Review

Inflammation, oxidative stress, DNA damage response and epigenetic modifications interact behind the beneficial actions of melatonin on *H. pylori*-mediated gastric disorders

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ABSTRACT

Helicobacter pylori (*H. pylori*) infection is associated with several disorders of the gastrointestinal tract, including gastric cancer. Studies of ours and others suggest that *H. pylori* infection may affect melatonin synthesis in the gastric epithelial cells. On the other hand, melatonin ameliorates gastric disorders as shown in clinical trials and experimental studies. Moreover, melatonin not only suppresses the DNA-damaging reaction of diet-related mutagens that can initiate carcinogenesis in gastric mucosa, but also the oxidative DNA damage evoked by reactive oxygen and nitrogen species produced during *H. pylori*-related gastric inflammation. *H. pylori* infection is associated with several functional and organic gastric disorders, including gastritis, peptic ulcer disease and gastric cancer, but the precise mechanism behind this association is not known and many pathways can be involved. Some of beneficial effects of melatonin in the gastrointestinal tract are underlined by mechanisms that likely play a role in detrimental effects of *H. pylori* in the stomach. Therefore, melatonin may modulate these mechanisms resulting in ameliorating *H. pylori*-related symptoms. In this narrative review the role of inflammation, oxidative stress, DNA damage response and epigenetic modifications in *H. pylori*-associated gastric disorders will be discussed with an emphasis on gastric cancer. We also suggest that melatonin may have potential to inhibit *H. pylori*-mediated pathologies through its interaction with essential pathways as described herein. Overlapping mechanisms of *H. pylori*-associated pathogenesis and beneficial effects of melatonin justify further studies on the action of melatonin on gastric disorders associated with *H. pylori* infection, including clinical trials.

Key words: *H. pylori*, gastric mucosa, gastrointestinal disorders, gastric cancer, inflammation, reactive oxygen and nitrogen species (ROS/RNS), DNA damage response, epigenetic regulation, melatonin

1. INTRODUCTION

Helicobacter pylori (*H. pylori*) is indigenous to the human population and adapted so well to the human gastric mucosa that the rate of spontaneous eradication is as low as about 1% per year (1). Therefore, it is not surprised that the prevalence of *H. pylori* lies in the range from less than 40 to more than 70%, depending on country (2). In other words, *H. pylori* has colonized half of the world populations. In most cases, the infection is syndrome-less, but, it also associates with functional and organic diseases of the gastrointestinal (GI) tract, including gastric cancer in some individuals. The fraction of infected individuals with gastric cancer is estimated as 1-2% (3). The mechanism of the involvement of *H. pylori* in gastric carcinogenesis is complex and not fully known, but besides bacterial virulence and host genetic susceptibility, it includes environmental and lifestyle factors such as nutrition (4). The influence of the diet on the *H. pylori*-related gastric cancer is still the matter of debate (5). Melatonin, which is considered as a dietary supplement in the US and many other countries, shows anticancer properties in numerous studies and several mechanisms, including inflammation angiogenesis, cell cycle regulation, apoptosis, autophagy, endoplasmic reticulum stress and oxidative stress, may lay behind these properties [reviewed in (6, 7)]. We have shown an impaired melatonin synthesis in *H. pylori*-infected patients and beneficial effects of dietary supplementation with melatonin on the outcome of some functional GI disorders (8-11). However, there is no study on the effect of melatonin supplementation on the outcome of *H. pylori*-mediated GI diseases.

There are several common pathways in the pathogenic action of *H. pylori* and biological activity of melatonin, but oxidative stress may be the most pronounced candidate linking these two features. However, oxidative stress is reported to implicate in the pathogenesis of many diseases and is usually understood as a general term including many molecular pathways. In this narrative review we provide basic information on *H. pylori*-mediated mechanisms of GI disorders first of all gastric cancer. These mechanisms include inflammation, the action of reactive oxygen/nitrogen species (ROS/RNS), DNA damage response and epigenetic regulation of gene expression. We also present the rationale for further studies, including laboratory research and clinical trials, on melatonin as a protective agent against *H. pylori*-related GI disorders.

2. ROS AND RNS-MEDIATED PATHOGENICITY OF *H. PYLORI*

H. pylori has been classified by the International Agency for Research on Cancer as a group I carcinogen and is the only representant of the bacterial domain in this group (12). At present, the molecular mechanism of the involvement of *H. pylori* in gastric carcinogenesis is not clear, but it may result from either indirect or direct effects of the bacteria in the gastric epithelial cells (13). The indirect action is underlined by the induction of gastritis with the involvement of both the innate and adaptive immune systems. The direct action includes modulation of epithelial cell structure and functions through introducing bacterial genes, modulating cell growth, apoptosis, migration or inducing the hummingbird phenomenon (extremely elongated cell shape).

Flagella, lipopolysaccharide (LPS), vacuolating cytotoxin A (VacA), and cytotoxin-associated gene pathogenicity island (cagPAI) are the main *H. pylori* virulence factors plying role in its pathogenicity (14). Among these, cagPAI may play a particularly significant role as it is a 40 kbp DNA fragment encoding a type 4 secretion system (T4SS) and the virulence factor CagA (15). T4SS acts as a molecular syringe injecting bacterial macromolecules into the host cell cytosol. CagA becomes oncoprotein when translocated into gastric epithelial cells upon *H. pylori* infection (16). Furthermore, CagA may suppress RUNX family transcription factor 3 (RUNX3), a gastric

tumor suppressor, by its proteasomal degradation or silencing its gene by promoter hypermethylation (17, 18). Also, a key protein of cancer transformation, tumor protein p53 (TP53) was shown to be degraded in the proteasome with the involvement of CagA through its interaction with TP53 binding protein 2 (TP53BP2, ASPP2), another tumor suppressor (19). Therefore, CagA may play a crucial role in *H. pylori*-mediated gastric carcinogenesis and likely other pathological processes in the stomach and the rest of the GI tract. Consequently, CagA-positive strains are more often associated with gastric cancer than their negative counterparts (20). However, not only CagA, but also its interplay with VacA may play a role in the involvement of *H. pylori* in gastric carcinogenesis (21). Other pathways of *H. pylori* pathological action in the GI tract include its effects on inflammation, cell adhesion and proliferation and stem cell mobilization (22).

As *H. pylori* infection induces gastritis in the host, proteins involved in the immune inflammatory response, including interleukins 1β and 8 (IL1β and IL8), may play a role in the carcinogenic potential of the bacterium. Therefore, the gastric carcinogenesis may occur according to the Correa Cascade with the transition from chronic atrophic gastritis to intestinal metaplasia, dysplasia and invasive neoplasia (23). Changes of some transcription factors and DNA repair proteins may support this pathway (24, 25).

The host immune reaction induced by *H. pylori* infection is associated with oxidative stress in the gastric mucosa cells to clean the bacterium (26). The stress is accompanied by the increased production of ROS/RNS that may damage biomolecules, including DNA, proteins and lipids. An excess of DNA damage that cannot be coped with DNA damage response (DDR) may lead to genomic instability, a prerequisite in cancer transformation. Damage to proteins may also contribute to gastric cancer and other GI pathologies. Therefore, ROS/RNS action may be a key event in the pathogenesis of *H. pylori*-mediated GI disorders. DNA damage induced by ROS/NRS activates DDR, which, in turn, modulates the expression of genes whose products are needed to counteract DNA damage and its consequences. Changes in the cellular epigenetic profile are an important aspect of such modulation. Therefore, a cause-effect chain events: *H. pylori* infection, inflammation induction, ROS/RNS overproduction, DDR and changes in the epigenetic profile may be an important element in the pathogenesis of *H. pylori*-mediated GI disorders and might be considered in preventive and therapeutic strategies in such disorders.

3. BENEFICIAL ACTION OF MELATONIN IN *H. PYLORI* INFECTION

We showed that the levels of mRNA expression of genes encoding arylalkylamine-N-acetyltransferase (AANAT) and acetylserotonin methyltransferase (ASMT), enzymes involved in melatonin synthesis, decreased in gastric mucosa of patients with symptomatic *H. pylori* infection (10). The main symptom of the infection was abdominal pain. After *H. pylori* eradication the expression of both genes returned to their normal levels and the pain symptoms became less penetrating. Moreover, we found a negative correlation between intensity of the infection and ASMT expression in the antral mucosa of those patients. Therefore, gastric production of melatonin may be inhibited by *H. pylori* through the inhibition of the enzymes involved in its synthesis. Moreover, these results suggest that melatonin might ameliorate epigastric pain syndrome. This suggestion was confirmed in another study showing a decreased level of the expression of AANAT and hydroxyindole-*O*-methyltransferase (HIOMT), the main components of melatonin homeostasis, in gastric mucosa of patients with epigastric pain syndrome, but without *H. pylori* infection (9). As stated above, inflammation and ROS/RNS overproduction, DDR and changes in the epigenetic profile may be considered as important events in the pathological consequences of *H. pylori* infection.

3. 1. Inflammation.

Melatonin displays immunoregulatory activity in several inflammatory diseases (27). Immunohistochemical analysis showed an increased expression of the melatonin receptors MT1 and MT2 in the gastric mucosa of *H. pylori*-infected mice (28). Lower levels of transforming growth factor beta 1 (TGFB1, TGF-β1) in the liver of the infected mice increased 2 weeks after treatment with melatonin, but 4 and 6 weeks after treatment TGFB1 levels were lower than in non-infected mice. Qualitatively similar results were obtained for forkhead box protein 3 (FOXP3) and RAR related orphan receptor B (RORB, RORβ). These results suggest that melatonin may improve gastric disorders mediated by *H. pylori* through the modulation of the expression of TGFB1 and FOXP3 via membrane and nuclear receptors.

Many inflammatory molecules were found to be upregulated in gastric mucosa cells of *H. pylori*-infected patients. These include interleukins IL1β, IL8, IL12, IL21, IL32, tumor necrosis factor alpha (TNF-α) and C-C motif chemokine ligand 5 (CCL5, RANTES) (29-32). Injection of CagA into gastric mucosa cells by T4SS activates nuclear factor-κB (NF-κB) mediated by mitogen activated kinase 1/2 (MAPK1/2) (33). NF-κB is a transcription factor inducing the expression of pro-inflammatory genes, including those coding for cytokines, chemokines and involved in the regulation of inflammasome (34). Chronic mucosa gastritis induced by *H. pylori* is featured by an increased number of CD4T-positive cells, which are essential for the development of gastritis (35). *H. pylori* also stimulates the synthesis of growth factors, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and modulators of inflammation, such as cyclooxygenase 2 (COX-2), which are important in cancer-related inflammation (36). Inflammatory reaction is associated with oxidative stress and ROS/RNS overproduction which will be addressed in the next section.

H. pylori infection induces host inflammatory and oxidative stress responses to clean the pathogen. However, that oxidative stress is associated with an increased production of ROS/RNS that may damage host proteins, lipids, and nucleic acids. That effects may result in pro-carcinogenic changes in the gastric epithelium (26). This reflects the conception that *H. pylori*-induced host response rather increases than suppresses the bacterium's pathogenicity (37).

Many studies showed that melatonin reduced chronic and acute inflammation [reviewed in (38)]. Some of them include inflammation-related oxidative stress and will be summarized in the subsequent section. In general, a direct beneficial effect of melatonin on *H. pylori*-related inflammation in the gastric mucosa has not been evidenced, but it was shown that melatonin might support the action of omeprazole, a proton pump inhibitor that increases the ratio of *H. pylori* eradication, in healing gastric and duodenal ulcers (39).

Melatonin may prevent the translocation of NF-κB to the nucleus and its binding to DNA, thereby, reducing the upregulation of a variety of proinflammatory cytokines, including interleukins and TNF-α (40). Melatonin may suppress the production of adhesion molecules that promote sticking of leukocytes to endothelial cells, resulting in transendothelial cell migration and edema, which contribute to tissue damage (41). However, the most important effect for anti-inflammatory action of melatonin is linked with the inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation through the modulation of the inflammatory genes including *NLRP3*, PYD and CARD domain containing (*PYCARD, ASC*), caspase-1 and IL1β (42, 43). However, *H. pylori* controls the expression of NLRP3 inflammasome by various mechanisms, including epigenetic regulation, addressed below, and regulation of the expression of *IL10* (44). Therefore, melatonin may ameliorate the *H. pylori*-related inflammation in the gastric mucosa by

several mechanisms, including regulation of NLRP3 inflammasome and controlling the expression of interleukins. Other mechanisms are also possible.

3.2. Oxidative stress.

Oxidative stress in the gastric mucosa induced by *H. pylori* is mainly associated with the inflammatory reaction generated by the host immune and epithelial cells to clean the infection (26). Failed to do so prolongs oxidative stress and the production of ROS/RNS, as well as induce of cancer transformation mainly through DNA damage and epigenetic mechanisms. Although ROS/RNS are produced by a variety of cells, neutrophils are mainly responsible for their generation (45). ROS/RNS are used to kill the bacteria on the cellular surface generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) (46). During this process, superoxide ($O_2^{\bullet -}$) is produced and then converted to hydrogen peroxide (H_2O_2) by superoxide dismutase. H_2O_2 is a substrate for the production of more toxic species, including hypochloric acid and hydroxyl radical (OH•), which is one of the most reactive oxygen species. Therefore, response of the host to clean *H. pylori* results in ROS/RNS production and such state is referred as to oxidative stress. Oxidative stress, understood as an unbalanced ROS/RNS production, is claimed to be involved in the pathogenesis of many disorders. In that sense, it is rare to find a human disease that would not have oxidative stress in its pathophysiology. However, humans like other species have the antioxidant system consisting of antioxidant enzymes, DNA repair proteins and small molecular weight antioxidants to prevent and counteract ROS/RNS and the consequences of their activity. Therefore, even the production of RON/RNS at a high rate will not necessarily lead to oxidative stress. In addition, ROS/RNS also play many important signaling functions in both physiological and pathological phenomena. Therefore, it is more precise and safer to consider ROS/RNS action instead of oxidative stress in the pathogenesis of human diseases, including ROS/RNS generated in gastric mucosa in response to *H. pylori* infection.

Also, phagocytic cells, mainly macrophages and neutrophils arriving to assist to clean the infection, produce ROS/RNS and host neutrophils can use inducible nitric oxide synthase to produce NO (47). In the presence of metals, NO reacts with superoxide to produce peroxynitrite ($ONOO^-$), whose reactivity is comparable with hydroxyl radical.

ROS/RNS produced during *H. pylori* infection are considered to contribute to pathogenesis of many gastric disorders, including gastric cancer. However, such contribution has not been unequivocally evidenced and as mentioned, DNA damage and genomic instability seem to be a direct intermediate between *H. pylori*-mediated inflammation/oxidative stress and gastric cancer.

Melatonin is a well-established ROS/RNS scavenger and an important positive regulator of cellular antioxidative reaction [reviewed in (48)]. Although many cellular mechanisms can be considered beyond these activities, virtually all of them can lead to beneficial effects of melatonin in *H. pylori* infection. Moreover, also the involvement of melatonin in DDR, and not only DNA repair, may contribute to such effects (49).

3.3. DNA damage response.

DNA damage response is a complex, evolutionarily evolved set of cellular reactions to DNA damage to preserve integrity and informational content of the genome (50). Genomic instability is a prerequisite for cancer transformation and may be involved in the pathogenesis of other diseases. When the extent of DNA damage exceeds the capacity of DNA repair system, cell cycle may be arrested to give the cell more time to deal with the damage. If this failed, the cell may activate

programmed cell death, usually apoptosis to prevent its entering mitosis with damaged genome. DNA repair, regulation of cell cycle, programmed death along with chromatin remodeling are main functional components of DDR. It was observed that *H. pylori* infection evoked genomic instability in both the nuclear and mitochondrial genomes in human gastric mucosa cells (51). Moreover, CagA reduced apoptosis in gastric epithelial cells with damaged DNA, fueling cancer transformation of those cells (52).

We showed that the extent of basal and oxidative DNA damage in *H. pylori* infected gastric mucosa cells after treatment with hydrogen peroxide or amoxicillin, an antibiotic used to eradicate *H. pylori*, was higher than in non-infected cells (53). Therefore, *H. pylori* infection may induce ROS/RNS that may damage DNA and add to the extent of the damage induced by other factors, including dietary mutagens. Accordingly, we showed that *H. pylori* infection increased DNA damage in gastric mucosa cells induced by heterocyclic amines (54). These agents are recognized mutagens and carcinogens that are formed during high-temperature cooking of protein-rich foods, primarily meat and therefore they are present in many Western diets (55). Melatonin reduced the extent of DNA damage induced by heterocyclic amines in gastric mucosa cells and did so more efficiently in the infected than non-infected cells. Moreover, melatonin was more efficient in retarding DNA damage than vitamin C. Therefore, melatonin may play anticancer role through protection against DNA damage induced by environmental/lifestyle agents potentiated by *H. coli* infection. In a similar study, we showed that melatonin reduced the extent of DNA damage in gastric mucosa cells exposed to N-methyl-N'-nitro N-nitrosoguanidyne (MNNG), a chemical mutagen whose interaction with DNA is similar to many nitrosamines that can be found in foods (56). These studies encourage us to speculate that the process of stomach carcinogenesis may be initiated by a dietary mutagen and supported and/or promoted by *H. pylori* infection and melatonin may inhibit the action of mutagen if its synthesis is not inhibited by *H. pylori* as we showed a reduced activity of melatonin-synthesizing enzymes in *H. pylori*-infected gastric mucosa cells (10).

It was shown that *H. pylori* infection was associated with an increased levels of phosphorylated H2AX histone, a marker of DNA double-strand breaks, a serious DNA damage that if not repaired or misrepaired may lead to chromosomal aberrations, cancer transformation and cell death (57). Also, DNA repair systems, including base excision repair and mismatch repair, were reported to be affected by *H. pylori* infection [reviewed in (26)].

Beneficial action of melatonin in DDR was showed in several other studies. It may be underlined by improving the functions of basic DNA repair pathways: base excision repair, nucleotide excision repair, mismatch repair, homologous recombination repair and non-homologous end joining (reviewed in (49). These and other beneficial actions of melatonin in DDR may be underlined by its modulation of the main DDR signaling pathways, from sensors of DNA damage, through DDR mediators, transducers and effectors to final cellular response. Also, melatonin nay be involved in chromatin remodeling, cell cycle regulation and programmed cell death control (58-60).

In summary, *H. pylori* infection may be associated with genomic instability, a prerequisite of cancer transformation and DNA damage in genes, whose mutations fuels the transformation. Such changes in the genome may also result in other than cancer pathological outcome in the phenotype. Melatonin was reported to decrease DNA damage induced by various factors and ameliorate different pathways of DDR [reviewed in (49, 61)]. This is not the objective of this work to consider all molecular mechanisms beyond beneficial effects of melatonin on DNA damage and DDR which are described in many reviews, e.g. (62, 63). In general, the involvement of melatonin in reducing DNA damage induced by exogenous and endogenous factors in the cell may be divided into cell-independent and dependent. In the former, melatonin inactivates a DNA-damaging factor, preventing DNA damage, in the latter melatonin assists DDR through various mechanism,

including improving DDR signaling and stimulation of many pathways of DNA repair, regulating chromatin structure, cell cycle and apoptosis.

3.4. Epigenetic modifications.

Epigenetic regulation of gene expression with three main elements: DNA methylation, posttranslational histone modifications and action of non-coding RNAs, an emerging field in biomedicine. Global DNA hypomethylation and hypermethylation of tumor suppressor genes are important steps in many malignant transformations (64). As mentioned above, CagA hypermethylates the promoter of the *RUNX3* gene, a gastric tumor suppressor, resulting in its silencing (17). An enhanced level of DNA methylation was shown in *H. pylori*-infected gastric mucosa with gastritis and in non-cancerous mucosa of gastric cancer patients with or without *H. pylori* infection, suggesting that changes in DNA methylation pattern induced by *H. pylori* may be persistent and contribute to cancer transformation even after eradication of the bacteria (65-67). These results do not resolve whether aberrant DNA methylation results from *H. pylori*-induced events in the host cells or from the bacterium itself, but the result from the CagA role on DNA hypermethylation suggest that both scenarios are possible.

Although so far DNA methylation has been most intensively studied among all epigenetic modifications associated with *H. pylori* infection, non-coding RNAs become an emerging research subject in recent years. Among them, three species are considered to have the most pronounced influences in gene regulation and so they contribute significantly to cellular epigenetic profile. They are micro RNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). They can regulate gene expression in a variety of ways, and it is not a purpose of this review to provide details on this subject, which can be found elsewhere (68-70). In general, miRNAs bind to regulatory regions of the target gene transcript, usually their 3' untranslated region (3'UTR) on the basis of complementarity (sense-antisense interaction, RNA interference), form complexes with proteins and support mRNA degradation or inhibit translation of the target mRNA. LncRNAs may regulate gene expression by several mechanisms, including antisense interaction with target mRNAs, guiding and scaffolding regulatory proteins to target mRNAs and sequestering regulatory proteins from their target mRNAs (a decoy function). However, an important function of lncRNAs is to bind to other regulatory ncRNAs, in particular miRNAs, to prevent their interaction with target mRNAs (a sponge effect). CircRNAs act in a similar way as lncRNAs with sponging miRNAs as an important component of their regulatory mechanisms.

N-terminal tails of histones bear a set of chemical modifications that are shaped after translation. They are read by proteins involved in the maintenance of chromatin structure and determine the accessibility of associated DNA for proteins of gene expression machinery. That is why this set is referred as to histone code. *H. pylori* infection may change the histone code in many ways with implications for gastric carcinogenesis [reviewed in (71)]. It was shown that *H. pylori* induced dephosphorylation of histone H3 at serine 10 and decreased acetylation of H3 at lysine 23 (72). That work showed that deletion of cagPAI restored the H3 Ser10 phosphorylation to control levels. That modification was associated with the expression of the Jun proto-oncogene, AP-1 transcription factor subunit (JUN, c-Jun) and heat shock protein family A (Hsp70) member 4 (*HSPA4, hsp70*) gene expression. In other studies, it was shown that *H. pylori* upregulated the cell cycle control protein cyclin dependent kinase inhibitor 1A (CDKN1A, p21) in the gastric carcinoma cell line NCI-N87 and in primary normal gastric cells (73). That effect was associated with the departure of histone deacetylase 1 (HDAC1) from the promoter of the *CDKN1A* gene and hyperacetylation of histone H4. CDKN1 is tightly regulated by TP53 and its deregulation may

contribute to cancer transformation. Therefore, *H. pylori* can alter the histone code in a cagPAI-dependent manner resulting in alterations in the expression of genes involved in different aspects of its pathogenesis. Melatonin may change the epigenetic code in many ways and its action can be underlined by various mechanisms. Firstly, melatonin was reported to modulate the expression of enzymes establishing and changing the histone code, including HDAC1, which was reported to change during *H. pylori* infection (74). In general, melatonin was reported to modulate the action of sirtuins, a class III HDAC enzymes [reviewed in (75)]. Apart from direct modulation of the activity of enzymes responsible for histone modifications, melatonin may modulate the activity of NFE2 like BZIP transcription factor 2 (NFE2L2, Nrf2) that along with kelch like ECH associated protein 1 (KEAP1) promotes site-specific histone acetylation and/or inhibition of histone deacetylation [reviewed in (76)].

Non-coding RNAs are intensively studied in the context of *H. pylori* infection. As in other pathologies miRNAs are most intensively studied. Many miRNA species have been identified to change their expression in gastric mucosa and circulation after *H. pylori* infection [reviewed in (77)]. Some changes in these miRNAs were associated with the action of *H. pylori* virulence factors and attributed to *H. pylori* gastric cancer transformation. Apart from miRNAs also two other ncRNAs species: lncRNAs and circRNAs were investigated in the context of *H. pylori* infection. CircMAN1A2 was shown to upregulate in *H. pylori*-infected cells and promoted gastric cancer development (78). It was suggested that *H. pylori*-related lncRNA expressional profile may be used as a predictive marker in gastric cancer patients (79). Changes in the profile of ncRNA expression induced by *H. pylori* may be also relevant to other than gastric cancer disorders of the GI tract, including peptic ulcer, gastritis and functional gastrointestinal diseases (80, 81).

Melatonin signaling was reported to modulate the action of ncRNAs also in the context of cancer transformation [reviewed in (82)]. Melatonin was reported to interact with many miRNAs with different functionalities [reviewed in (83)]. The same concerns on lncRNAs, but the interaction of melatonin with circRNAs was not investigated intensively as miRNAs and lncRNAs [reviewed in (84)]. However, some circRNAs have been identified to play an import role in melatonin synthesis, but their association with the consequences of *H. pylori* infection requires further studies (85). Interestingly, Circ-ERC2 involved in such regulation does so by interaction with other regulatory ncRNAs, including miR-125a-5p (86).

4. CONCLUSIONS AND PERSPECTIVES

Although infection with *H. pylori* affect about half of the world population and can cause the serious outcomes including gastric cancer, it is not treated as a pandemic disease since excessive 90% of the cases are asymptomatic. However, once the cancer transformation is clinically detected in many cases, it is too late to undertake an action for its full recovery. The exact mechanism of carcinogenesis induced by *H.* pylori is not known. Although *H. pylori* is a class I carcinogen it may also assist cancer transformation initiated and promoted by other factors, including dietary compounds. Therefore, prevention of *H. coli* infection, its detection and eradication may be of a prime importance in healthcare. Importantly, the consequences of *H. pylori* infection may persist for a long time after its eradication, as shown in experimental research.

Melatonin is considered as a dietary supplement in many countries and displays a plethora of health-related beneficial effects in clinical and experimental studies. We showed that melatonin ameliorated some disorders of the GI tract and *H. pylori* infection decreased its synthesis in gastric mucosa cells in humans. Moreover, the infection increased the extent of DNA damage and disturbed DDR. Furthermore, it potentiates the genotoxic action of DNA-damaging agents,

including dietary mutagens/carcinogens. These results clearly indicate that further research on melatonin administration in prevention and treatment of *H. pylori*-mediated GI diseases may bring profitable results and is justified.

In this review, we discussed several aspects associated with *H. pylori* infection and reported or anticipated beneficial effects of melatonin in possible consequences of such infection, first of all gastric cancer. We considered the following aspects of *H. pylori* infection: inflammation, ROS/NOS generation, DDR and changes in the cellular epigenetic profile. Those aspects form a cause-and-effect relationship: the infection induces inflammatory response and ROS/RNS production which damage DNA to evoke DDR. Furthermore, DDR modulates expression of some genes and epigenetic regulation is an important element of that modulation. All those aspects may be modulated by melatonin in many pathways with beneficial outcomes. We postulate that further studies should be performed to reveal molecular mechanisms behind observed and anticipated beneficial effects of melatonin in *H. pylori*-mediated gastrointestinal diseases. Such studies should also include controlled clinical trials.

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AUTHORSHIP

All authors contributed equally to this work.

CONFLICT OF INTEREST

Authors declare no conflict of interest associated with this work.

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