Bacterial Pathogen *Helicobacter pylori*: A Bad AKT or Inhibits p53 Protein Activity

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Gastric colonization by *Helicobacter pylori* is the most prominent known risk factor for gastric cancer. A complex interplay between host and bacterial factors underlies tumorigenic alterations induced by the bacteria, of which many aspects are not well understood. Recent studies have provided new data regarding regulation of the host protein p53 by *H. pylori*. The interest in p53 originates from its key role in tumor suppression, paraphrased in the scientific literature as “the guardian of the genome.” Indeed, inactivation of p53 is strongly associated with an increased susceptibility to numerous tumors in animals and humans, with p53 commonly inactivated during gastric tumorigenesis.

Functionally, p53 protein is a transcription factor that is activated in response to multiple cellular stresses including DNA damage and aberrant induction of cellular oncogenes. Activated p53 protein induces transcription of multiple target genes, which regulate key cellular processes such as programmed cell death and cell cycle arrest, with the net effect of inhibiting abnormal cellular proliferation and promoting the death of cells likely destined for tumor development. Since p53 is central to the cellular “life-or-death decision,” p53 activity is tightly controlled by MDM2 ubiquitin ligase, which in and of itself is a

transcriptional target of p53. MDM2 ubiquitinates p53 and facilitates its proteasomal degradation, thus forming a regulatory feedback loop.

Although *H. pylori* infection damages DNA and activates multiple oncogenic pathways, the bacteria also inhibit p53 [1]. Several studies have demonstrated that *H. pylori* infection not only enhances mutagenesis of the *P53* gene (*TP53*) but also inhibits p53 in a mutation-independent manner [1–4]. The latter phenomenon is less understood but may be important during early stages of gastric tumorigenesis. *Helicobacter pylori* activates AKT and ERK protein kinases, which enhance activity of MDM2 and degradation of p53 [1, 3]. Nevertheless, activation of MDM2 alone is not sufficient to degrade p53. The fate of p53 is dependent on levels of host protein p14ARF, which inhibits MDM2 activity (Fig. 1). *Helicobacter pylori* efficiently degrades p53 protein in ARF-deficient cells, whereas degradation of p53 is halted and its level is increased in *H. pylori*-infected cells expressing ARF [5].

In this issue of *Digestive Diseases and Sciences*, Xu et al. [6] investigated alterations of the AKT-MDM2-p53 pathway by *H. pylori*. The authors first compared protein expression of AKT, phosphorylated AKT (pAKT), MDM2, p53, and BAX in gastric tissues collected from 160 infected and uninfected individuals. Gastric specimens were grouped according to clinical diagnosis: chronic non-atrophic gastritis (CNAG), metaplastic atrophy (MA), gastric dysplasia (Dys), and cancer (GC). Similar to a previous report by Sasaki [7], the authors reported increased expression of pAKT in CNAG patients infected with *H. pylori*. Notably, the level of pAKT correlated significantly with expression of MDM2 protein, indicating potential crosstalk between pAKT and MDM2 in infected mucosa. Furthermore, *H. pylori* infection was significantly associated with increased levels of p53 and MDM2

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Fig. 1 Schema of signaling pathways activated by infection of gastric epithelial cells by *H. pylori*

proteins in patients with MA and Dys, respectively. BAX levels were increased in CNAG and MA patients. One important aspect that was not addressed in the study is how bacterial factors such as CagA regulate MDM2 and p53 [1, 3, 4].

In second part of the study, the authors investigated the AKT-MDM2-p53 signaling using immortalized gastric epithelial cells (GES-1) in vitro. This cellular model has a plausible advantage over gastric cancer cell lines, which are characterized by multiple genetic alterations. Another important distinction of the study is that while *H. pylori* infection is commonly recapitulated by co-culture of gastric cells with live *H. pylori* bacteria, the authors chose to treat cells with *H. pylori* culture filtrates. Similar to the aforementioned analyses of patients' tissues, treatment with *H. pylori* filtrates increased expression of pAKT, MDM2, p53, and BAX in vitro. Inhibition of AKT phosphorylation with phosphatidylinositol 3-kinase (LY294002) decreased MDM2 levels concomitantly with upregulation of p53, providing evidence that *H. pylori* inhibits p53 through the AKT-MDM2 signaling. The authors speculated that the level of p53 is determined by a balance between upregulation of p53 protein expression by DNA damage and p53 degradation by MDM2 induced by *H. pylori*. Although it was not explored in this study, another possibility is that p53 is upregulated via inhibition of MDM2 by p14ARF protein, as has been reported previously [5].

The authors also reported that *H. pylori* filtrates have cytostatic and cytotoxic effects on gastric cells by inducing DNA damage, G₁/S cell cycle arrest, and apoptosis. Interestingly, the viability of infected cells was further reduced after inhibition of pAKT and MDM2.

Reduced survival and increased proliferation of *H. pylori*-infected cells have been reported previously [8].

These seemingly opposing results reveal the diverse effects of *H. pylori* infection that could often be reconciled by differences in experimental models [8]. An interesting example is a recent study by Wroblewski et al. [9], who have provided evidence that the *H. pylori* strains which inhibit growth of gastric cells in a co-culture model induce cellular proliferation in gastric organoids.

In summary, Xu et al. [6] have methodically investigated the p53 pathway and advanced the field by providing new evidence on the regulation of p53 by *H. pylori* through MDM2-pAKT signaling, thus opening up new opportunities for a better understanding of host–bacterial factors interaction with tumorigenic potential.

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