Association Between Horizontal Gene Transfer and Adaptation of Gastric Human Pathogen *Helicobacter pylori* to the Host

Surekha Challa and Nageswara Rao Reddy Neelapu

Abstract *Helicobacter pylori* exhibit remarkable survival even in the vulnerable environments such as acidic, peristalsis, phagocytosis and oxidative stress. These stresses on the pathogen in the host induce damage of DNA in the pathogen. *H. pylori* acquired the ability to survive DNA damage by transformation-mediated recombination DNA repair. This repair mechanism helps the pathogen in successfully infecting the host. While many pathogens are competent for transformation only in certain environmental conditions such as starvation, *H. pylori* is competent throughout the growth. *H. pylori* may acquire the genetic material from the surrounding environment and contribute to evolution and genetic diversity. The mechanism in acquiring genetic material is 'horizontal gene transfer', the major contributing factor in the development of bacterial diversity. Horizontal gene transfer may help the pathogen *H. pylori* in acquiring antigenic determinants, genes of antibiotic resistance and virulence factors from other organisms to alter and influence pathogenicity. In this chapter, we review and discuss the association between horizontal gene transfer and adaptation of gastric human pathogen *H. pylori* to the host.

Keywords Antibiotics resistance · Evolution · Horizontal gene transfer · *H. pylori* · Macro-diversity · Multidrug resistance · Nickel-binding proteins · Nickel transporter genes

1 Introduction

Helicobacter pylori was discovered in human stomach, dental plaque, oral lesions, saliva, tonsil and adenoid tissue. *H. pylori* was known for causing gastrointestinal disorders like gastritis, ulcers and gastric cancer (Neelapu et al. 2014; Neelapu

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2018). Sometimes *H. pylori* may trigger some other diseases like otitis, sinusitis, phyrangitis, laryngitis and glossitis (Kurtaran et al. 2008). Microorganisms survive in nature either as individuals or in a community known as biofilm (Challa et al. 2018). *H. pylori* uses biofilm lifestyle to survive in unfavourable environmental conditions such as pH, antibiotics, immune defences, disinfectants, nutritional changes and high temperatures (Challa and Neelapu 2018). Biofilm provides a strong platform for interaction and communication among the individuals present in the colony (Mohana Sheela et al. 2018; Neelapu et al. 2018). Till date research to prevent bacterial infections involved identification of drug targets, drugs (Neelapu et al. 2013, 2015, 2016; Neelapu and Pavani 2013; Nammi et al. 2016, 2017), vaccines (Pasupuleti et al. 2017) and antibiofilm agents (Challa and Neelapu 2018). This review discusses how bacterium *H. pylori* acquire traits via horizontal gene transfer (HGT) and adapt to the particular niche.

2 Role of HGT and Mechanisms of *H. pylori* Adaptation to the Host

The "selective pressures on the invading *H. pylori* bacteria would expose it to environment (e.g., exposure to antibiotics and changes in gastric pH or mucosal defences) and host factors (e.g., specific and nonspecific defence mechanisms) (Ferrero and Jenks 2001). These pressures are harmful damaging DNA of *H. pylori* and sometimes may also prevent the colonization of *H. pylori* strain (O'Rourke et al. 2003). *H. pylori* are competent enough to pick DNA from the surroundings either from other *H. pylori* strains, or from other bacteria in the gut of the host (via HGT) or sometimes even in from the host (Fig. 1). Then *H. pylori* use acquired transformation-mediated recombination DNA repair for successful infection of the pathogen" (Dorer et al. 2010). This transformation is helping the bacteria to adapt itself in the gastric niche of the host (Schuster et al. 2008). Literature also reports changes in the genomic material of *H. pylori* when transmitted between individuals of the host. Burst of mutations will be induced when exposed to selective pressures mentioned above (O'Rourke et al. 2003). These bacteria (*H. pylori*) harbour genes which are affected and/or not mutated changing the surface components of bacteria (Linz et al. 2013). This becomes disadvantage to the pathogen, where it is indirectly recognized by the host. During evolution some of the genes will be deleted and some genes will be imported via HGT from the already adapted bacteria which are coexisting in the gut of the host altering the surface components (Linz et al. 2013). This importation helps the bacteria to shape its genome and adapt to the host of the genome (Schuster et al. 2008; Eppinger et al. 2006). This demonstrates the role of HGT in shaping the genome of bacteria to adapt it to the new host.

HGT, the "key evolutionary force", transferred genetic material between genomes and thereby shape the genome of bacteria. This helped many bacteria to

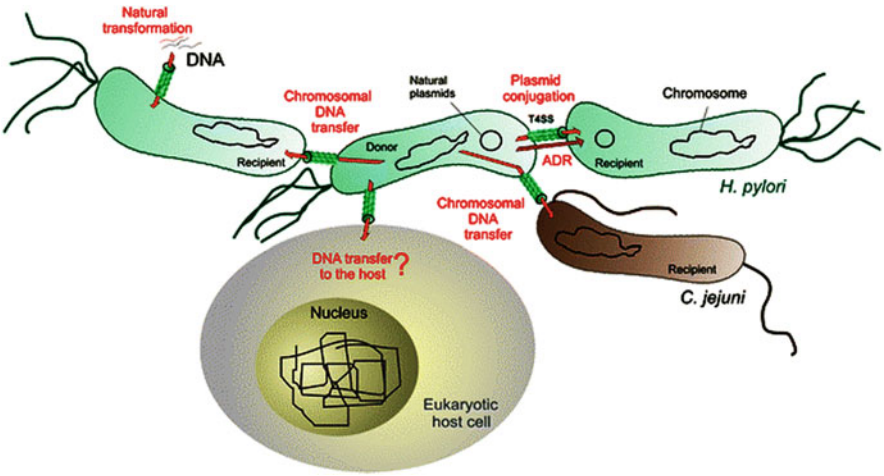

Fig. 1 *H. pylori* are competent enough to pick DNA from the surroundings either from other *H. pylori* strains or from other bacteria (*Campylobacter jejuni*) in the gut of the host (via HGT) or sometimes even from the host (Source: Fernandez-Gonzalez and Backert 2014)

gain genes and selectively provided advantages to the bacteria (Fernandez-Gonzalez and Backert 2014; Garcia-Aljaro et al. 2017). Literature reports that adaptation of *H. pylori* to the gastric niche (Vinella et al. 2015; Fischer et al. 2016), micro- and macrodiversity in *H. pylori* (Alm et al. 1999; Hofreuter and Haas 2002) and antibiotic resistance in *H. pylori* (Von Wintersdorff et al. 2016; Lood et al. 2017) are due to HGT. This section discusses in detail (a) HGT of nickel-binding proteins, nickel transporter genes and their role; (b) macrodiversity in *H. pylori* and HGT; and (c) antibiotic resistance in *H. pylori* and HGT. This section further discusses how HGT has shaped the genome of *H. pylori* in due course of evolution.

2.1 HGT of Nickel-Binding Proteins, Nickel Transporters Genes and Their Role

H. pylori utilizes specific enzymes or Ni proteins like urease and [NiFe] hydrogenase for colonization of gastric tract in humans (Fischer et al. 2016). The pH in the stomach is acidic and urease (Ni protein) of *H. pylori* helps in changing/converting the acidic pH in the stomach to neutral pH. Urease needs a cofactor nickel to convert urea into CO_2 and NH_3 (Neelapu et al. 2014; Fischer et al. 2016). These compounds are used by the bacteria to maintain the pH in the bacterium cytoplasm near to neutral. [NiFe] hydrogenase (Ni protein) is another enzyme where a bacterium utilizes molecular hydrogen as a source of energy (Fischer et al. 2016). Nickel is scarcely or meagrely available in the human body. So, *H. pylori* requires nickel transporter genes for acquisition of nickel and colonization of *H. pylori*. Thus,

"...acquisition of nickel transporters and Ni-binding proteins by gastric *Helicobacter* species was a key event for the emergence of one of the most successful bacterial pathogens, *H. pylori*..." (Vinella et al. 2015; Fischer et al. 2016). Transporters (NixA, NiuBDE, NikABCDE and NikZOppBCDE), Ni-dependent enzymes (urease, hydrogenase) or Ni-binding proteins (Hpn and Hpn-2) were reported in all *Helicobacter* species (Vinella et al. 2015; Fischer et al. 2016).

2.1.1 HGT of Nickel-Binding Proteins Histidine-Rich Proteins

Histidine-rich proteins, Hpn and Hpn-2, are known to protect gastric *Helicobacter* species against nickel overload. They also accumulate intracellular nickel and store this nickel indirectly helping them to colonize the stomach of the host. Vinella et al. (2015) revealed that histidine-rich proteins (Hpn) emerged in the last common ancestor (LCA) of gastric *Helicobacter* species. Hpn and hpn-2 genes are specific to the gastric *Helicobacter* species and are not in enterohepatic species (Vinella et al. 2015). Hpn plays a major role in the protection of *H. pylori* against nickel overload and participates in the accumulation of intracellular nickel storage, while Hpn-2 is not required for both these functions (Fig. 2) (Vinella et al. 2015). Hpn interacts with

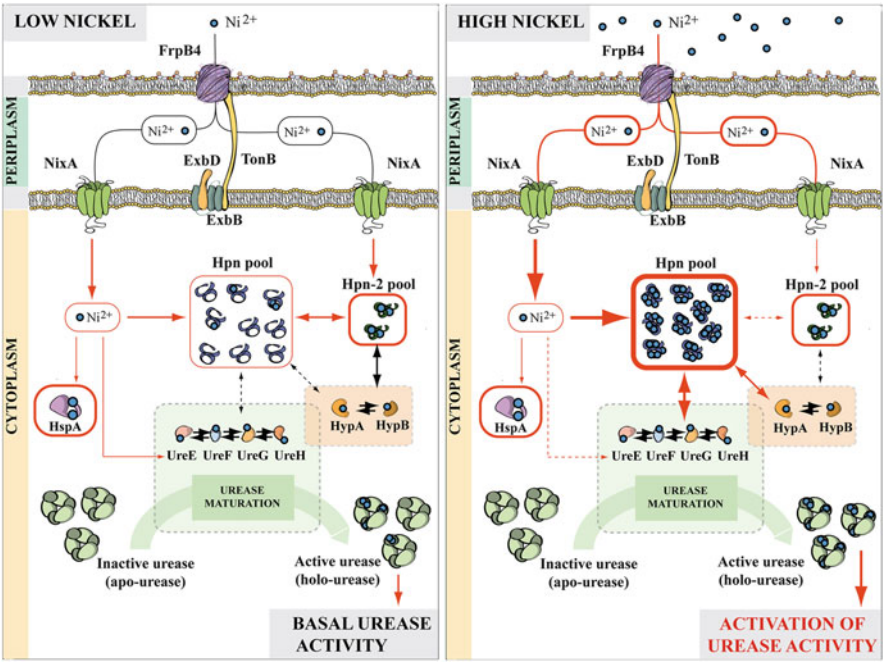

Fig. 2 Role of Hpn and Hpn-2 in nickel trafficking, protection against nickel overload, urease activity and colonization of the host stomach (Source: Vinella et al. 2015)

the UreA urease subunit, while Hpn and Hpn-2 interact with the HypAB hydrogenase maturation proteins (Fig. 2) (Vinella et al. 2015). Hpn and Hpn-2 are essential for colonization of gastric *Helicobacter* species in the host stomach (Vinella et al. 2015). Vinella et al. (2015) proved that *hpn* and *hpn* mutants of *H. pylori* were not able to colonize the stomach in the mouse model, whereas *hpn* and *hpn* mutants of *H. pylori* when complemented with wild genes were able to establish and colonize in the mouse model (Fig. 2). This allowed the *Helicobacter* gastric species to thrive in the stomach by protecting them against nickel overload, participating in the accumulation of intracellular nickel storage and colonization of the host stomach. Thus acquisition of Ni-binding proteins (Hpn and Hpn-2) via HGT followed by a ". . .decisive evolutionary event allowed the bacteria to adapt the human stomach a niche that no other bacterium colonized and helped in the emergence of *Helicobacter* species . . . ."

2.1.2 HGT of Nickel Transporters Genes

Emergence of Ni-binding proteins (Hpn and Hpn-2) in gastric *Helicobacter* species was further supported by HGT of nickel transporter genes NixA and NiuBDE. Gastric *Helicobacter* species were able to pick up nickel-binding proteins and nickel transporter genes via HGT and adapted itself to the gastric niche. Fischer et al. (2016) revealed that LCA of gastric *Helicobacter* species and *H. pylori* acquired Ni-binding proteins and nickel transporter genes via HGT to survive in the stomach (Fig. 3). The successful acquisition of nickel transporters genes NixA and NiuBDE via HGT allowed the bacteria to utilize nickel transporter genes for urease activity (nickel-dependent urease activity) by a decisive evolutionary event. This evolutionary event can be considered as a significant change in the genome of gastric *Helicobacter* species allowing the bacteria to adapt the human stomach a niche that no other bacterium colonized and helped in the emergence of *Helicobacter* species.

The key role of nickel transporter genes and Ni-binding proteins shows that nickel plays a very important role in the colonization of *H. pylori*. Campanale et al. (2014) carried out a pilot study by supplementing *H. pylori*-infected patients with the nickel-free diet for 1 month and found that the nickel-free diet was able to enhance the efficiency of eradication therapy. This study recommends nickel-free diets for those patients who are infected with *H. pylori*, and further clinical trial studies are also required to prove the safety of the diet.

2.2 *Macrodiversity in* H. pylori *and HGT*

Macrodiversity between *H. pylori* strains is due to intragenomic rearrangements like deletion, inversion, or translocation (Alm et al. 1999). *H. pylori* possess insertion sequences like IS605 and IS606 and several plasticity zones in strains like Hp26695

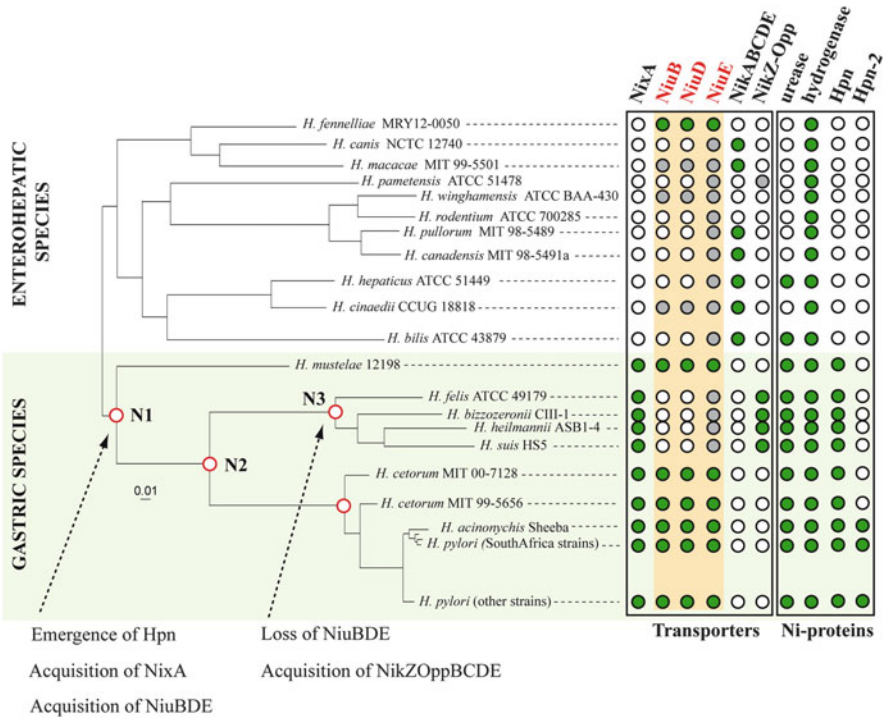

Fig. 3 Distribution, phylogeny and evolutionary history on acquisition of nickel transporter genes by gastric *Helicobacter* species (Source: Fischer et al. 2016)

and HpJ99. Plasticity zones are not limited to these *H. pylori* strains, but were also present and reported in other strains of *H. pylori*. These plasticity zones differ in GC content when compared to chromosomal GC content. For example, Hp26695 contains five plasticity zones with GC contents of 33% (zone 1), 35% (zone 2), 33% (zone 3), 43% (zone 4) and 33% (zone 5), which differ from the chromosomal GC content of 39% (Tomb et al. 1997). These plasticity zones in *H. pylori* might have been received via horizontal gene transfer. Conjugation and natural transformation are the mechanisms of HGT identified in *H. pylori*.

Nedenskov-Sorensen et al. (1990) first described the natural transformation in *H. pylori*, and several genes were identified in *H. pylori* which are acquired via transformation process (Schmitt et al. 1995; Hofreuter et al. 1998; Ando et al. 1999; Smeets et al. 2000). Natural transformation in *H. pylori* is mediated by type IV secretion system (Hofreuter et al. 2001). *H. pylori* encodes four T4SSs including cagPAI (mediates injection of CagA protein and induces proinflammatory signalling), comB (system involved in the uptake of DNA from the environment) and tfs3 and tfs4 genes (role not yet known). *H. pylori* also contain diverse genetic modules ". . .due to the modular structure, plasmids might either pick up chromosomal genes of *H. pylori* or integrate sequence modules from foreign plasmids, which are taken

up by the bacteria during its natural transformation competence (gene shuffling) leading to macrodiversity among *H. pylori* strains and rapid generation of substrains (Hofreuter and Haas 2002)...".

2.3 *Antibiotic Resistance in* H. pylori *and HGT*

H. pylori has developed antibiotic resistance to proton-pump inhibitors, clarithromycin, metronidazole, macrolide, amoxicillin, levofloxacin, etc., or combinations of them (Savarino et al. 1997; Bardhan et al. 2001; Torres et al. 2001; Osaki et al. 2006; Zullo et al. 2007; Ndip et al. 2008; Boyanova et al. 2009; Gao et al. 2010; Sun et al. 2010; Wüppenhorst et al. 2011; Bolor-Erdene et al. 2017; Lee et al. 2018). Multidrug resistance (MDR) or antibiotic resistance in *H. pylori* can be eradicated by identifying new or alternative drug targets, developing new drug combinations (Neelapu et al. 2013, 2015, 2016; Neelapu and Pavani 2013; Nammi et al. 2016, 2017; Pasupuleti et al. 2017) and using Chinese herbs (Huang et al. 2015). The new drug combinations developed for *H. pylori* in view of MDR are levofloxacin or moxifloxacin (novel class of fluoroquinolones) with amoxicillin, rifabutin and furazolidone. The Chinese herbs, namely, emodin, baicalin, schizandrin and berberine, can also be used to treat MDR in *H. pylori* (Huang et al. 2015).

Literature reports interspecies and intraspecies gene transfer of metronidazole and clarithromycin resistance between *Helicobacter* species (Table 1). Pot et al. (2001) proved interspecies transfer of antibiotic resistance genes between *H. pylori* and *Helicobacter acinonychis*. To prove these Kusters and group demonstrated that

Table 1 Antibiotic resistance genes metronidazole and clarithromycin transferred to *H. pylori* and *Helicobacter acinonychis* via HGT

S. no	Recipient strain	Donor DNA	Antibiotic resistance
1	*H. pylori* 26,695	*H. acinonychis* NCTC12686 MtzR	Metronidazole
2	*H. pylori* 26,695	*H. acinonychis* Sheeba MtzR	Metronidazole
3	*H. pylori* J99	*H. acinonychis* NCTC12686 MtzR	Metronidazole
4	*H. pylori* J99	*H. acinonychis* Sheeba MtzR	Metronidazole
5	*H. acinonychis* Sheeba MtzS	*H. pylori* 1061 MtzR	Metronidazole
6	*H. acinonychis* Sheeba MtzS	*H. pylori* NCTC11637	Metronidazole
7	*H. acinonychis* Sheeba MtzS	*H. pylori* pRdxA	Metronidazole
8	*H. acinonychis* Sheeba MtzS	*H. pylori* 1061 MtzR/ClaR	Clarithromycin
9	*H. acinonychis* Sheeba MtzS	23S rDNA PCR product of 1061 MtzR/ClaR	Clarithromycin
10	*H. acinonychis* NCTC12686 MtzS	*H. pylori* 1061 MtzR	Metronidazole
11	*H. acinonychis* NCTC12686 MtzS	*H. pylori* NCTC11637	Metronidazole
12	*H. acinonychis* NCTC12686 MtzS	*H. pylori* 1061 MtzR/ClaR	Clarithromycin

Source: Pot et al. (2001)

". . .*H. acinonychis* is competent for natural transformation and *H. pylori* can acquire antibiotic resistance by uptake of DNA (HGT) from other *Helicobacter* species and vice versa. . . ." (Pot et al. 2001). Pot et al. (2001) isolated DNA from *H. acinonychis* isolate NCTC12686 (NCTC12686 MtzR) and *H. acinonychis* isolate Sheeba (Sheeba MtzR) metronidazole-resistant strains. This isolated DNA was used for natural transformation of two metronidazole-sensitive *H. pylori* as per the standard protocol of Wang et al. (1993). Upon transformation metronidazole-resistant transformants were obtained for both *H. pylori* strains. Similarly, *H. acinonychis* strains were readily transformed to clarithromycin resistance strains by uptake of PCR product via natural transformation. The above two experiments demonstrate that bacterium like *H. pylori* can acquire antibiotic resistance genes like metronidazole and clarithromycin via HGT contributing to the antibiotic resistance of the pathogen *H. pylori*. This also shows that *H. pylori* naturally has a way to successfully infect the host even in the presence of harmful antibiotics.

3 Conclusion

Helicobacter pylori survives even in the vulnerable environments such as acidic, peristalsis, phagocytosis and oxidative stress. These stresses induce damage in pathogen DNA and *H. pylori* had acquired the ability to survive DNA damage by transformation-mediated recombination DNA repair. *H. pylori* is competent throughout the growth which may help in acquiring the genetic material via HGT from the surrounding environment and contribute to evolution and genetic diversity especially macro-diversity. *H. pylori* has acquired nickel-binding proteins (Hpn and Hpn-2) and nickel transporter genes (NixA and NiuBDE) via HGT which helped the pathogen to establish itself as gastric species during the course of evolution. This further helped the pathogen *H. pylori* to adapt itself and survive in the gastric niche. *H. pylori* also has the capability to acquire genes of antibiotic resistance (metronidazole and clarithromycin) in addition to antigenic determinants and virulence factors via HGT from other organisms to alter and influence pathogenicity. This review clearly reveals the role of horizontal gene transfer in gastric human pathogen *H. pylori* to adapt itself to the host.

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Authors Contribution CS and NNR initiated the review, participated in writing and revised the manuscript.

Conflict of Interest The authors declare that there is no potential conflict of interest.

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