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Review

Genetic host factors in *Helicobacter pylori*-induced carcinogenesis: Emerging new paradigms☆,☆☆

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ABSTRACT

Helicobacter Pylori is a gram negative rod shaped microaerophilic bacterium that colonizes the stomach of approximately half the world's population. Infection with *c* may cause chronic gastritis which via a quite well described process known as Correas cascade can progress through sequential development of atrophic gastritis, intestinal metaplasia and dysplasia to gastric cancer. *H. pylori* is currently the only bacterium that is classified as a class 1 carcinogen by the WHO, although the exact mechanisms by which this bacterium contributes to gastric carcinogenesis are still poorly understood. Only a minority of *H. pylori*-infected patients will eventually develop gastric cancer, suggesting that host factors may be important in determining the outcome of *H. pylori* infection. This is supported by a growing body of evidence suggesting that the host genetic background contributes to risk of *H. pylori* infection and gastric carcinogenesis. In particular single nucleotide polymorphisms in genes that influence bacterial handling via pattern recognition receptors appear to be involved, further strengthening the link between host risk factors, *H. pylori* incidence and cancer. Many of these genes influence cellular pathways leading to inflammatory signaling, inflammasome formation and autophagy. In this review we summarize known carcinogenic effects of *H. pylori*, and discuss recent findings that implicate host genetic pattern recognition pathways in the development of gastric cancer and their relation with *H. pylori*.

1. Introduction

According to the latest WHO statistics, gastric cancer (GC) is the third cancer-related cause of death after lung and liver cancer. Although the incidence of gastric cancer is declining in the western world, still over 950,000 patients were diagnosed with gastric cancer world-wide and more than 720,000 patients died from this disease in 2014 alone [1]. When diagnosed at early stages, GC has a fairly good prognosis with a 90–95% 5-year survival [2]. However, the 5-year survival rate drops to only 20% upon late diagnosis [3], and since most GC patients do not develop symptoms until very late, it is important to identify patients that are at risk for this disease.

More than a 1000 studies on the relationship between *H. pylori* colonization and gastric cancer overwhelmingly favor this rod-shaped gram-negative microaerophilic microorganism as a causative agent of gastric cancer [4]. The attributable risk of *H. pylori* on gastric cancer is estimated to be around 74%, which would make it one of the greatest cancer risk factors, second only to smoking [5]. Due to its pivotal role in gastric carcinogenesis, the WHO has assigned a class 1 carcinogen status to this pathobiont [6]. Despite being the leading cause of gastric carcinogenesis, only a very small proportion of *H. pylori*-colonized individuals develop neoplastic changes of the stomach epithelium, and only 1–3% develops gastric cancer [7]. This might partly be explained by the differences in virulence level between the various *H. pylori* strains infecting human stomachs, with more virulent strains more commonly associated with the development of intestinal metaplasia and gastric cancer. These virulence factors and the intracellular carcinogenic pathways they activate have received vast attention. However, even though *H. pylori* eradication reduces the risk for gastric cancer, individuals in whom *H. pylori* has been successfully eradicated may still develop gastric cancer, suggesting that *H. pylori* is capable of inducing long lasting molecular changes which are not dependent on continuous

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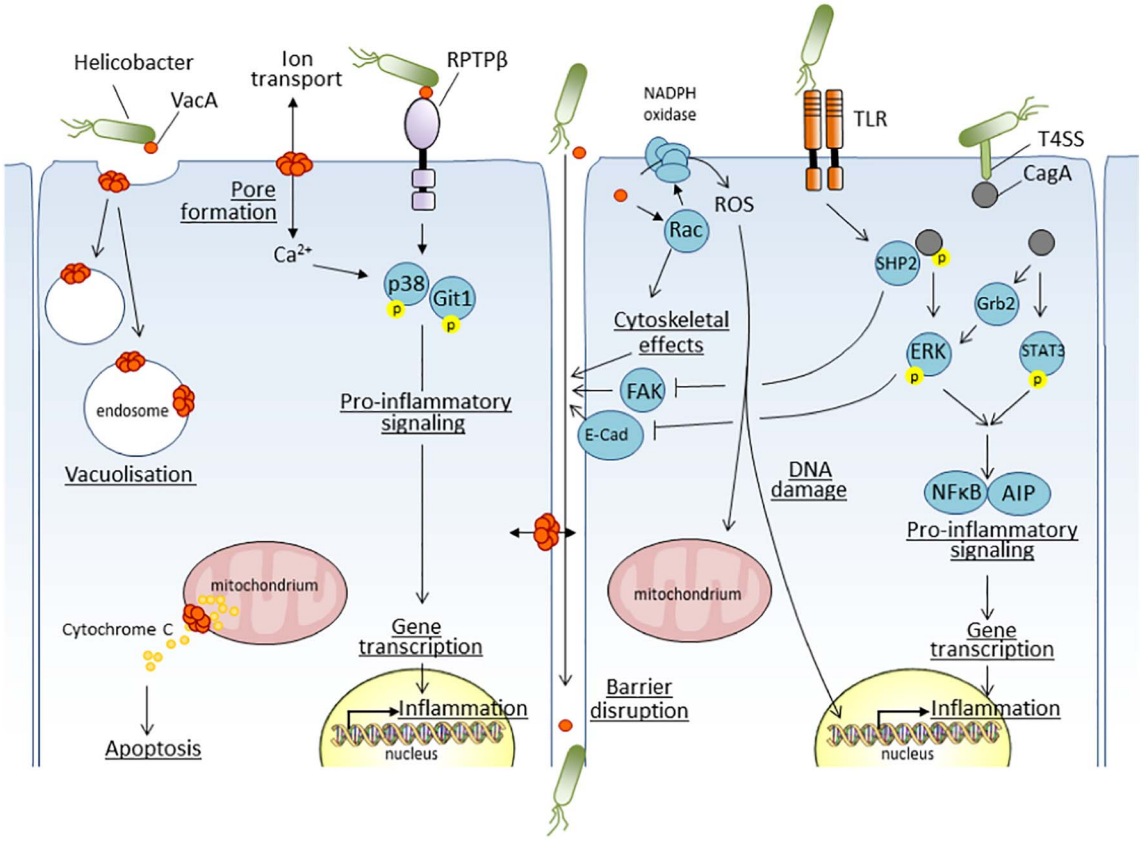

Fig. 1. Schematic view of pro-inflammatory signaling induced by *H. pylori* and its virulence factors. VacA is able to form polymers causing vacuolization. Moreover these pores are also able to facilitate ion transport and cause ca^{2+} influx leading to p38 phosphorylation. VacA pores can also cause Cytochrome C release from the mitochondria leading to apoptosis of the cell. VacA monomers can also facilitate pro-inflammatory signaling by binding to the RPTPβ receptor leading to p38 and GIT1 phosphorylation as well. Lastly VacA monomers cause ROS production through RAC activation and NAPDH leading to DNA damage and cytoskeletal effects. CagA is introduced in to the cell by the T4SS there it can be phosphorylated by SHP-2 after phosphorylation it is able to inactivate FAK which can cause elongation of cells (hummingbird phenotype). Phosphorylated CagA further contributes to these cytoskeletal malformations by phosphorylating ERK which leads to inhibition of e-Cad and also to pro inflammatory gene transcription. Lastly unphosphorylated CagAby itself is able to phosphorylate ERK through Grb2 and able to stimulate pro-inflammatory gene transcription by phosphorylating STAT3. TLR: Toll-like receptor; VacA: vacuolating cytotoxin A; CagA: cytotoxin-associated gene A; T4SS: type IV secretion system; E-Cad: E-Cadherin; FAK: Focal adhesion kinase; RPTPβ: receptor-type protein tyrosine phosphatase beta; STAT3: signal transducer and activator of transcription 3; ERK: extracellular signal regulated kinase; ROS: reactive oxygen species; NADPH: nicotinamide adenine dinucleotide phosphate.

active infection. Furthermore, increasing evidence suggests that host factors, including genetic make-up, are also important determinants for carcinogenesis in *H. pylori* infection.

Ever since a Swedish twin study in the nineties showed a higher concordance rate for *H. pylori* infection in monozygotic than in dizygotic twins, a genetic predisposition for *H. pylori* infection has been suspected [8]. Recently, genome-wide association studies (GWAS) have uncovered several single nucleotide polymorphisms (SNPs) associated with *H. pylori* colonization, and the development of intestinal metaplasia. These studies shed light on the genetic host factors predisposing to gastric carcinogenesis and provide potential clues for the molecular mechanisms by which an individual's genes may contribute to the *H. pylori*-induced carcinogenic sequence. Several of the SNPs identified are involved in bacterial handling and the induction of intracellular inflammatory pathways. Upon infection, *H. pylori* is initially recognized by innate immune cells and gastric epithelial cells through pattern recognition receptors (PRRs), and SNPs in bacterial recognition genes including several Toll-like receptors (TLRs) predispose for *H. pylori* colonization [9]. In addition, bacterial clearance involves the activation of intracellular protein degradation machinery, and SNPs in genes affecting these pathways have been shown to increase the risk of gastric cancer. The involvement of these genes, which include the autophagy and inflammasome mediators *ATG16L1*, *IL1β* and *CARD8*, suggests a thus far little recognized role for these molecular processes in *H. pylori*-mediated gastric dysplasia [10–13]. This review summarizes current hypotheses of *H. pylori*-mediated carcinogenesis, and puts forward novel pathways of gastric carcinogenesis based on the emerging evidence on the involvement of bacterial handling pathways.

2. *Helicobacter pylori* virulence factors and oncogenic signaling

Two subtypes of gastric cancer can be distinguished. The most common is the differentiated type (also known as the intestinal type adenocarcinoma), which shows atypical differentiation and follows Correa's cascade. The undifferentiated type (also known as the diffuse type) is not dependent on chronic inflammation, does not form glandular structures and commonly affects younger people. While *H. pylori* is associated with both types of gastric cancer, different mechanisms are likely to underlie these types, and this review will concentrate mainly on the intestinal type of gastric adenocarcinoma (which we will call gastric cancer unless otherwise noted). Gastric carcinogenesis is multifocal and follows a well-defined path known as Correa's cascade. The process starts with inflammation – most often through *H. pylori* infection, although other causes of inflammation, like autoimmune gastritis, are also observed [14]. Chronic *H. pylori* infection of the gastric epithelium causes chronic gastritis, which may develop into precancerous lesions like atrophic gastritis and intestinal metaplasia, and eventually progress into dysplasia and cancer.

H. pylori survives the hostile acidic environment of the stomach by producing urease, thereby catalyzing the hydrolysis of urea to ammonia and carbon dioxide, causing a locally buffered environment allowing it to enter the mucous layer [15]. Upon reaching the epithelium, *H. pylori*