Review Article

The Relationship between Toll-like Receptors and Helicobacter pylori-Related Gastropathies: Still a Controversial Topic

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Received 9 October 2018; Accepted 2 January 2019; Published 4 February 2019

Academic Editor: Kurt Blaser

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Innate immunity represents the first barrier against bacterial invasion. Toll-like receptors (TLRs) belong to the large family of pattern recognition receptors (PRRs), and their activation leads to the induction of inflammatory cytokines, chemokines, antigen-presenting molecules, and costimulatory molecules. Recent studies have focused on identifying the association between TLRs and Helicobacter pylori- (H. pylori-) related diseases. Therefore, this minireview focuses on assessing the role of these TLRs in the development of H. pylori-related gastropathies. Both TLR2 and TLR were found to be involved in H. pylori LPS recognition, with contradictory results most likely due to both the inability to obtain pure LPS in experimental studies and the heterogeneity of the bacterial LPS. In addition, TLR2 was found to be the most extensively expressed gene among all the TLRs in gastric tumors. High levels of TLR4 were also associated with a higher risk of gastric cancer. TLR5 was initially associated with the recognition of H. pylori flagellin, but it seems that this bacterium has developed mechanisms to escape this recognition representing an important factor involved in the persistence of this infection and subsequent carcinogenesis. TLR9, the only TLR with both anti- and proinflammatory roles, was involved in the recognition of H. pylori DNA. The dichotomous role of TLR9, promoting or suppressing the infection, depends on the gastric environment. Recently, TLR7 and TLR8 were shown to recognize purified H. pylori RNA, thereby inducing proinflammatory cytokines. TLR1 and TLR10 gene polymorphisms were associated with a higher risk for gastric cancer in H. pylori-infected individuals. Different gene polymorphisms of these TLRs were found to be associated with gastric cancer depending mostly on ethnicity. Further studies are required in order to develop preventive and therapeutic strategies against H. pylori infections based on the functions of TLRs.

1. Introduction

Helicobacter pylori (H. pylori), a Gram-negative, microaerophilic, and spiral-shaped bacterium, infects the human gastric mucosa at an early age, colonizes the mucosal gel layer, and leads to chronic inflammation in the stomach [1–3]. This bacterium is present in the gastric mucosa of up to 50% of the world’s population and is responsible for different conditions, such as chronic gastritis, peptic ulcers, gastric cancer, lymphomas of the gastric-associated lymphoid tissue, and gastric adenocarcinoma [4]. Nevertheless, gastropathies can also be caused by other factors and conditions, such as drugs, portal hypertension, bile reflux, uremia, Henoch-Schönlein purpura, and radiation [5, 6]. H. pylori was considered as a class I carcinogen by the World Health Organization (WHO), with gastric cancer being identified as the third leading cause of cancer-associated deaths worldwide [7, 8]. Individuals suffering from H. pylori infection were found to have a sixfold higher risk of developing gastric cancer and up to a 50% higher risk for all gastric cancers as compared to uninfected individuals [9, 10]. Carcinogenicity of H. pylori is regulated by 3 factors, namely, bacterial virulence constituents, host genetic susceptibility, and environmental factors [11]. The eradication of H. pylori infection in symptomatic individuals has been unsuccessful in recent years due to a constant increase in the antimicrobial resistance [12].
Among European individuals, resistance rates against metronidazole and clarithromycin have reached 34.9% and 17.5%, respectively, and strains that are more resistant to levofloxacin (14.1%), which was used as a rescue therapy for this infection, have also emerged [13]. This may be due to the fact that *H. pylori* has developed the ability to regulate T-cell responses [14]. Moreover, gastric biopsies from gastritis patients infected with *H. pylori* that failed to respond to a proper eradication regimen revealed that some strains of this bacterium, such as those with an altered lipopolysaccharide structure or those which inhibit cathepsin X, are able to mediate resistance against such drugs [15].

The immune system has an essential role in controlling infections, and both innate and adaptive immunity contribute to this process [14]. The innate immunity is considered as the first line of defense against pathogens [16]. Therefore, epithelial cells of the gastric mucosa are considered as the first line of innate immunity against an *H. pylori* infection [17]. The pathogen recognition receptors (PRRs) are known to recognize different bacterial molecular patterns, playing a major role in the stimulation of adaptive immunity [18]. The crosstalk between innate and adaptive immunity is critical for the successful eradication of different bacteria. Mammalian toll-like receptors (TLRs) belong to the large family of PRRs, and the activation of their signaling pathways results in the induction of inflammatory cytokines, chemokines, antigen-presenting molecules, and costimulatory molecules [19]. Multiple studies have focused on the identification and elucidation of such TLRs, and 10 types of TLRs in humans have been identified [20]. These receptors express the pattern of type I transmembrane proteins, which involves a leucine-rich repeat-containing ectodomain, a transmembrane region, and an intracellular domain, which is involved in the activation of downstream signaling pathways. Some of these TLRs, TLR1, 2, 4, 5, and 6, recognize different membrane components like lipids, lipoproteins, and proteins, binding their ligands on the cell surface, while others, including TLR3, 7, 8, and 9, play a major role in the recognition of microbial nucleic acids, which are identified in intracellular vesicles [18, 21–26]. The expression and activation of different TLRs in the gastric mucosa have been widely investigated by recent studies, but their precise role and functions are not yet fully understood. Additionally, due to the recently discovered increase in antimicrobial resistance, novel therapies involving innate immunity are required.

This review aims at identifying and characterizing the role of TLRs in *H. pylori*-related gastric pathologies.

1.1. TLR2 and *H. pylori*. TLR2 has been shown to recognize bacterial lipopolysaccharide (LPS), acting as a primary barrier against *H. pylori* [21, 27]. Its expression results in the activation of different transcription factors, such as nuclear factor-κB, stimulating the production and secretion of proinflammatory cytokines, such as interleukin- (IL-) 1β, IL-2, IL-6, IL-8, and IL-12 [28, 29]. An interaction between TLR2 and TLR4 has also been identified. This interaction consists of an unraveled subsequent expression of TLR4 as a result of the activation of TLR2, eventually leading to metaplasia, dysplasia, and adenocarcinoma [30, 31]. Together with TLR4, TLR2 is one of the best characterized TLRs. Besides recognizing LPS, TLR2 is also involved in the recognition of other bacterial components, such as lipoproteins or peptidoglycan [32]. In addition, it seems that TLR2 recognizes bacterial LPS with a different structure compared to those recognized by TLR4 [32]. A study performed on cell lines proved that *H. pylori* LPS acts as a classic TLR2 ligand by involving key TLR-signaling components [29]. This bacterial LPS also stimulates a mild chemokine expression in TLR2-expressing epithelial cells [29]. Nevertheless, the reports whether TLR2 is responsible for the recognition of *H. pylori* LPS remain contradictory. Multiple studies have shown that the recognition of this LPS by TLR2 results in the activation of nuclear factor-κB, suggesting that the down-regulation of TLR2 leads to the inhibition of cytokines mediated by TLR4 LPS [29, 33–36]. On the contrary, other studies have found TLR4 to be involved in the recognition of *H. pylori* LPS [17, 37–40], most likely based on its proven interaction with TLR2. In addition, as we have previously mentioned, TLR4 might be involved in the recognition of LPS having a different structure than that recognized by TLR2. Nevertheless, a recent study, performed on cell lines, stated that the *H. pylori* LPS induced a discrete pattern of chemokine expression only in TLR2-expressing cells and not in TLR4-expressing cells; this effect was mediated through the interaction between the LPS and TLR2 [29]. Nevertheless, when assessing these experimental studies, performed on a cultured cell line, we must take into account that it is very difficult to obtain pure LPS and to create the exact same conditions as in vivo. Besides these studies performed on cultured cell lines, TLR2 expression was found to be increased in gastric biopsy samples obtained from patients who tested positive for *H. pylori* infection [37, 41–43].

In addition to *H. pylori* LPS recognition, it was shown that TLR2 also triggers a Th1 immune response by binding to *H. pylori* neutrophil-activating protein [44]. TLR2 is also involved in the pathogenesis of gastric cancer worldwide. Different ethnic studies performed on gastric biopsy samples identified that genetic polymorphism in TLR2 is associated with an increased risk of gastric cancer, with variations between different geographic areas and populations [45–47]. Contrariwise, certain TLR2 polymorphisms, such as TLR2 c. -196 to -174 del carriers (ins/del+del/del) were shown to be significantly associated with a decreased risk of gastric cancer in Chinese [45]. On the other hand, other studies performed in Japanese failed to identify any association between this polymorphism and gastric malignancies, suggesting that ethnic differences may modify the *H. pylori*-related carcinogenesis [48]. Moreover, the TLR2 functional polymorphisms found in Caucasians, Pro631His, Arg677Trp, and Arg753Gln, differ from those identified in Asiatic people, TLR2-688G>T, -264G>C, and c.2242ACA>del [45, 49–51]. As in the case of gastric biopsy samples, the risk of gastric cancer due to peptic ulcers differs among individuals who harbor different TLR2 gene polymorphisms [52], depending also on ethnic features as mentioned above. In addition, TLR2/MyD88 signaling is crucial for the successful eradication of different bacteria. This review aims at identifying and characterizing the role of TLRs in *H. pylori*-related gastric pathologies.
proven by studies involving mouse models [53]. Therefore, the inhibition of this signaling pathway could represent a major preventive and therapeutic approach against gastric cancer [54]. In addition, in mice, TLR2 was found to be the most significantly upregulated gene among the TLRs in gastric tumor samples, its expression being predominantly identified in tumor epithelial cells [55]. Based on these findings, it is clear that TLR2 is involved in the recognition of H. pylori LPSs and that there is an interaction between TLR2 and TLR4. There is strong evidence suggesting the role of TLR2 in the development of gastric cancer despite ethnic differences. Nevertheless, the differences regarding TLR polymorphisms between different people suggest that ethnicity is an essential factor that can modulate the response to H. pylori infection and its persistence. Therefore, despite limited literature, it is clear that TLR2 plays a major role in H. pylori recognition and gastric tumorigenesis.

1.2. TLR4 and H. pylori. TLR4 was the first TLR identified in humans, and similar to TLR2, it was associated with the recognition of bacterial LPSs, an essential component of the outer membrane of Gram-negative bacteria [22]. Due to the wide structural diversity of the bacterial LPSs, as mentioned above, TLR4 is not able to recognize all types of LPSs. In order to stimulate an adequate response against an LPS and to induce secretion of inflammatory cytokines, TLR4 requires the aid of other molecules, such as MD-2, LPS-binding protein, and CD14 [16]. The initiation of the nuclear factor-κB pathway due to H. pylori LPS recognition leads to the activation of the IL-8 pathway, which acts as a promoter of proinflammatory cytokines [56]. H. pylori heat shock protein 60 is another essential component of this bacteria that activates both TLR2 and TLR4, resulting not only in the increase of nuclear factor-κB activity but also in the production of IL-8 in cultured gastric epithelial cells [57]. Nevertheless, it seems that the TLR4 expression remains unaltered in the gastric epithelium independently of the presence of H. pylori [58]. TLR4 is expressed at the apical and basolateral levels of the membrane compartment [58]. A more recent study performed on gastric biopsy specimens showed that expressions of both TLR4 and TLR2 are upregulated as a result of H. pylori infection in antral and gastric body areas [43]. The same study suggested that the expression of both the TLRs changed significantly only in the antral region compared to the control [43]. In order to perform their functions, both TLR4 and TLR2 need to be internalized into the cytoplasmic compartment. In a study conducted on cell lines infected with H. pylori strains from patients in whom the eradication of bacteria was unsuccessful, cathepsin X was shown to influence the internalization of both TLRs. Therefore, the inhibition of this cathepsin resulted in a suppression of their redistribution to the intracytoplasmic compartment, leading to a delay in the successful immune response against H. pylori [59]. The ability of H. pylori to trick the immune system has evolved progressively resulting in a persistent infection. Thus, this bacterium has acquired the ability to modify the lipid A core of its LPS, representing a possible ligand for the immune complex TLR4-MD2, in order to avoid TLR4 recognition [11]. In addition, H. pylori LPS was proven to have approximately 1000-fold less endotoxic properties in comparison to other bacteria due to this modification to the core [60, 61]. Therefore, it seems that the reduced functioning of TLR4 in individuals that carry hyporeactive polymorphisms in the gene for this TLR is associated with a reduced inflammatory response eventually leading to a persistent infection [62, 63]. T regulatory cells play an immunosuppressive role, and their numbers were shown to be higher in H. pylori-infected individuals [64]. A recent study performed on mice demonstrated an association between the TLR4 signaling pathway and T regulatory cells. The study showed that suppressing the TLR4 signaling pathway will eventually lead to an increase in T regulatory cells resulting in an exacerbation of H. pylori colonization [65]. However, the same study pointed out that inhibiting the CD25 expression could decrease T regulatory cells and, as a result, could suppress H. pylori colonization [65].

Even though certain TLR4 polymorphisms have been associated with a higher risk of developing premalignant conditions, such as hypochlorhydria and gastric atrophy [46], other studies, performed on bigger cohorts, failed to identify any such relationships [66, 67]. Similar to TLR2, the association between TLR4 polymorphisms and the risk for carcinogenesis related to TLR4 most likely depends on ethnicity. Thus, a study performed on Chinese population suggested an association between TLR4 3725 G/C polymorphism and an increased risk of developing gastric cancer [68]. Nevertheless, other studies failed in proving this association in the Caucasian or Japanese populations [48, 69]. On the other hand, TLR4Asp299Gly gene polymorphism was found to increase the risk of developing gastric neoplasia in Caucasians [46] but not in Chinese patients [70, 71]. It seems that TLR4 is involved in the recognition of bacterial LPS structure that is different from the one recognized by TLR2. Moreover, it can be considered as a suppressor of H. pylori infection, and therefore, it could be valuable as a potential therapeutic regimen against this bacterium, especially in patients that fail to respond to the conventional therapeutic options.

1.3. TLR5 and H. pylori. TLR5 was identified as the receptor which recognizes bacterial flagellin, which is a protein component of the polymeric flagellum filament of certain Gram-positive and Gram-negative bacteria [23]. H. pylori contains approximately 5-7 flagella per cell, which provide motility and consist of two subunits, the major flagellin and the minor flagellin [72, 73]. The recognition of H. pylori by TLR5 is achieved through the p38 MAP kinase signaling pathway [24, 30, 74]. It is well documented that TLR5 is present on both primary gastric epithelial cells and gastric cell lines [24, 41]. Similarly, a recent study showed an association between a TLR5 rs5744174 polymorphism and H. pylori infection [45]. However, a study performed on cell lines suggested that H. pylori flagellin cannot be recognized by TLR5 in case of a mutation in the conserved domain of the major subunit [75]. Moreover, the authors suggested that the major subunit of H. pylori flagella demonstrated low immunogenic features, as they were unable to activate TLR5 [75]. Thus, it was proven that Epsilonproteobacteria gastric pathogen H.
*H. pylori* evolved its flagellin involving several amino acid changes within the D1 domain in order to escape TLR5 recognition, but it conserved its motility [75]. A more recent study performed on human embryonic kidney cell lines proved that the D0 domain also owns a role in TLR5 evasion along with specific amino acid residues that must be altered in the evolution of this Epsilonproteobacteria in order to accomplish its evasion [76]. Moreover, it seems that the TLR5 receptor does not necessarily require a specific ligand for its activation. Thus, it was proven that the autoactivation of the chimeric TLR5 relies on the specific binding of the linked flagellin to the TLR5 ectodomain similar to the binding of free flagellin to wild-type TLR5 [77]. These findings suggest the fact that TLR5 may become active without requiring a direct recognition of specific bugs or ligands. Additionally, Jeral et al. designed a fusion protein containing the *H. pylori* flagellin A, but they replaced the amino-terminal and carboxyl-terminal segments with sequences of the flagellin from a bacterium that is able to activate TLR5 [78]. This invention was conceived for the preparation of the vaccine against bacteria whose TLR5 can recognize pathogenic DNA via its structural components such as the saccharide backbone, in a sequence-independent manner [84–86]. The expression of this receptor differs in healthy individuals and individuals infected with *H. pylori*. TLR9 is located in the apical compartment of the gastric epithelial cells in healthy controls, while in individuals infected with *H. pylori*, it is located only in the basolateral compartment [58]. Rad et al. proved in a study performed on murine models that the in vivo recognition of *H. pylori* by TLR9 results in proinflammatory responses [87]. On the contrary, a more recent study performed on mice suggested that during the acute phase of *H. pylori* infection, TLR9 is able to promote anti-inflammatory signaling, thus acting as a suppressor for *H. pylori*-induced gastritis [88]. The microenvironment can also influence TLR9 to induce either proinflammatory or anti-inflammatory signaling resulting in a dichotomous role of this TLR in the presence of *H. pylori* [11]. Therefore, *H. pylori* can attenuate inflammatory response via TLR9 during the acute phase in order to establish persistent infection [11]. Nevertheless, the inflammatory microenvironment that contains cells without polarity can stimulate TLR9 to promote proinflammatory cascades and eventually result in the development of gastric cancer [30, 58, 89]. This hypothesis is additionally sustained by the fact that TLR9 is upregulated in cancer tissue [30, 58, 89]. Moreover, different TLR9 SNPs have been associated with an increased risk of gastric malignancies [90–92]. A recent study performed by Varga et al. proved that the levels of TLR9 are significantly higher within the epithelial gastric cells of Colombian people from the high gastric cancer risk areas compared to those residing in the low-risk regions [26]. Additionally, the authors underlined that the *H. pylori* cancer-associated cag type IV secretion system (T4SS) is mandatory for the activation of TLR9 and that the *H. pylori* DNA is actively translocated by this system to engage this host receptor [26]. Ethic differences were reported also in the case of this TLR. Thus, a study performed on 168 healthy Caucasian from the West of Scotland, first-degree relatives of gastric cancer patients, showed a significant association between a functional polymorphism TLR9-12371>C and *H. pylori*-related premalignant gastric lesions [93]. Contrariwise, this polymorphism was rarely found in Chinese people [94]. Therefore, TLR9 plays a dichotomous role, being the only receptor that has both proinflammatory and anti-inflammatory roles. Its function is influenced by the
microenvironment and especially by the presence of *H. pylori*. The discordant findings could be due to the fact that most of the studies were performed on animal models, and the human microenvironment is considerably different. Therefore, further studies on gastric biopsy specimens must be performed in order to identify the precise conditions that trigger either the proinflammatory or the anti-inflammatory function of TLR9.

1.5. Other TLRs and *H. pylori*. TLR7 and TLR8 have been shown to recognize purified *H. pylori* RNA which induces proinflammatory cytokines in an MyD88-dependent manner [87]. In addition, certain genetic polymorphisms of different proinflammatory cytokines, such as IL-6 190 C/T, IL-6 572 G/C, tumor necrosis factor alpha 308 G/A, and angiotensin-converting enzyme I/D, were associated with *H. pylori* infection in children [95]. Peng et al. showed that T regulatory cells expressed high levels of TLR8 [96]. Also, it seemed that TLR8 stimulation of T regulatory cells hinders their inhibitory action [96]. A recent study proved that TLR1 rs4833095 and TLR10 rs10004195 gene polymorphisms are associated with a higher risk of gastric cancer in *H. pylori*-infected individuals [97]. In addition, a recent genome-wide association study and meta-analysis showed that the TLR1-TLR6-TLR1 locus is associated with *H. pylori*-positive serology generated through TLR1 [98]. TLR1 and TLR6 could also be binding partners for TLR2, aiding in its ability to recognize different ligands [99]. More recent findings underlined that *H. pylori* seroprevalence could be attributed to TLR10 rather than TLR1, suggesting that TLR10 can be considered a functional receptor involved in the innate immune response triggered by *H. pylori* [100]. These TLRs are less studied than the ones mentioned above, but they seem to also play an important role in *H. pylori*-related gastropathies. Therefore, they should be the focus of future studies.

1.6. *H. pylori* and MALT Lymphomas. Most of the data reported in the literature focus on the interaction of *H. pylori* infection, TLRs, and gastric carcinomas. Despite the fact that studies regarding gastric lymphomas are scarce, the fact that *H. pylori* represents a definitive cure of low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma was recognized worldwide and proven by multiple studies. Thus, a recent study underlined that the eradication of *H. pylori* resulted in complete remission in 84 of 99 patients diagnosed with this type of lymphoma, of which 94% presented long-term complete remission [101]. Moreover, persistence of *H. pylori* represents the most important risk factor for the recurrence of gastric low-grade MALT lymphoma requiring a proper eradication regimen accurate regular assessment of *H. pylori* infection [102]. On the other hand, *H. pylori* pathogenic features, like cagA, were also proven to influence lymphomagenesis by promoting the ability of lymphocytes to escape apoptosis [103].

Besides its well-documented carcinogenic role, it was recently proven that *H. pylori* might also be used as an anti-carcinogenic agent. Thus, a study performed on mice showed that *H. pylori* neutrophil-activating protein (HP-NAP) might be useful in treating bladder cancer [104].

1.7. *H. pylori* Virulence Factors and TLRs. *H. pylori* infection may have a wide range of outcomes depending on both the pathogenic features of the bacteria and the individual’s immune system. Therefore, in an ideal world, gastric epithelial cells are the first line of the innate immune response against this bacteria, and they own the ability to trigger multiple cell signaling cascades resulting in an outcome related to the host’s inflammatory response. Human gastric epithelial cells were found to express both TLR2 and TLR4 leading to the contradictory results regarding *H. pylori* LPS recognition. As mentioned above, studies report that both TLR2 and TLR4 recognize this LPS. Thus, multiple hypotheses were postulated in order to explain these contradictory results, such as the differences in experimental studies and the difficulties related to the contamination during the LPS preparation or to the heterogeneity of its structures. Despite the difficulty of obtaining a pure LPS in experimental studies, a viable, final statement would be that both TLR2 and TLR4 are involved in *H. pylori* LPS recognition depending probably on both the host’s immune system and *H. pylori* strain differences [105]. *H. pylori* flagellin is another bacterial component that owns a greater role in long-term bacterial persistence. Though it was proven to be recognized by TLR5, in vivo this bacterial flagellin is a less potent stimulator of the TLR5 signaling as compared to other Gram-negative bacteria [24, 73], providing *H. pylori* another potential mechanism to escape host immune response and persist in the human stomach [14, 24]. Another important component of *H. pylori* is the 60 kDa heat shock protein which is able to stimulate the IL-8 induction in the gastric epithelial cells, being related to gastric inflammation and MALT development [57]. This immune antigen was shown to be recognized by TLR2 [57, 106]. Peptidyl-prolyl cis-trans isomerase is a powerful compound secreted by *H. pylori*, and it owns the ability to induce gastric epithelial cells being recognized by TLR4 [107–109] resulting in subsequent promotion of Th1 immune responses [14]. *H. pylori* DNA is recognized by TLR9, while TLR8 and TLR7 are involved in the recognition of *H. pylori*-purified RNA [87]. As mentioned above, TLR9 is able to play a dichotomous role, promoting or suppressing *H. pylori* infection depending on the microenvironment. Besides all these *H. pylori*-virulent factors resulting in different escaping mechanisms that may promote the persistence of this infection within the stomach, hyporeactive polymorphisms of the TLRs, as mentioned above, are an additional risk factor for individuals who carry them to develop gastric malignancies.

2. Conclusions

Innate immunity plays an essential role in the promotion or suppression of *H. pylori* infection via TLRs. The discordant findings of different studies might suggest that each TLR can either promote or suppress an *H. pylori* infection, depending on other host-related factors. Moreover, the study design, the number of subjects included in the studies, or the
methods used in each study can also influence the results. Taking into account all these facts, the findings of the studies performed on human gastric biopsies are probably the most accurate ones. Nevertheless, further studies are required in order to identify the exact role of each TLR in the development and pathogenesis of H. pylori infection and, subsequently, in gastric cancer.

Abbreviations

H. pylori: Helicobacter pylori
HP-NAP: H. pylori neutrophil-activating protein
IL: Interleukin
LPS: Lipopolysaccharide
MALT: Mucosa-associated lymphoid tissue
PRRs: Pathogen recognition receptors
TLRs: Toll-like receptors

Disclosure

All authors have no financial relationships relevant to this article to disclose.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Authors’ Contributions

Dr. Lorena Elena Meliț, Dr. Cristina Oana Mârginean, and Dr. Maria Oana Mârginean conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Cristian Dan Mârginean Stud was involved in the design of our manuscript, and he helped us with the correction and final revision of our manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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