REVIEW

Helicobacter pylori infection and gastric carcinoma

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Abstract

Helicobacter pylori infection is considered to be the main cause of gastric cancer and the most frequent infection-induced cancer. *H. pylori* is a heterogeneous species which can harbour pathogenic factors such as a cytotoxin, a pathogenicity island (*cag*) encoding a type 4 secretion system, and the first bacterial oncoprotein, CagA. This oncoprotein appears to be involved in the carcinogenic process in addition to the inflammation generated. This process may concern either local progenitors *via* an epithelial–mesenchymal transition, or recruited bone marrow–derived mesenchymal cells. There are also environmental factors such as iron deficiency or high-salt diets which interact with the bacterial factors to increase the risk of gastric cancer as well as genetic polymorphism of certain cytokines, e.g. IL-Iβ. Recent data suggest that a break in coevolution of a particular phylogeographic lineage of *H. pylori* and its usual host may also be a risk factor. Studies are currently being performed to assess the feasibility of organized *H. pylori* eradication programmes to prevent gastric cancer.

Keywords: CagA oncoprotein, cancer stem cells, carcinogenesis, epithelial–mesenchymal transition, prevention, VacA cytotoxin
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Introduction

Among the cases of cancer which could be attributed to infection, in the world in 2008, i.e. 16.1% of new cases (about 2 million out of 12.7 million) according to the International Agency for Research on Cancer, *Helicobacter pylori* infection was the leading cause and represented 5.5% of the total number of cases, while the other main agents were viruses [1].

H. pylori was discovered relatively recently, in 1982, and has proved to be the cause of gastric and duodenal ulcers [2]. For this discovery, Warren and Marshall were awarded the Nobel Prize for medicine in 2005.

However, *H. pylori* infection is also considered to be the main risk factor of gastric cancer development, namely gastric carcinoma and gastric mucosa-associated lymphoid tissue lymphoma [3] (Fig. 1). Here we will only consider the former, while the latter will be discussed in another article. We will review the characteristics of *H. pylori* and the consequences of the infection, the risk factors other than *H. pylori* for cancer development and the current status of prevention of gastric cancer.

Helicobacter pylori

H. pylori is an epsilonproteobacterium and a member of the *Helicobacteraceae* family, separated from *Campylobacteraceae* in 1989 [4]. Helicobacters are classified into two types according to their customary niche: gastric and enteric. The *Helicobacter* species adapted to humans is *H. pylori* and is a gastric *Helicobacter*. Others originating from pets or food animals can rarely be found in humans as zoonotic bacteria.

H. pylori is a very heterogeneous species but characteristics important for colonization and pathogenesis are found in most of the strains. *H. pylori* harbours various adhesins, the most important being BabA and SabA, which allow it to colonize the epithelial layer, mainly in the antrum. Indeed, despite living in the stomach, *H. pylori* is relatively acid sensitive. It can grow at pH 5 but does not grow and only survives at pH 4. A key factor is its production of urease, which is quantitatively important

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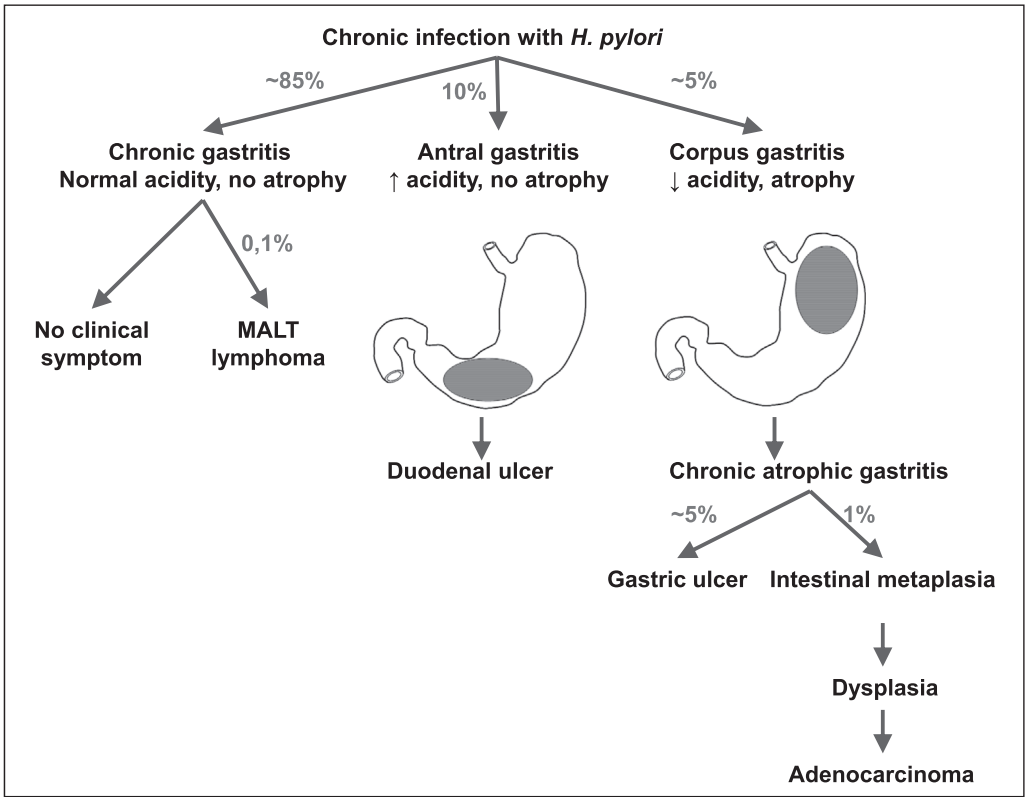

FIG. 1. Various consequences of *Helicobacter pylori* infection.

and allows it to buffer its microenvironment by breaking down the low amount of urea present in the gastric mucosa, producing ammonia [5].

Once colonization is established, the infection can last for decades and can even be lifelong. The basic lesion observed in all cases is gastritis, i.e. an infiltrate of lymphocytes and polymorphs in the gastric mucosa. In some individuals, and especially youngsters, it may even take on the aspect of lymphoid follicles, normally absent in the stomach [6].

Among the pathogenic factors is a cytotoxin named VacA. There is a polymorphism of the *vac*A gene, and according to the allele present, varying amounts of the toxin can be produced influencing the outcome [7]. A pathogenicity island is also present in about half of the strains. Among the 30 genes present in the island, some code for a type 4 secretion system (T4SS), which is similar to a syringe allowing the introduction of bacterial molecules in the epithelial cell. The most important of these compounds is CagA, considered to be the first bacterial oncoprotein. Once in the epithelial cell, CagA is phosphorylated by cellular kinases and then interacts with a number of signalling pathways [8]. CagA is also heterogeneous with regard to the number and type (A, B, C, D) of phosphorylation motifs present. Types C and D have been associated with the highest risk of cancer [9].

Other *H. pylori* molecules can also be introduced into the epithelial cells, such as muramyl dipeptide (MDP), which is part of the peptidoglycan cell wall of the bacterium. MDP is detected by the intracellular NOD receptors which activate the NF-κB pathway with production of IL-8 and attraction of inflammatory cells [10].

Oncogenic consequences of *H. pylori* infection

Gastric adenocarcinoma is a heterogeneous cancer. First, it is necessary to distinguish the tumours arising from the gastric proximal stomach (cardia), as most of them are not linked to *H. pylori* infection from those found in the distal part of the stomach. Among tumours from the distal stomach, on the basis of histology, it is usual to differentiate two types of cancer lesions: the intestinal type and the diffuse type according to the Lauren classification [11].

Intestinal type cancer is the most frequent. It corresponds to a slow evolution of the gastric mucosa which becomes atrophic; then intestinal metaplasia appears, followed by dysplasia and ultimately *in situ* gastric carcinoma and metastatic carcinoma (Fig. 2). This is the so-called Correa cascade, which was described before *H. pylori* was discovered and appears late in life [12].

