Steffen Backert · Yoshio Yamaoka
Editors

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From Bench to Bedside

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Foreword

Helicobacter pylori, the Gastric Bacterium Which Still Infects Half the World's Population, Is an Important Part of Gastroenterology and Infectious Disease

It is exciting to participate in this new "state-of-the-art" book about *Helicobacter pylori*, the gastric bacterium which still infects half of the human race and which promises to challenge clinicians and scientists for decades to come. The book is structured so as to place *H. pylori* in perspective as the gastric bacterium attached itself to prehistoric humans and followed their migrations, through the stone-age into the twenty-first century. Thus the first chapter, by Yoshan Moodley, sets us up to ask the questions which can then be answered in depth by the other experts. Where did *H. pylori* come from? How does it survive in the stomach? What unique adaptations have taken place, which allow it to persist throughout life? If it colonised mankind for so long, was there once a useful purpose in having *H. pylori*? Is it still useful in some way? As complete genome sequencing technology becomes widespread, many will use this in-depth initial chapter as a hypothesis generating knowledge-base for our own molecular epidemiology studies. Examples are even given of newer technologies such as RNAseq, for examining gene expression and intergenic control regions. Later, Ichizo Kobayashi predicts that further breakthroughs via OMICS analyses will also provide more insight into the evolution of both the genome and methylome of this highly diverse model organism.

Once the big picture has been described, we want to know how *H. pylori* accomplishes this and "what makes it tick?" So we delve into *H. pylori* biochemistry realising that the metabolism of the bug mirrors the microenvironment of the gastric mucosa (Fischer and deReuse, Praszkier, Sutton and Ferrero; Backert, Zanotti, Lind, Asche and Tegtmeyer; Cover, Holland and Blanke; Arnqvist; Wessler; Pernitzsch, Darfeuille and Sharma). In a hostile acidic milieu, but under the mucus layer, *H. pylori* solve the problems of immediate survival but then must deal with the host's attempts to remove the invader. Certainly, its very plastic

genome is an advantage coupled with the massive numbers of organisms competing for life in that niche. But other mechanisms exist whereby *H. pylori* regulate the immune response, optimising its nutrition without allowing the mucosa to be totally disrupted by too vigorous tissue reaction. Subtle degrees of positive and negative feedback must be at work. A clear explanation of the interrelated virulence factors, primarily CagA and VacA, and then the several newer surface antigens is given in subsequent chapters, perhaps explaining how *H. pylori* disguises itself from the immune response.

As we move from basic to clinical research in *H. pylori*, animal models of the infection become even more important. Chapters on this theme describe the 100-year-long history of various related *Helicobacters* in animals and more recent insights into their genomics and taxonomy (Flahon, Haesebrouck and Smet; Solnick, Eaton and Peek; Müller and Hartung; Oshima, Nakayama and Oshima; McLean; Nicoll, Saw, Hold and El-Omar). How the animal infections provide guidance into the realm of animal models remains important. Chapters on the trials and tribulations of current animal models serve to emphasise that the perfect animal model is yet to be discovered, unless it is still the human. Nevertheless, selection of or direct manipulation of small animal genetics serves to tease out important predictors of epidemiology, colonisation, inflammation and carcinogenesis.

In this context, the clinician will be delighted to study the detailed clinical chapters on human diseases related to *H. pylori* infection (Boltin and Niv; Genta and Lash; Wroblewski and Peek; Sagaert; Koletzko and Megraud). The reasons to treat *H. pylori* and features of the host and the bacterium which drive the various phenotypes of asymptomatic, ulcerated and malignant gastric disorders will give confidence to the clinician seeing patients with gastric disorders. In addition, the spectre of rarer non-gastric disorders is exposed, as these will be seen from time to time and the gastroenterologist or infectious disease specialist will be expected to assist decisions into their management too. Very relevant here is the controversial area of immune modulation from *H. pylori*. It is relevant to many areas, but the tantalising possibility exists that *H. pylori* could still play a useful role, as an immune modulator, like "oil on troubled waters" to decrease the apparent overshoot which commonly occurs in allergy susceptible individuals. Certainly the negative association with asthma in New York children and in adults with various inflammatory gastrointestinal diseases is worthy of study and is authoritatively reviewed in immunology-related and paediatric chapters.

Finally, it is great to see that the common, real-world issues of *H. pylori* treatment are dealt with by authors who have many years of experience successfully curing difficult to treat patients (Molina-Infante and Graham; Malfertheiner and Selgrad; Torres, Correa, Herrero, Piazuelo and Ferrecio; Miftahussurur and Yamaoka; Vale, Vitor and Oleastro; Raghavan and Quiding-Järbrink). While the level of antibiotic resistance has been creeping up, most notably to macrolides and quinolones, logical planning of treatment, with sophisticated microbiological testing, can give us confidence. Several new antibiotics and/or combinations of well-known drugs mean there is a bright, *H. pylori*-free future for patients with the bacterium.

Finally, we are shown glimpses of the twenty-first century future where *H. pylori* infection might be prevented, or eradicated rather simply, in each continent. This is already starting and will become easier as the knowledge in this book is disseminated. Strategies to improve hygiene, vaccinate, treat and even suppress *H. pylori* with foods and probiotic supplements are all relevant here and are now being tested.

In summary then, every science graduate will enjoy the intelligent structure of this book which uses in-depth explanation of the current knowledge to suggest how gastric colonisation with *H. pylori* might be a tool to unlock secrets related to the physiology of the gastrointestinal tract and the gastrointestinal immune system. The clinician also will be delighted with the extensive discussions of important disease associations and then, most importantly, how to render the patient *H. pylori* negative.

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Part I
Bacteriology and Molecular Biology

Chapter 1
Helicobacter pylori: Genetics, Recombination, Population Structure, and Human Migrations

Yoshan Moodley

Abstract Humans and their stomach bacterium *Helicobacter pylori* share a coevolutionary relationship that spans at least the last 100,000 years and quite possibly even longer. Population and evolutionary genetic research has demonstrated a species-wide phylogeographic structure that faithfully mirrors that of its human host. However, because of its very high genetic diversity and fast generation time, *H. pylori* DNA sequences are often better able to resolve prehistoric human migrations than human DNA markers. The worldwide genetic diversity of *H. pylori* has, thus far, been divided into 7 populations and 14 subpopulations, most of which are now established markers for recent and prehistoric human migrations. Key developments such as the inference of hypothetical ancestral populations and the implementation of coalescent models have provided a clearer understanding of the population historical role of admixture and recombination and helped superimpose a chronology onto the human *H. pylori* association, from which the timing, direction, and magnitude of migration events can be accurately inferred. However, there remain large parts of the world from which *H. pylori* has never been cultured, and this, along with a move to sequence whole genomes rather than just housekeeping genes, will form the basis of future evolutionary genetic research.

Keywords *Helicobacter pylori* • Coevolution • Population • Recombination • Phylogeography • Coalescence • Migrations

1.1 Introduction

In 1984, Barry Marshall and Robin Warren discovered the spiral-shaped stomach bacterium *Helicobacter pylori*, and for demonstrating its role in gastritis and peptide ulcer formation (Marshall and Warren 1984; Marshall et al. 1985), they

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were awarded the Nobel Prize for medicine in 2005. Since its discovery, ongoing research has shown that this bacterium is present in 50 % of human stomachs worldwide, the vast majority of whom are asymptomatic. *H. pylori* is usually contracted early in childhood, and once acquired, bacterial colonization is generally lifelong. The bacterium can be transmitted within families (e.g., from parents to children, Kivi et al. 2003; Tindberg et al. 2001) but also between unrelated people living in close proximity (Delport et al. 2006; Schwarz et al. 2008). Unusually high mutation (Björkholm et al. 2001; Morelli et al. 2010) and homologous recombination rates (Falush et al. 2001; Suerbaum et al. 1998) have resulted in very high DNA sequence diversity that is much greater than that of other bacteria (Achtman et al. 1999) and 50-fold greater than its human host (Li and Sadler 1991). Unlike chromosomal mutations, which can occur at random in any part of the species distribution, recombination necessarily requires mixed colonization (Falush et al. 2001; Raymond et al. 2004; Kersulyte et al. 1999; Taylor et al. 1995) and, by extrapolation, very close human proximity. The end result is a human bacterial species whose range-wide genetic structure mirrors that of its host. In the following review, I will outline the stages of development of evolutionary genetic research that have helped transform our understanding of *H. pylori* – from a newly discovered human pathogen to our species' oldest-known and most faithful commensal.

1.2 The Coevolution of *Helicobacter pylori* and Humans

1.2.1 H. pylori*'s Housekeeping Genes*

Meaningful population and evolutionary analyses of DNA data must dissect out demographic processes (genetic drift and gene flow) from selection processes, since both have the ability to alter allele frequencies. Typically, the selection issue is circumvented in eukaryotic species by only analyzing genes or regions that are, or are at least thought to be, selectively neutral – such as mitochondrial DNA (Cann et al. 1987), nuclear intronic sequences (Matthee et al. 2001), and repeat elements (Bruford and Wayne 1993). The smaller, more conserved genomes of bacteria, however, make such approaches untenable. Instead, the genes chosen for analyses are necessary housekeeping genes, encoding cytoplasmic enzymes. They are distributed across the *H. pylori* genome (Achtman et al. 1999) and are unlinked to genes encoding putative outer membrane or secreted or hypothetical proteins that might be under selection. They are more likely therefore to represent genome-wide selectively neutral variation.

The most incisive evolutionary or population genetic knowledge about *H. pylori* has, until very recently, been inferred from the DNA sequences of a set of seven housekeeping gene fragments. These genes, *atpA*, *efp*, *mutY*, *ppa*, *trpC*, *ureA*, and *yphC*, were originally the basis of an attempt at multilocus sequence typing (MLST) of *H. pylori* (Achtman et al. 1999) along the lines of what was then recently and