Biofilm of *Helicobacter pylori*

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Helicobacter pylori is a gastric pathogen that infects nearly half of the global population and is recognized as a group 1 carcinogen by the Word Health Organization. The global rise in antibiotic resistance has increased clinical challenges in treating *H. pylori* infections. Biofilm growth has been proposed to contribute to *H. pylori's chronic* colonization of the host stomach, treatment failures, and the eventual development of gastric diseases. Several components of *H. pylori* have been identified to promote biofilm growth, and several of these may also facilitate antibiotic tolerance, including the extracellular matrix, outer membrane proteins, shifted morphology, modulated metabolism, efflux pumps, and virulence factors.

Helicobacter pylori | biofilms | planktonic | antibiotic resistance | extra polymeric substance

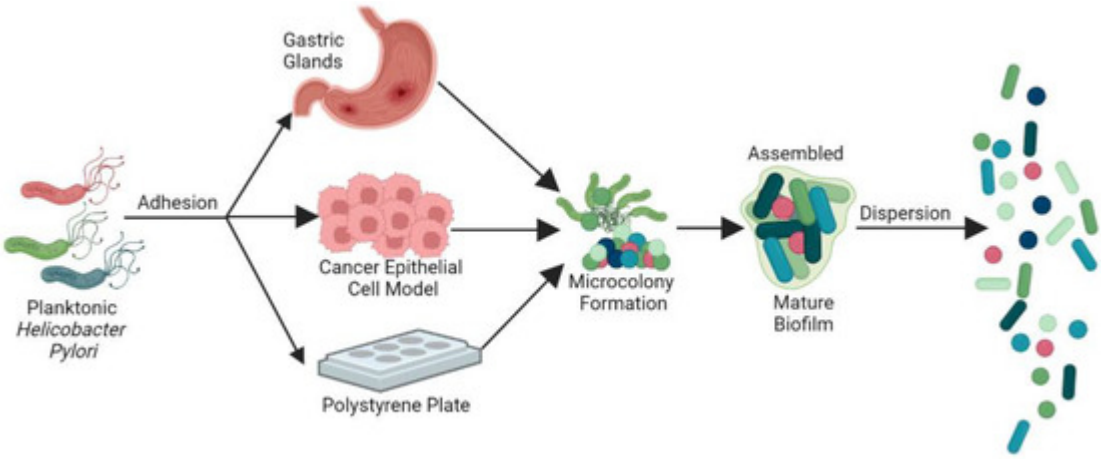
1. Introduction

Helicobacter pylori is a Gram-negative, spiral-shaped, bacterial pathogen that colonizes the gastric epithelium [1][2][3]. *H. pylori* has been globally recognized as a high priority pathogen as it has been associated with various gastric diseases, including peptic ulcers, chronic gastritis [4][5], gastric mucosa-associated tissue lymphomas [6], and gastric adenocarcinomas [7][8][9][10]. Mechanisms of transmission remain unknown [10], but antibiotic therapies used to treat *H. pylori* infection have alarmingly been losing efficacy in regions with high infection burden [11]. Antibiotic-resistant *H. pylori* was reported to disproportionately affect children in Asian, African, and European countries [12], and in underserved communities in the US [13]. One current perspective is that *H. pylori* in biofilms, a low growth state, may substantially promote antibiotic resistance and persistence in the host stomach [14]. *H. pylori* were initially observed in vitro to form water-insoluble biofilms which are defined as stationary aggregates of cells encased in extra polymeric substances (EPS) [15][16]. *H. pylori* with biofilm state have also been observed in the gastric mucosa of patients with peptic ulcers [17][18].

2. General Features of *H. pylori* Biofilms

H. pylori biofilms consist of stationary aggregates of cells encased by an extracellular matrix composed of proteins [19], extracellular DNA [20], and polysaccharides [21]. *H. pylori* biofilm formation starts from planktonic cells that adhere to either abiotic or biotic surfaces, leading to the formation of microcolonies with three-dimensional structures [22][23]. Additionally, *H. pylori* cells can cluster together as non-surface-attached aggregates, a form that has been recently observed and recognized as a biofilm format in other bacterial studies [24]. Once adhered, *H. pylori* biofilm formation was found to occur optimally under conditions lacking nutrients, such as fetal bovine serum [25][26].

Aside from biofilm growth on abiotic surfaces, additional studies have also suggested that *H. pylori* can form a microcolony network that adhered and grew between epithelial cell junctions on human cells [27][28] and in murine gastric glands [29]. Mature *H. pylori* biofilms consist of different cell shapes within one multicellular population. For example, both spiral and coccoid *H. pylori* cells were simultaneously observed from one gastric biopsy [17]. Similarly, on abiotic surfaces, most cells adopt the coccoid morphology, with the minority displaying a rod shape [30][31]. As found in other bacteria, *H. pylori* biofilm formation exhibits a similar multiple-step process, including bacterial adherence, biofilm assembly, mature biofilm formation, and dispersion (Scheme 1). In the next sections, researchers dissect the features of each step in *H. pylori* biofilm growth.



Scheme 1. *Helicobacter pylori* Biofilm Lifecycle. *H. pylori* adheres to both abiotic and biotic surfaces, where it forms microcolonies that susbquently assemble into mature biofilms characterized by the presence of extracellular polymeric susbtances (EPSs). Dispersion allows bacteria to colonizes new niches.

3. *H. pylori* Clinical Treatment Strategies Become Less Efficient, Highlighting the Requirement of Alternative Strategies

Due to the persistence of disease development in *H. pylori* infections that has been exacerbated due to the COVID-19 pandemic, a recent consensus report states a need for consistent updates in clinical treatments, including effective testing and preventative measures for gastric illness [32]. Globally, different geographic regions have variable patterns of anti-microbial resistance [12], a component which should be used to determine treatment strategies according to recent European [32], Chinese [33], and Canadian [34] consensus reports. A challenge to developing effective treatments strategies for these infections is the rising rate of antibiotic resistance and the diversity of clinical and symptom scenarios associated with *H. pylori* infections [32].

In regions with a high prevalence in *H. pylori* infection, current clinical guidelines recommend a quadruple therapy that consists of bismuth, proton pump inhibitor (PPI) or potassium-competitive acid blocker and two different antibiotics (i.e., including clarithromycin, metronidazole, levofloxacin, or amoxicillin) [12][32][33][35]. Non-bismuth quadruple therapies are also recommended and have the following components: PPI and three antibiotics [32][35].

However, this classical therapeutic strategy has been being less effective due to the continuing global rise of antibiotic resistance [36]. For example, in 2016 a national consensus on Chinese management of *H. pylori* infections where quadruple therapy is used reported that metronidazole, levofloxacin, and clarithromycin resistance was 40–70%, 20–50%, and 20–50%, respectively [33]. Similarly, the elevation of antibiotic resistance was also noticed in other countries, like Indonesia, that apply the triple therapy approach consisting of PPI and two antibiotics [37]. Metronidazole and levofloxacin, two commonly applied antibiotics, were observed to be resisted by 46.7% and 31.2% of *H. pylori*-infected population, respectively; while those less commonly applied antibiotics exhibited relative lower resistance prevalence, including amoxicillin (5.2%), tetracycline (2.6%), and clarithromycin (9.1%) [37]. In 2020, a case study reported that triple therapies in Indonesia were further decreased to only 67.6% efficient [38].Aside from Indonesia and China, alarming clarithromycin resistance rates are observed in the Americas (10%), the African region (15%), Eastern Mediterranean region (29%), Europe (32%) which is why the WHO has designated clarithromycin-resistant *H. pylori* as a high priority research pathogen [36].

A meta-analysis review based on global WHO regions reported that clarithromycin resistance decreased the efficacy empiric eradications to less than 80%; additionally, metronidazole resistance was observed in >27% strains and levofloxacin resistance in >14% strains from all surveyed WHO regions in 2018 [36]. To counter potential therapy failure caused by antibiotic resistance, clinicians have proposed using a tailored treatment approach based on antibiotics susceptibility tests and localized resistance [34][38][39][40][41]. A clinical study that analyzed the failure of treatment revealed that isolated *H. pylori* has either individually or populationally developed multidrug resistance [42]. A study genotyped 112 *H. pylori* strains isolated from a region with prevalent *H. pylori* infection that apply quadruple treatment found strains with dual resistance to metronidazole and levofloxacin (20.5%) and triple resistance to metronidazole, clarithromycin, and levofloxacin (~7%) [11]. A study investigating the tailored treatment strategy found that out of 40 patients, some patients were infected with multiple strains or singular strains that exhibited different resistance phenotypes depending on the region of stomach the strain was isolated from [42]. Clarithromycin resistance is attributed to mutations in the 23S rRNA [43]; metronidazole resistance was associated to the mutations in *rdxA* and *frxA* loci [44]; levofloxacin resistance was caused by *gyrA* and *gyrB* mutations [45]. These mutations are naturally occurring, but increased prevalence in the population can occur by exposing strains to sub-MIC levels of antibiotics, such as levofloxacin [46]. To address these resistance-based challenges, a clinical trial evaluated the effectiveness of tailored therapies in comparison with the traditional bismuth quadruple therapy, and it was demonstrated that the tailored bismuth/quadruple therapy was more effective [34]. Intriguingly, another case study examined 101 clinical *H. pylori* isolates from Indonesian patients with gastritis (90.1%), peptic ulcer disease (8.9%), and gastric cancer (1%) and discovered that 93% of the isolates formed biofilms [38]. These studies strongly suggest that biofilm formation may plays a vital role in facilitating *H. pylori* to acquire high antibiotic tolerance; therefore, the eradication of *H. pylori* biofilm is likely a key process for clinical therapy. Nevertheless, there are challenges in clinal therapies: (1) planktonic susceptibility of minimal inhibitory concentration (MIC) may not be a reliable indicator of Minimal Biofilm Eradication Concentration (MBEC) with certain antibiotics [38][47][48]; (2) the isolation of clinical strains is not always a simple procedure as it requires the acquisition of gastric biopsies through endoscopic procedures which are not recommended as first line treatments for *H. pylori*-infected patients

[11][32]. Therefore, it would be very interesting to understand if targeting biofilm formation would enhance *H. pylori* treatment.

4. Regulation in *H. pylori* Biofilm

Accumulating evidence suggests that *H. pylori* biofilm formation is under complicated regulations. It includes the small molecules-mediated signaling, such as AI-2 induced quorum sensing [22] and (p)ppGpp-mediated stringent response [49], two component systems, such as ArsRS acid response system [19][50][51], and transcriptional re-programing [52]. For example, dysfunction of autoinducer molecule AI-2 secretion coding gene *luxS* lead to the more robust biofilm, indicating that quorum sensing plays a regulatory role in biofilms [22]. Similarly, increased (p)ppGpp production and transcriptional upregulation of its coding gene *spoT* was both found in *H. pylori* biofilm. In turn, the absence of *spoT* results in a biofilm defect, indicating that (p)ppGpp-mediated stringent response may play an important role in regulating *H. pylori* biofilm formation [49]. In addition, mutations in the ArsRS acid response system also leads to hyper biofilm formation. In *H. pylori*, biofilm formation has also been suggested to regulations of several transcriptional regulators, such as *fliA*, *flgR*, *hp1021*, *fur*, *nikR*, and *crdR* [52].

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