GI microbes themselves. This study provides a new perspective for the prevention and treatment of GI cancers.

**Keywords** Gastrointestinal microbes, Gastrointestinal cancers, Redox, Reactive oxygen species, Oxidative stress

## Introduction

According to Global Cancer Statistics 2020, gastrointestinal (GI) cancers, including colorectal cancer and gastric cancer, account for approximately one-third of the total global cancer incidence and mortality [1]. The GI tract is estimated to contain over 70% of all microbes in the human body [2]. Arguably, the most important microbial

communities in humans can be found in the GI tract. A finely regulated relationship exists within the GI tract, however, microorganisms essential for host health can also contribute to the occurrence and development of GI cancers [3–5]. For example, *Helicobacter pylori* induces gastric cancer by modulating CagA, the oligotoxin VacA allele and other cytokines that affect the body's immune system [6, 7]; *Haemophilus ducreyi* induces cell cycle arrest by inducing the tripartite cytolethal distending toxin that creates DNA lesions [8]; *Enterococcus faecalis* mediates colorectal cancer (CRC) by producing genotoxic peroxides that influence the cell cycle and ploidy precipitation [9, 10]; *Salmonella* promotes CRC by releasing the multifunctional protein AvrA, which inhibits  $\beta$ -catenin degradation, or by altering  $\beta$ -catenin ubiquitination and acetylation levels [11].

The reduction and oxidation (redox) state of the GI tract depends on the balance of antioxidants and oxidants. Common antioxidants in the GI tract are

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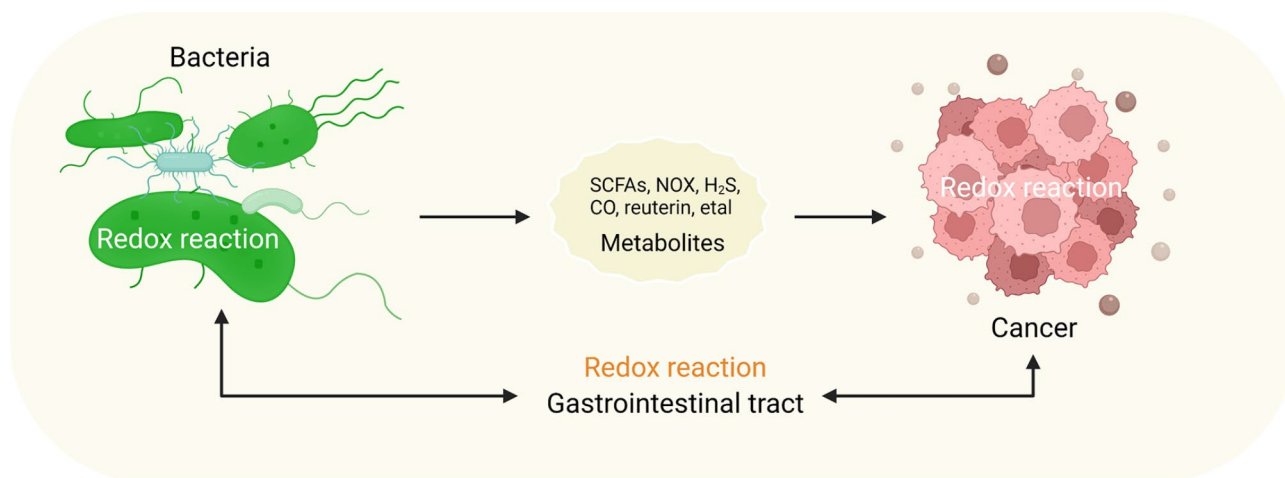
glutathione and superoxide dismutase (SOD) [12–14]. In addition, common oxidants in the GI tract are free radicals, including superoxide ( $O_2^{\cdot-}$ ) and hydroxyl ( $OH\cdot$ ); reactive oxygen, including hypochlorous acid (HOCl) and hydrogen peroxide ( $H_2O_2$ ); nitrogen species, including nitric oxide (NO) and nitrogen dioxide ( $NO_2$ ); and sulfur species, including hydrogen sulfide ( $H_2S$ ), persulfides and polysulfides [14–22]. When the redox state is unbalanced due to an increase in oxidants or a decrease in antioxidants, GI cells undergo oxidative stress. Exogenous and endogenous sources of antioxidants and oxidants both have effects on the overall redox state of the GI tract. Xenobiotics, including gut microbes, are important regulators of redox potential in the GI tract. For example, Sannasimuthu A et al. found that mice treated with broad-spectrum antibiotics showed a change in the “redox potential” of their gut environment [23]. Mitochondrial respiratory chain enzymes, including the cytochrome P450 enzyme family and xanthine oxidase in the endoplasmic reticulum, cytoplasm and nuclear membrane, are the main endogenous sources [24–26]. Homeostasis of GI cells is influenced in a variety of ways by the GI redox state, including modulation of signal-transduction pathways, induction of DNA strand breaks and modifications of proteins and lipids [27–29]. Oxidative stress has been implicated in a series of GI diseases, including GI cancers [30].

GI microbes are involved in the occurrence and development of GI cancers and influence the redox level of the GI tract. Understanding the regulatory mode of GI microbes from the redox view may be a guide for the prevention and treatment of GI cancers. Therefore, this paper reviews the redox changes in cancer-related GI microbes and cancer cells affected by GI microbes and their metabolites in detail (Fig. 1).

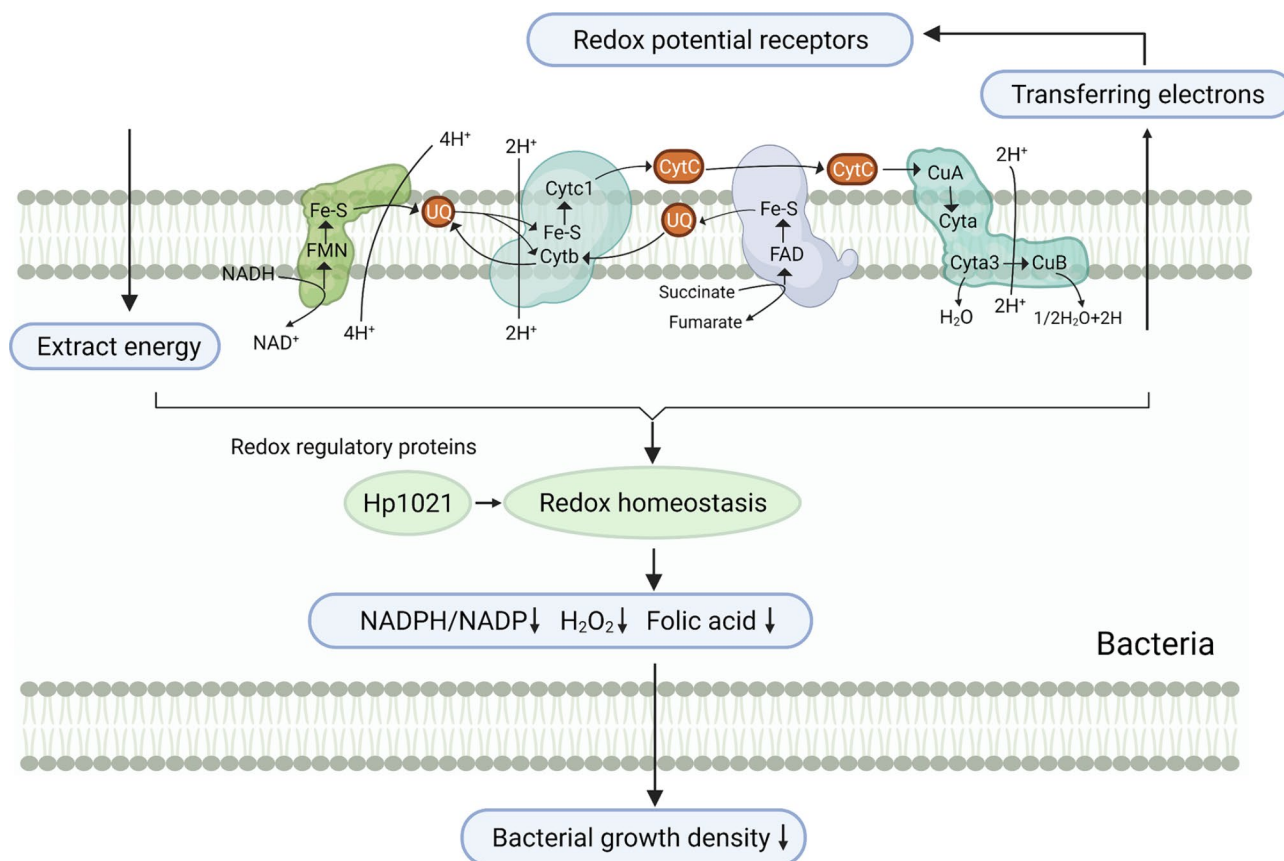
### Redox reactions in carcinogenic bacteria influence redox balance in the GI tract

GI bacteria are one of the sources of GI redox potential, and there are redox systems, including the respiratory chain, in GI bacteria. Bacteria are prokaryotes, and their respiration mainly occurs on the cell membrane and is catalyzed by enzymes on the cell membrane. Therefore, the cell membrane is the main site of oxidizing agents produced by bacteria. Most oxidants in bacteria are produced by a continuous univalent electron transfer reaction of oxygen molecules catalyzed by enzymes in the respiratory chain (Fig. 2). For example, *Escherichia coli* produces approximately 87% hydrogen peroxide in its respiratory chain [31]. Microbes use a very complex electron transport system to extract energy from the intestinal environment, while the bacterial respiratory cascade ultimately transfers electrons to higher redox potential receptors in the extracellular space. During normal bacterial proliferation, this universal, inducible electron outflow mechanism leads to changes in the redox potential in the GI tract, the extent of which depends on the growth stage, microbial population, and physiology of the organism [32]. The GI redox potential is also related to the intestinal microbial composition. For example, intestinal oxidation status was negatively correlated with the abundance of *Lactobacillus* and *Bifidobacterium* and positively correlated with the abundance of *Escherichia coli* [33].

Carmelini et al. indicated that bacterial cells respond to oxygen stress in the GI tract by slowing growth and regulating the expression of proteins involved in carbohydrate uptake and metabolism, redox homeostasis, the DNA damage response and bacterial movement [34]. *Clostridium butyricum* responds to obvious redox during the growth process by changing from an oxidized state to a reduced state and growing at a slower rate. When



**Fig. 1** The relationship between bacteria, their metabolites, and cancer involves redox reactions. Bacteria and their metabolites regulate cancer through redox reactions



**Fig. 2** Redox reactions in bacteria regulate the redox level of the gastrointestinal tract. Bacteria obtain the energy needed for growth through the respiratory chain and transfer electrons in vivo and in vitro through the respiratory chain at the same time, thereby regulating the redox level in vivo and in vitro. Redox regulatory proteins such as HP120 exist in bacteria. Oxidative metabolism in bacteria can affect the production of its metabolites, such as folic acid. Reduced production of folic acid contributes to the occurrence of cancer. The change in redox level in the gastrointestinal tract caused by bacteria can also affect the growth of other bacteria

*Clostridium butyricum* cells undergo stress, the expression levels of several genes are upregulated, including those associated with pyruvate metabolism, the conversion of acetyl-CoA to acetaldehyde and the stress response [35]. *Helicobacter pylori* is a microaerobic carcinogen that encodes a redox switch protein, Hp1021. The cysteine residues of Hp1021 are sensitive to oxidation in vitro and in vivo, and the DNA-binding activity of Hp1021 to oriC depends on the redox state of the protein. Hp1021 is directly involved in the oxygen-dependent control of the *Helicobacter pylori* feca3 and GLUP genes, which are related to the oxidative stress response [36]. Menadione and H<sub>2</sub>O<sub>2</sub> have been used to induce oxidative stress in the model intestinal bacterium *Enterococcus durans* (MTCC 3031). Oxidative stress significantly reduced the redox ratio (NADPH/NADP) by 55% (menadione) and 28% (H<sub>2</sub>O<sub>2</sub>). The reduction in the redox ratio caused by oxidative stress decreased bacterial folate

synthesis. Reduced folic acid levels can induce colorectal cancer [37]. In addition, oxidative stress significantly reduced bacterial growth density by 61% (menadione) and biological yield by 21% (H<sub>2</sub>O<sub>2</sub>) [38].

### GI bacteria induce oxidant and antioxidant production in cancer cells

Several types of gut bacteria can influence the production of oxidants and antioxidants in gastrointestinal cells [39]. Oxidants produced by gastrointestinal cells drive abnormal cell proliferation and survival by activating signaling pathways such as HIF-1 $\alpha$ . Wen J, et al. indicated that *Helicobacter pylori* infection could significantly upregulate the expression of AQP3 and HIF-1 $\alpha$  in human gastric epithelial AGS and GES-1 cells and increase ROS levels. *Helicobacter pylori* infection could stimulate the ROS-HIF-1 $\alpha$  axis and ROS-HIF-1 $\alpha$ -AQP3-ROS ring, promoting the occurrence of gastric cancer [40]. Zhang X

et al. reported that *Lactobacillus* stimulated the production of NADPH oxidase-1 (Nox1)-dependent ROS and induced cell proliferation of GI stem cells [41]. Lesiow MK et al. showed that under the stimulation of two fragments of FomA adherin from *F. nucleatum* and its complexes with copper (II) [Cu(II)-Ac-KGHGNG-NH<sub>2</sub> (1Cu) and Cu(II)-Ac-PTVHNE-NH<sub>2</sub> (2Cu)], large quantities of hydroxyl radicals were produced inside and outside of colon cancer CT-26 cells. The intense oxidative stress caused by these compounds could trigger a cascade of free radicals in CT-26 cells, leading to substantial lipid peroxidation [42]. Microbes in the GI tract may also increase oxidation levels by reducing antioxidant levels. For example, Nie Seru et al. found that *Clostridium* infection in gastric cancer was negatively correlated with three metabolites, including glutathione, uric acid and pyrophosphate, and confirmed that glutathione levels decreased if the nuclear abundance of *Clostridium* was high. In addition, some microorganisms in the GI tract can reduce high oxidation levels by upregulating the expression of antioxidants in GI cells [43]. In GES-1 cells with acute infection, nuclear *Clostridium* upregulated GSH peroxidase 4 (GPX4) and GSH synthetase (GSS) expression and reduced glutathione (GSH) to oxidized glutathione (GSSG), resulting in the reduction of intracellular ROS levels and increasing the ability of cells to combat self-damage [44]. Wang Yue et al. showed that *Streptococcus thermophilus* CGMCC 7.179, under oxidative stress induced by 2 mM H<sub>2</sub>O<sub>2</sub>, could improve the activities of major antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) in CRC HT-29 cells and protect CRC cells against oxidative stress [45, 46].

### **Excess oxidants from the GI tract or GI cells may be involved in the destruction of DNA, proteins and lipids in cancer cells**

#### **Excess oxidants are involved in cancer cell DNA damage**

GI symbiotic microbes affect genomic stability in GI cells by overproducing oxidants. *Enterococcus faecalis* and *Bacteroides fragilis* have been found to be associated with colorectal cancer, and *Enterococcus faecalis* and *Bacteroides fragilis* infection are accompanied by excess ROS production [47, 48]. ROS can induce DNA base oxidation (e.g., formation of 8-oxo guanine) and single strand breaks, which can be repaired by base excision/single strand breaks. Both base excision repair and single strand break repair are performed by DNA polymerase, which forms long or short fragments that are ligated under the action of DNA ligase III or DNA ligase I. If single strand breaks and base excision repair/single strand break repair occur simultaneously on opposing strands, DNA double-strand breaks can be generated [49–52]. Wang S et al. found that *Helicobacter pylori* infection could induce

gastric cancer cells to activate the NF- $\kappa$ B signaling pathway and upregulate peroxyredoxin2 (PRDX2) expression [53, 54]. ROS can affect replication fork progression through the dissociation of PRDX2 oligomers. PRDX2 can form a replica-related ROS sensor. The ROS sensor is combined with the DNA replication fork accelerator Timeless. The increase in ROS leads to the separation of PRDX2 and Timeless, thus slowing the speed of replication bifurcation [55]. Oxidized bases occurring from ROS activity also present a physical obstacle to replication forks, resulting in the breakdown of replication forks at fragile sites across the genome [56, 57]. Fork breakdown leads to DSBs and ultimately underreplicated or overreplicated DNA, with concomitant genomic instability in cancer cells. Chronically high ROS levels can outpace a host's DNA repair mechanisms, leading to DNA damage and mutations [58]. At present, ROS have not been found to directly affect the function of DNA double-strand break repair proteins. Break-induced replication has been recently implicated in the repair of replication stress or nuclease-induced DNA double-strand breaks at telomeres [59]. With the clinical implications of interfering with DNA repair pathways becoming apparent, the direct effect of bacteria-inducing ROS on DNA repair proteins requires more investigation.

#### **Excess oxidants are involved in the redox modifications of proteins in cancer cells**

Multiple studies have suggested that ROS participate in a series of biological processes, such as metabolism and oxidative stress defense. The common mode of action of ROS is to react with the nucleophilic mercaptan group (–SH) in a specific protein cysteine, which results in a series of oxidative posttranslational modifications (oxiPTM). Mercaptan can be oxidized to S-sulfinic acid (–SOH) by ROS. S-sulfinic acid has high activity and can be continuously converted into more stable forms, including S-sulfinic acid (–SO<sub>2</sub>H) and disulfide (–SS–). The cysteine regulation of reversible oxidized proteins is an important mechanism that changes the function of proteins after translation [60, 61]. The metabolic enzymes in many metabolic processes, including glycolysis, the tricarboxylic acid cycle, lipid metabolism, energy metabolism and amino acid metabolism, could be regulated by redox modification [62–64]. *Escherichia coli* may induce metabolic reprogramming changes in heterogeneous cancer cell populations by modulating glycolytic pathway-inducer genes and oxidative phosphorylation-related genes (such as pyruvate dehydrogenase kinase 1, pyruvate dehydrogenase phosphatase, and malonyl-CoA-acyl carrier protein transacylase). After metabolic reprogramming, the migration and self-renewal capacity of cancer cells can be enhanced [65]. ROS produced by bacteria and GI cells can oxidize cysteines 45 and 392 of PDHK2

(Cys45 and Cys392), thereby inhibiting PDHK2 activity, dephosphorylating PDH, and ultimately promoting the tricarboxylic acid cycle [66]. As a result, cancer cells can continuously obtain the energy they need to survive.

**Excess oxidants are involved in the redox modifications of lipids in cancer cells**

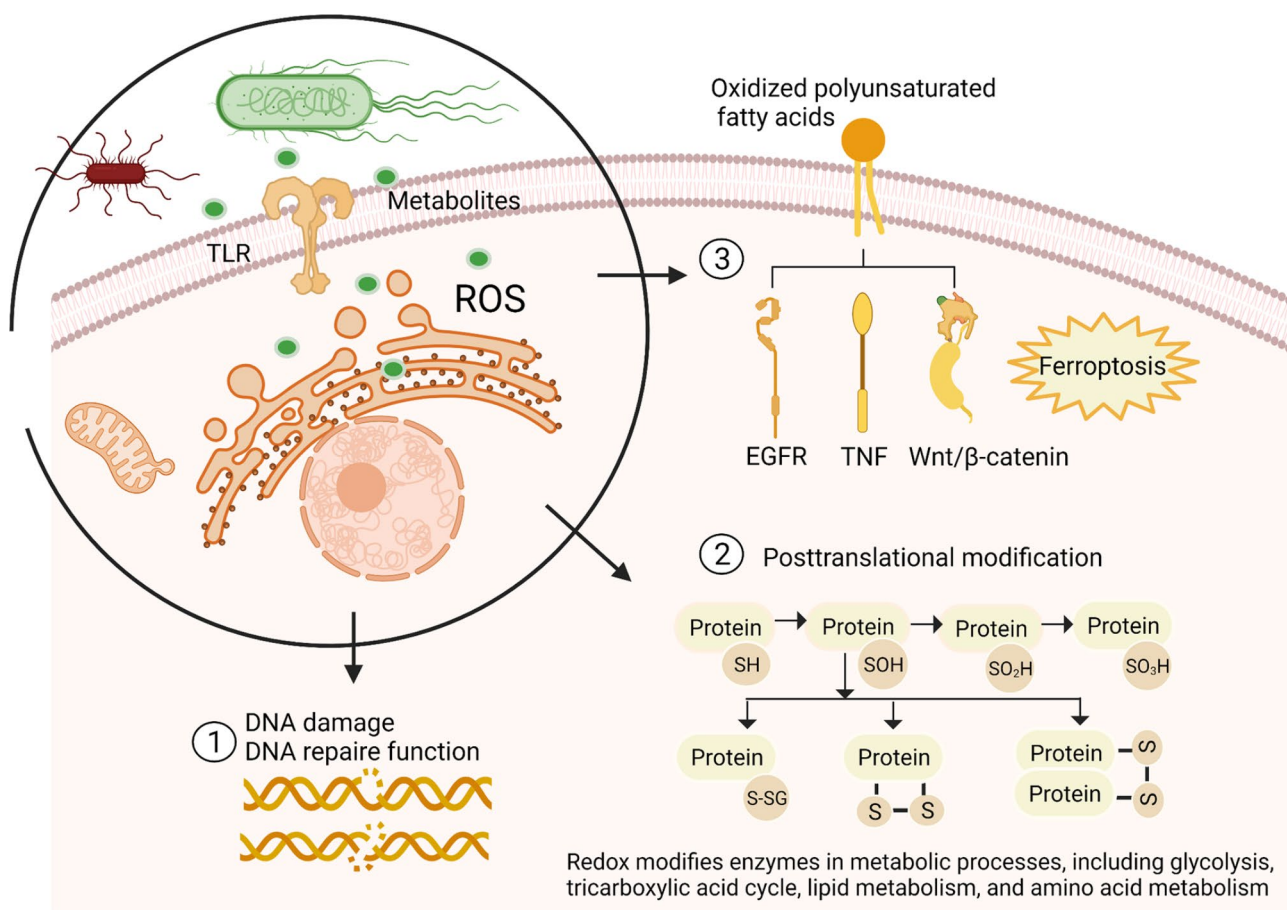
Lipids are one of the main structural and functional components of biological tissue, especially the cell membrane. After lipid peroxidation, GI cell membrane fluidity and cell membrane properties are changed [67, 68]. Excess peroxidation of free radicals can lead to iron overload [69]. Membrane-associated phospholipid peroxide glutathione peroxidase (GPX4) protects against iron-associated cell death by preventing the accumulation of lipid peroxide, demonstrating the damage of excess oxidants to lipids on GI cancer cell membranes [70]. Oxidants on

the GI cell membrane regulate signaling receptors on the cell membrane and various downstream signaling pathways, including cytokines such as tumor necrosis factor (TNF) and growth factors such as epidermal growth factor receptor (EGFR)[71]. Alterations in signaling receptors on the membrane of GI cancer cells can affect the function of cancer cells.

Excess ROS-mediated destruction of DNA, proteins and lipids is shown in Fig. 3.

**Microbial metabolites are involved in cancer cell redox reactions**

Bacteria can interact with GI cancer cells by secreting metabolites, including short-chain fatty acids (SCFAs), sulfides, gas molecules and even specific metabolites.



**Fig. 3** Bacteria regulated redox reactions in gastrointestinal epithelial/cancer cells. Bacteria link to gastrointestinal epithelial/cancer cells through their receptors or secreting metabolites, affecting the release of ROS from gastrointestinal epithelial/cancer cells. The overproduction of ROS can lead to DNA single strand breaks, DNA double strand breaks, DNA recombination repair system damage, and DNA mutations. Excess ROS mainly act on the sulfhydryl (RSH) side chain of the active cysteine of the protein (metabolism-related enzyme). In response to ROS, the reduced sulfhydryl groups on cysteine deprotonate and are oxidized to form sulfenic acids (RSOH). Subsequently, sulfonic acid can react with o-sulfhydryl groups to form intramolecular or intermolecular disulfide bonds (RS-SR or RS-SR') or bind to glutathionylation (RS-SG) of glutathione (GSH). Sulfonic acid can also be further oxidized to form sulfonic acids (RSO<sub>2</sub>H) or sulfonic acids (RSO<sub>3</sub>H). The modified protein usually loses activity or function. Excess ROS react directly with polyunsaturated fatty acids on the cell membrane, causing cell membrane protein damage and influencing signal receptors on the cell membrane and various downstream signaling pathways, including the EGFR, TNF, and Wnt signaling pathways

### SCFAs compete against oxidative stress in cancer cells

Colonic bacteria such as *Clostridium butyricum* and *Lactobacillus* can produce SCFAs, which mainly include acetate, butyrate acid, lactate, and propionate acid. The health benefits of SCFAs are related to their ability to regulate gene expression [72–75]. For example, *Escherichia coli* can mediate the protective effect of SCFAs on oxidative stress through the KEAP1-NRF2 signaling pathway. Under static conditions, NRF2 is blocked by its cytoplasmic inhibitor KEAP1 (Kelch-like ECH-associated protein 1). However, under oxidation and electrophilic stress, NRF2 can be synthesized and accumulate in the nucleus. NRF2 binds small Maf protein to antioxidant response elements (ARE) in target gene promoters and upregulates the expression of phase II enzymes and antioxidant enzymes to combat oxidative stress [76]. The epigenetic regulation of butyrate-induced NRF2 nuclear translocation is the main mechanism of antioxidant action [77]. Inhibitor for the apoptosis-stimulating protein of p53 (IASPP) in cancer cells can improve the stability of the NRF2 protein and promote the nuclear translocation of NRF2 by competitively binding the main inhibitory factor Keap1 of NRF2 with the DLT amino acid sequence (motifs) located at its N-terminus. NRF2 transcriptional activation of its downstream antioxidant target genes (such as NQO1, HMOX1 and FTH1) plays a role in ROS inhibition [78]. Moreover, Pant K et al. reported that butyrate could induce ROS-mediated apoptosis by modulating the miR-22/SIRT-1 pathway in hepatic cancer cells [79]. Inoue T et al. reported that butyrate could mediate ROS-related apoptosis through a complex signaling feedback loop involving p21, ROS, and p53 [80, 81]. Schlörmann W et al. reported that butyrate could mediate ROS-related proliferation and apoptosis by regulating antioxidant-relevant proteins (Cyclin D2, p21, PARP, Bid, GPx2) in colon cancer cells [82].

### Gas molecules are involved in cancer cell antioxidative stress

Sulfur-metabolizing microbes, including *Bilophila wadsworthia*, *Fusobacterium nucleatum*, and *Desulfovibrio*, have the capacity to metabolize organic compounds for energy and reduce dietary sulfur to hydrogen sulfide ( $H_2S$ ) [83, 84]. The abundance of sulfur-reducing bacteria in the colonic mucosa of patients with CRC, such as *Bilophila wadsworthia* and *Pyramidobacter*, was higher than that of healthy individuals [85, 86].  $H_2S$  is mainly synthesized by L-cysteine and L-homocysteine through cystathionine- $\beta$ -synthase, 3-mercaptopyruvate thio-transferase (3-MST) and cysteine- $\gamma$ -lyase (CTH/CSE). At 37 °C and pH 7.4, excess  $H_2S$  molecules can dissolve in water and decompose into  $H^+$ ,  $HS^-$  and  $S^{2-}$  ions.  $HS^-$  has strong single-electron chemical inertia and has considerable scavenging capacity for ROS. Excessive

$H_2S$  production may inhibit carcinogenesis through several mechanisms, including the Wnt signaling pathway, microRNA regulation and cancer metabolism. For instance, excess  $H_2S$  can upregulate the expression of miR-200b and miR-22. Wnt1 was found to be a target of these two miRNAs, and a synergistic effect between miR-200b and miR-22 in the inhibition of gastric cancer growth was reported [87–89].

*Nitrobacter* and *Nitrosomonas* can produce NO in the gut [90]. The interaction between  $O_2$  and NO leads to the formation of peroxynitrite (ONOO). The increased reactivity of peroxynitrite leads to the production of various other NO-derived factors, called reactive nitrogen species (RNS), including reactive radical compounds nitrogen dioxide ( $NO_2$ ), hydroxyl radical (HO), and non-free radical dinitrogen trioxide ( $N_2O_3$ ). ONOO, together with RNS, is responsible for protein tyrosine residue nitrosation, mitochondrial energy consumption, and the induction of DNA strand breaks [91–93]. NO in the sub-micromolar range ( $<1 \mu M$ ) can reversibly inhibit cytochrome-c oxidase. It may transiently increase the leakage of superoxide from the electron transport chain. Then, superoxide can react with NO to generate peroxynitrite, which inactivates the iron/sulfur centers in cancer cell mitochondria and causes irreversible injury to the mitochondria [94]. Nitrite ( $NO_2^-$ ) and nitrate can transfer an (NO)+ moiety to exocyclic amino groups of DNA bases (purine nucleosides and nucleotides). N-nitro tyrosine residues produce uracil. Removal of uracil by uracil glycosylase without restoration of cytosine leaves an abasic site. A lesion is commonly misrepaired by insertion of adenine opposite the site during replication. Misrepair can produce a G:C-A:T transition. Hence, nitrification and deamination may lead to genetic changes in living cells [95]. High concentrations of exogenous NO are mainly toxic to cells and microorganisms, which is reflected in the inhibition of bacterial growth and the regulation of biofilm formation [96]. During cancer chemotherapy, NO can accumulate in cancer cells, resulting in cytotoxic and anticancer effects [97].

Other gaseous molecules, such as  $H_2O_2$  [98, 99] and  $H_2$  [100, 101], are additional metabolites of microorganisms that may play important roles in multiple systems throughout the body.

### Specific metabolites are involved in regulating cancer cells

*Lactobacillus reuteri* and its oxidation metabolite reuterin inhibit ribosomal biogenesis and downstream protein translation in SW480 cell lines, thereby inhibiting cancer growth in vitro [102]. *Lactobacillus reuteri* is a natural colonizer of the human gut, and reuterin is an intermediate product of the conversion of glycerol to 1,3-propanediol [103]. Reuterin is a highly selective electrophilic substance that can interact with cysteine,

resulting in irreversible oxidation, loss of protein function, and cell death [104]. Sodium sulfide protects colorectal cancer cells from reuterin-induced growth inhibition by binding to cysteine, resulting in protective and reversible oversulfidation that prevents protein oxidation.  $\beta$ -Galactosidase secreted by *Streptococcus thermophilus* can inhibit cell proliferation, reduce colony formation, induce cell cycle arrest, promote apoptosis of cultured CRC cells and retard the growth of CRC xenografts. The  $\beta$ -galactosidase-dependent production of galactose interferes with energy homeostasis to activate oxidative phosphorylation and downregulate Hippo pathway kinases, partially mediating the anticancer effects of *S. thermophilus* [105]. *Lactobacillus brevis* can produce NADPH oxidase (NOX) in an aerobic environment [106]. ROS produced by NOX inactivate nucleoredoxin, thus releasing nucleoredoxin-dependent Wnt- $\beta$ -catenin signal inhibition through the separation of nucleoredoxin and dishevelled. NOX inhibits the response of cells to Wnt, including stabilizing  $\beta$ -catenin, expressing cyclin D1 and c-Myc through the TCF transcription factor, and accelerating cell proliferation. In colon cancer cells with a normal Wnt pathway, Nox1 mediates Wnt-induced cell growth, but not in APC-deficient colon cancer cells, which have constitutive Wnt signaling activity [107, 108].

### Application and treatment

ROS concentration is directly related to cancer cell death. Regulating ROS concentrations can be a cancer therapy strategy [109]. Based on this, synthetic biological modification of bacteria to regulate redox levels in the gut has been developed as a potential anticancer treatment. Fan et al. designed and engineered a bacterium, *Escherichia coli* MG1655, which overexpressed the NDH-2 (Type-II NADH-Menaquinone Oxidoreductase) enzyme to colonize cancer areas and increase local  $H_2O$  production. In their study, magnetic  $Fe_3O_4$  nanoparticles were covalently linked to bacteria to convert  $H_2O_2$  into toxic hydroxyl radicals ( $\bullet OH$ ) for cancer treatment [110]. *Escherichia coli* Nissle 1917 (EcN) is an oral probiotic that has been genetically engineered to overexpress catalase and superoxide dismutase to restore redox levels in the gut, thereby alleviating GI diseases [111]. *Onaيدا Shewanella* MR-1 (SO) can selectively use lactic acid instead of glucose as an energy source for respiration. During lactic acid consumption, SO can simultaneously mediate the electron transfer process that transforms reduced iron ions to bivalent iron ions. The resulting ferric ions can also be reoxidized to ferric ions by overexpressed hydrogen peroxide, thus achieving cyclic lactic acid catabolism. Using the principle of SO redox, an *Onaيدا Shewanella*-coupled MDH (an MOF material loaded with adriamycin) self-driven bioreactor was constructed. SO@MDH

can enhance the chemotherapy effect of GI tract cancer and alleviate cancer [112–114].

Restoring ROS levels in the GI tract is a favorable way to alleviate GI diseases, including cancer. ROS nanoscavengers can be delivered to the GI tract to enhance the clearance of ROS by using the intestinal colonization ability of probiotics. In addition, a protective layer can be included on the surface of probiotics to enhance the environmental resistance and intestinal adhesion of probiotics and regulate the balance of GI microbes [115–118]. For example, the probiotic *Saccharomyces cerevisiae* JKSP39 might regulate GI microbes by reducing the levels of ROS (myeloperoxidase, superoxide dismutase, catalase,  $H_2O_2$ , and malondialdehyde) to inhibit endoplasmic reticulum (ER) stress [115]. Hydrogel-coated *Lactobacillus reuteri* could partially remove ROS from the GI tract and protect colon HT-29 cells from oxidative damage [116]. EcN can restore ROS levels in the GI tract, enhance the abundance and diversity of GI microbes, and prevent and treat CRC-related diseases such as colitis. The retention time of EcN in the GI tract can be prolonged by coupling hyaluronic acid-polypropylene sulfide nanoparticles (HPNs) to the surface of modified EcN using a polymer of hyaluronic acid-polypropylene sulfide (HA-PPS) and encapsulating EcN cells with a polynorepinephrine layer. The prolonged presence of HPN-NE-EcN in the gut assists the ROS scavenging ability of EcN, thereby alleviating GI diseases [117].

### Conclusion

A large number of studies have shown that GI microbes such as *Escherichia coli* and *Helicobacter pylori* play an important role in the development of GI cancer. GI bacteria participate in the regulation of redox potential in the GI tract through the electronic respiratory chain and the release of metabolites. GI bacteria dynamically regulate their redox reaction according to the redox potential in the GI tract. GI bacteria can also regulate the redox potential of cancer cells by affecting the production of oxidants and antioxidants in GI cancer cells. Once oxidants (such as ROS) from the GI tract or cancer cells are present, the redox balance and homeostasis of cancer cells are destroyed. This imbalance causes redox-mediated modifications of various cellular components, such as DNA, lipids and proteins that then change the function of cancer cells. However, GI bacteria can also combat oxidative stress in cancer cells by releasing substances such as short-chain fatty acids, NO, and specific metabolites such as Reuterian proteins and NADPH oxidase.

In conclusion, GI microbes play an important role in the regulation of GI cancer-related redox levels. Using GI microbes to reduce ROS levels in the GI tract may be a beneficial pathway for alleviating GI diseases, including cancer.

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## Authors' contributions

Wang Yangyanqiu, Chu Jian, Yang Yuqing and Qu Zhanbo drafted the manuscript and draw the figures. Han Shuwen conceptualized the idea and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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## Data availability

Not applicable.

## Declarations

### Competing interests

The authors declare no competing interests.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Conflict of interest

The authors declare no conflict of interest.

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