Expression of p53-MDM2 feedback loop related proteins in different gastric pathologies in relation to Helicobacter pylori infection: Implications in gastric carcinogenesis

Zhen Yang¹, Xu Shu¹, Lian Chen, Jiang Chen, Yong Xie, Nong-Hua Lu¹

Department of gastroenterology, The First Affiliated Hospital, Nanchang university, Nanchang, 330006, Jiangxi, China

Available online 3 February 2012

Summary
Aim: To explore the association of p53-MDM2 feedback loop related proteins with gastric pathologies in relation to Helicobacter pylori infection.
Methods: Gastric biopsies were obtained from 157 H. pylori-negative and positive patients, including normal gastric mucosa (NGM), chronic gastritis (CG), intestinal metaplasia (IM), dysplasia (Dys), and gastric cancer (GC). The expression of mutant p53, MDM2, Bax and PUMA in gastric tissues was detected by immunohistochemistry.
Results: Overall expression of MDM2 and Bax is progressively increased from NGM to GC. PUMA expression is increased in CG but subsequently decreased after the development of IM. H. pylori infection is associated with increased mutant p53 and Bax expression but decreased PUMA expression in IM, and increased MDM2 expression in Dys.
Conclusions: These results suggest that different p53-MDM2 feedback loop related proteins are distinctly expressed in the various stages of gastric carcinogenesis; their roles in gastric carcinogenesis in the presence of H. pylori infection need to be further investigated.

Introduction

Helicobacter pylori, which was first described in 1983, is recognized as the pathogen of several gastroduodenal diseases, such as active and chronic gastritis, peptic ulcer, and mucosa-associated lymphoid tissue lymphoma [1–4]. Moreover, it has been classified as a class I (definite) carcinogen for gastric cancer by the International Agency for Research of Cancer (IARC), based on epidemiological, animal and clinical studies [5]. H. pylori infection plays a critical role in the development of gastric carcinoma through a multistep process from chronic superficial gastritis to chronic atrophic gastritis, intestinal metaplasia, dysplasia and finally gastric carcinoma [6].
**H. pylori** infection also increases apoptosis and proliferation in human gastric tissue [7–10]. It has been postulated that aberrantly increased apoptosis in gastric epithelium induced by *H. pylori* infection may be the initial trigger in gastric carcinogenesis [11]. Thus, elucidation of apoptosis related proteins involved in *H. pylori* induced apoptosis in gastric epithelium are critical for understanding the initial steps of gastric carcinogenesis.

p53, a tumor suppressor gene, up-regulates apoptosis and inhibits cell growth [12]. Mutation of this gene is an early event in the atrophy-metaplasia-carcinoma process of gastric carcinogenesis [13,14]. Murine double minute gene 2 (MDM2), an oncoprotein, is a negative regulator of the p53, and has also been implicated in carcinogenesis [15]. On one hand, MDM2 can inhibit p53 bioactivity by blocking the transcriptional activity of p53 and promoting p53 protein degradation [16]. On the other hand, p53 can also regulate the synthesis of MDM2 [17]. This so-called p53- MDM2 auto-regulatory feedback loop plays a crucial role in carcinogenesis [17]. p53 up-regulated modulator of apoptosis (PUMA) and Bcl-2-associated X protein (Bax) are the important downstream effectors of p53 [17]. However, little is known on the roles of PUMA and Bax proteins in the p53-MDM2 feedback loop. PUMA is a pro-apoptotic protein that is up-regulated by p53. In turn, PUMA can displace p53 from Bcl-xL, allowing p53 to induce mitochondrial permeabilization, cytochrome C release and apoptosis [18]. Bax is also a pro-apoptotic protein that translocates from the cytosol to the mitochondria following a pro-apoptotic stimulus, and initiates apoptosis [19,20]. Bax also binds to the mitochondria membrane and mediates apoptosis through the mitochondrial pathway [21,22]. Previous studies have elucidated the mechanism by which *H. pylori* infection may contribute to gastric cancer. However, there are controversies on the relationship between p53 and *H. pylori* infection [23–26]. Moreover, the role of the p53-MDM2 feedback loop in the *H. pylori*-associated process of gastric carcinogenesis has not been elucidated. Therefore, the aim of the present study was to determine the expression of mutant p53, MDM2, PUMA and Bax proteins and their correlations in the different stages of the development of gastric carcinoma with or without *H. pylori* infection, in order to explore the roles of p53-MDM2 feedback loop related proteins in different gastric pathologies in relation to *H. pylori* infection.

**Methods**

**Patients**

Gastric samples of the patients who underwent upper gastrointestinal endoscopy from January 2007 to September 2009 at the first affiliated hospital of Nanchang University were retrospectively reviewed and examined. A total of 157 patients (67 females and 90 males, with a mean age of 53.3 [± 12.9] years) were enrolled in this study including 20 with normal gastric mucosa (NGM, all *H. pylori*-negative), 20 with chronic gastritis (CG, all *H. pylori*-positive), 40 with intestinal metaplasia (IM, 20 *H. pylori*-positive and 20 *H. pylori*-negative), 37 with dysplasia (Dys, 19 *H. pylori*-positive, and 18 *H. pylori*-negative), and 40 with gastric cancer (GC, 20 *H. pylori*-positive and 20 *H. pylori*-negative) (Table 1). There was no significant difference in the age and gender distribution among these groups. All patients had not been treated with any regimens aiming at *H. pylori* eradication.

The study design was approved by the Institute review board of the first affiliated hospital, Nanchang University. All patients gave written informed consent for participating in the study.

**Detection of Helicobacter pylori infection**

An ‘‘in-house’’ rapid urease test (RUT) and modified Giemsa staining were employed for the detection of *H. pylori* infection. The effectiveness of RUT is more than 95% (data not shown). The modified Giemsa staining was carried out in a double-blind fashion. *H. pylori* infection was diagnosed as positive only if both of the methods produced positive results. An *H. pylori*-negative diagnosis was confirmed if both of the methods yielded negative results.

**Histological examinations of gastric samples**

Gastric samples were obtained from the patients who underwent endoscopy of the upper gastrointestinal tract. All biopsies were taken from the gastric antrum and the location of lesions of individual patients. The tissues used for historical analysis were fixed in 10% formaldehyde in Ca2+ and Mg2+ free phosphate-buffered saline (PBS) overnight at 4 °C before paraffin embedding. Paraffin sections of 4 μm were cut with a microtome and stored at room temperature. Pathologic diagnosis and classification were made according to the criteria of the World Health Organization [27] and the updated Sydney system [28].

**Immunohistochemical detection of mutant p53, MDM2, Bax and PUMA proteins**

Primary antibodies used in this study were mouse monoclonal anti-human mutant p53, MDM2, and Bax proteins (Santa Cruz Biotechnology, Santa Cruz, CA, USA), and rabbit polyclonal anti-human PUMA protein (Cell Signaling biotechnology, Danvers, MA, USA). Anti-human mutant p53, anti-human MDM2 and anti-human Bax antibodies were diluted to 1:100, and anti-human PUMA antibody was diluted to 1:200.

Paraffin sections were mounted on slides and dewaxed in xylene and sequentially dehydrated in 100, 95 and 85% ethanol. Sections were stained using the PV-9000 Polymer Detection System (Zhongshan Goldenbridge, Beijing, PRC) staining protocol. They were washed in PBS and endogenous peroxidase was blocked using 3% H2O2. After the specimens were incubated with the primary antibody overnight at 4 °C, they were washed with PBS, followed by incubation with polymer helper for 30 min and polyperoxidase-anti-mouse or rabbit IgG for 30 min. After the sections were washed with PBS, they were incubated with 3,3-diaminobenzidin (DAB, Zhongshan Goldenbridge). Control sections incubated with PBS, instead of primary antibodies, were used as negative controls. Sections were counterstained with hematoxylin.
Table 1  Expression of mutant p53, MDM2, PUMA and Bax in patients with different histological findings, in relation to *H. pylori* infection.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Overall score of the protein expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mutant p53</td>
<td>MDM2</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Overall</td>
<td>157</td>
<td>116</td>
</tr>
<tr>
<td>NGM</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>CG</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>IM</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Dys</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>GC</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

NGM: normal gastric mucosa; CG: chronic gastritis; IM: intestinal metaplasia; Dys: dysplasia; GC: gastric cancer.
Slides were examined under a light microscope. Cells stained with yellow or brown colour in the nucleus and/or cytoplasm were defined as positive. Five randomly selected fields per section were analysed. In a randomly selected field from representative areas, the immunoreactive cells among 100 cells were assessed and quantified by percentage. Then, the average percentage of the five fields was used for the assessment of the area of immunostaining, i.e. 0: < 5.0%; 1: 5.1%–25.0%; 2: 25.1%–50.0%; 3: 50.1%–75.0%; and 4: > 75.0%. In addition, the intensity of immunostaining was also semi-quantitatively assessed as 0: no staining; 1: weak staining; 2: moderate staining; and 3: strong staining. Then, the integrals of the ‘area × intensity’ were calculated, by which the overall expression levels of the proteins in the section were defined, as follows: negative (−): score 0–2; weak positive (+): score 3–5; moderate positive (++): score 6–8; and strong positive (+++): score 9–12. The assessment of the sections was performed blindly by two pathologists (L. Chen and J. Chen).

**Statistical analysis**

Data are expressed as mean± standard deviation (SD) or percentage. The Chi-square test (SPSS v. 16.0 for Windows; SPSS, Inc., Chicago, IL, USA) was used to evaluate the difference in categorical variables such as gender among different defined groups. The one-way Anova (SPSS v.16.0) was used to determine the differences such as patients’ ages in numerical variables among the groups. The Kruskal-Wallis test or Mann-Whitney test (SPSS v.16.0) was used to determine the differences in numerical variables between different defined groups. Correlations were analysed using Spearman’s rank correlation coefficient (SPSS v. 16.0). A P value of less than 0.05 was considered statistically significant.

**Results**

**Overall expression of mutant p53, MDM2, PUMA and Bax in patients with different histological findings**

Overall, the expression of MDM2 and Bax was significantly increased from NGM to GC (χ² = 31.98, P < 0.001 for MDM2 and χ² = 31.44, P < 0.001 for Bax). The PUMA expression was increased from NGM to CG, but then decreased from IM to GC (χ² = 30.75, P < 0.001). Weak expression of mutant p53 was observed in only 15% (3/20) of patients with NGM, whereas weak to strong expression of mutant p53 was observed in 25, 20, 27 and 37.5% of patients with CG, IM, Dys and GC, respectively, although there was no significant difference in the expression of mutant p53 among the groups (Table 1).

Overall, Bax protein levels were significantly increased in CG (Mann-Whitney U = 132.00, P = 0.023), IM (Mann-Whitney U = 148.00, P < 0.001), Dys (Mann-Whitney U = 90.00, P < 0.001) and GC (Mann-Whitney U = 164.00, P < 0.001), compared with NGM. In addition, there were significant differences in the expression of MDM2 (Mann-Whitney U = 170.00, P < 0.001) and PUMA (Mann-Whitney U = 216.00, P = 0.002) between GC and NGM, in the expression of MDM2 (Mann-Whitney U = 149.00, P < 0.001), PUMA (Mann-Whitney U = 155.00, P < 0.001) and Bax (Mann-Whitney U = 276.00, P = 0.037) between CG and GC, in the expression of mutant p53 (Mann-Whitney U = 632.00, P = 0.042), MDM2 (Mann-Whitney U = 348.50, P < 0.001) and PUMA (Mann-Whitney U = 437.00, P < 0.001) between IM and GC, and in MDM2 expression (Mann-Whitney U = 571.50, P = 0.044) and PUMA (Mann-Whitney U = 291.00, P < 0.001) between Dys and GC (Table 1).

**Expression of mutant p53, MDM2, PUMA and Bax in patients with different histological findings, in relation to Helicobacter pylori infection**

In the presence of *H. pylori* infection, the expression of MDM2 and Bax were significantly increased from CG to GC (χ² = 26.73, P < 0.001 for MDM2 and χ² = 13.48, P = 0.004 for Bax). The expression of PUMA was decreased from CG to GC (χ² = 13.27, P = 0.004, Table 1). In addition, the expression of MDM2 was significantly increased in Dys (Mann-Whitney U = 60.50, P < 0.001), and GC (Mann-Whitney U = 73.50, P < 0.001), whereas the expression of PUMA was significantly decreased in IM (Mann-Whitney U = 123.00, P = 0.029) and GC (Mann-Whitney U = 81.00, P < 0.001), compared with CG. There were significant differences in the expression of MDM2 (Mann-Whitney U = 90.00, P = 0.001) and Bax (Mann-Whitney U = 122.00, P = 0.025) between GC and IM, in the expression of PUMA (Mann-Whitney U = 102.00, P = 0.009) between GC and Dys, and in the expression of MDM2 (Mann-Whitney U = 72.00, P < 0.001) between IM and Dys. There was no significant difference in the expression of mutant p53 among the groups (Table 1).

In the absence of *H. pylori* infection, the expression of mutant p53, MDM2 and Bax was significantly increased (χ² = 9.29, P = 0.026 for mutant p53, χ² = 16.76, P = 0.001 for MDM2, and χ² = 22.57, P < 0.001 for Bax). The expression of PUMA was greater in IM and Dys than in NGM, however, the expression was decreased from IM to Dys, and even fell below the normal level in GC (χ² = 25.34, P < 0.001, Table 1). There were significant differences in the expression of mutant p53 (Mann-Whitney U = 141.00, P = 0.042), MDM2 (Mann-Whitney U = 85.50, P = 0.001), PUMA (Mann-Whitney U = 103.00, P = 0.005) and Bax (Mann-Whitney U = 84.000, P = 0.001) between GC and NGM, in the expression of mutant p53 (Mann-Whitney U = 127.00, P = 0.007), MDM2 (Mann-Whitney U = 84.50, P < 0.001) and PUMA (Mann-Whitney U = 54.00, P < 0.001) between GC and IM, and in the expression of MDM2 (Mann-Whitney U = 77.00, P = 0.001) and PUMA (Mann-Whitney U = 45.00, P < 0.001) between GC and Dys (Table 1).

The expression of the proteins was compared between *H. pylori*-positive and negative patients at different pathological stages. In patients with IM, the expression of mutant p53 (Mann-Whitney U = 140.00, P = 0.019, Fig. 1) and Bax (Mann-Whitney U = 116.00, P = 0.016, Fig. 2) was significantly higher but the expression of PUMA was significantly lower in the presence of *H. pylori* infection than in the absence of the infection (Mann-Whitney U = 104.50, P = 0.007 for PUMA, Fig. 3). The expression of MDM2 was similar between *H. pylori*-positive and negative patients. In patients with Dys, only MDM2 expression was significantly higher in the presence of *H. pylori* infection than in the absence of the
infection (Mann-Whitney \( U = 64.00, P < 0.001 \), Fig. 4). However, in patients with GC, there was no significant difference in the expression of all the four proteins between patients with and those without \( H. \) pylori infection.

Correlations among the expression of mutant p53, MDM2, PUMA and Bax in patients with different histological findings, in relation to \( H. \) pylori infection

Overall, MDM2 expression was positively correlated with PUMA expression \((r = 0.614, P < 0.01)\) in patients with CG, and negatively correlated with Bax expression \((r = -0.328, P < 0.05)\) in patients with Dys (Table 2). Furthermore, MDM2 expression was positively correlated with PUMA expression in patients with CG in the presence of \( H. \) pylori infection \((r = 0.614, P < 0.01)\), but negatively correlated with PUMA expression in patients with GC in the absence of \( H. \) pylori infection \((r = -0.459, P < 0.01)\) (Table 2). Mutant p53 expression was not correlated with MDM2, PUMA and Bax expression. There was no correlation between PUMA expression and Bax expression.

Discussion

It is well-established that \( H. \) pylori infection is a definite etiological factor in gastric carcinogenesis [5]. However, the mechanism through which \( H. \) pylori infection contributes to the development of gastric cancer has not been fully elucidated [29]. Obst et al. reported that \( H. \) pylori infection could cause DNA damage in gastric epithelial cells [30]. \( H. \) pylori infection can induce p53 gene mutations and appears to be involved in the pathway leading to Dys or carcinoma [23]. The mutant p53 loses the abilities of p53 and functions like an oncogene [31]. In normal cells, wild-type p53 is an unstable protein with a short half-life, but the mutant p53 is a stable protein [32]. The present study showed that in patients with IM, the expression of mutant p53 in gastric mucosa was significant higher in the presence of \( H. \) pylori infection than that in the absence of the infection (Fig. 1), whereas the expression of mutant p53 was not associated with \( H. \) pylori infection in patients with CG, Dys and GC. The expression of mutant p53 was increased following the progress of gastric carcinogenesis, but the increase reached a significant level only in patients without \( H. \) pylori infection.
In the present study, MDM2 expression was found to have progressively increased during all stages of gastric carcinogenesis, regardless of *H. pylori* infection. These results indicate that the enhanced expression of MDM2 is involved in the whole process of gastric carcinogenesis. Moreover, the present study observed that a significantly increased MDM2 expression level in *H. pylori*-positive patients, compared with that in *H. pylori*-negative patients, was observed only in Dys stage (Fig. 4), and not in any other stages. These findings confirm the previous observation reported by Nakajima et al. [33] that there was no significant difference in MDM2 expression between patients with and without *H. pylori* infection in CG stage, but were different from their observations that MDM2 expression was up-regulated in IM and GC in the presence of *H. pylori* infection. On the other hand, Kodama et al. found that there was a significant increase in MDM2 expression in *H. pylori*-infected gastric mucosa, compared with normal gastric mucosa. Moreover, they observed that eradication of *H. pylori* dramatically reduced the MDM2 protein level after six months [34], indicating that eradication of *H. pylori* infection may decrease MDM2 expression, and thus reduce the risk of gastric cancer. However, in vitro experiments have suggested that coculture of cells with *H. pylori* for 72 hours does not increase MDM2 expression [35]. The reasons for the discrepancy between in vivo and in vitro studies is unclear; however, we propose that the induction of the expression of MDM2 by *H. pylori* infection in vivo would be a long process, while the duration of the in vitro experiment was relatively short. Thus, MDM2 expression in the gastric mucosa may be one of the factors for gastric carcinogenesis; long-term *H. pylori* infection may contribute to the increased MDM2 expression levels during a certain stage or even all stages.

The present study showed that Bax expression was progressively increased following the process of gastric carcinogenesis in both *H. pylori*-positive patients and *H. pylori*-negative patients. Moreover, Bax expression was significantly increased in *H. pylori*-positive patients compared with *H. pylori*-negative patients in the stages of CG and IM (Fig. 2); there was no difference in Bax expression between the *H. pylori*-positive patients and *H. pylori*-negative patients with Dys and GC. In addition, in the presence of *H. pylori*-positive infection, Bax expression was the highest in IM stage among all the stages of gastric carcinogenesis. These findings indicate that Bax expression is induced by *H. pylori* infection in the very early stages which initiates apoptosis of gastric epithelial cells and results in the subsequent molecular, genetic and
Finally, correlations between these p53-MDM2 feedback loop related proteins in different stages of gastric carcinogenesis were determined in relation to H. pylori infection. Although we did not find any correlations between any two proteins when all patients were analysed, MDM2 and Bax were negatively correlated in the Dys stage. Moreover, we observed that MDM2 and PUMA were positively correlated in the stage of CG in the presence of H. pylori infection, but negatively correlated in the GC stage in the absence of H. pylori infection. We postulate that both MDM2 and PUMA proteins may be up-regulated at the early stage of gastric carcinogenesis and then, at the GC stage, the expression of MDM2 remains to be up-regulated while the expression of PUMA was down-regulated. In the present study, the expression of both MDM2 and PUMA tended to be higher in CG than in NGM although the difference was not statistically significant, likely due to the relatively small sample size. However, the underlying mechanisms for the opposite regulations of the two proteins and whether they are of biological and clinical significance need to be further elucidated in future studies.

Thus, further investigation is required to explore the underlying molecular mechanisms for these observations.

Based on the findings observed in the present study, we speculate that alterations in the expression of p53-MDM2 feedback loop related proteins occur in the early stage of gastric carcinogenesis, such as CG, IM and Dys, and H. pylori may be the trigger or stimulus of the alterations in the expression of certain proteins in a certain stage. For example, an increase in PUMA and Bax expression are mainly triggered in the CG stage, p53 gene mutation mainly starts to occur in the IM stage, and an increase in the expression of MDM2 is mostly prominent in the Dys stage, in the presence of H. pylori infection. Once the alterations have occurred, the altered expression of the proteins is sustained except cellular events [11]. Our findings are in agreement with the observations reported by Bartchewsky et al. [36], that in patients with CG H. pylori infection mostly increased Bax expression to initiate cell apoptosis, but in patients with GC, H. pylori infection mainly increased Bcl-2 expression, not Bax expression, to deregulate apoptosis-associated gene expression. The study suggests that H. pylori infection regulates Bax expression differently at the different stages of gastric cancer, which might explain the results observed in the present study.

Our data showed that overall PUMA expression was increased in H. pylori-associated CG, but then decreased during the late stages of gastric carcinogenesis, and the decrease was more prominent in IM in the presence of H. pylori infection (Fig. 3). These results suggest that PUMA expression is negatively correlated with the severity of late stages of gastric mucosal pathology during carcinogenesis, and H. pylori infection initially increases PUMA expression, but decreases the expression once IM develops. The non-parallel trend in the protein expression between PUMA and Bax and the down-regulation of PUMA in the late stages of gastric carcinogenesis indicates that PUMA is also regulated by a p53-independent pathway. For example, p73, a p53 family member that is also considered as a tumor suppressor due to its structural resemblance to p53, has been reported to induce apoptosis via PUMA transactivation [37]. Moreover, it has been demonstrated that p73 expression is increased in gastric epithelial cells in the presence of H. pylori infection, along with up-regulation of pro-apoptotic genes, including NOXA, PUMA, and CAS receptor, indicating that p73 plays an important role in H. pylori-induced gastric apoptosis [38]. However, the exact mechanisms by which p73 regulates PUMA and other pro-apoptotic genes in the presence of H. pylori infection, especially in the late stages of gastric carcinogenesis, need to be further investigated.

| Table 2 | Correlations among the expression of mutant p53, MDM2, PUMA and Bax in patients with different histological findings, in relation to H. pylori infection. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Correlation coefficient (r) | p53 and MDM2 | p53 and PUMA | p53 and Bax | MDM2 and PUMA | MDM2 and Bax | PUMA and Bax |
| Overall | 0.109 | -0.128 | 0.005 | -0.132 | 0.082 | 0.016 |
| NGM | 0.039 | -0.142 | -0.140 | 0.356 | 0.129 | 0.116 |
| CG | -0.066 | 0.032 | -0.045 | 0.614* | -0.258 | 0.294 |
| IM | 0.139 | -0.233 | -0.034 | -0.038 | -0.075 | -0.141 |
| Dys | -0.093 | 0.009 | 0.109 | -0.232 | -0.328* | 0.000 |
| GC | 0.078 | -0.127 | -0.168 | -0.199 | 0.206 | 0.048 |
| Helicobacter pylori+ | 0.099 | -0.088 | -0.011 | 0.015 | 0.005 | 0.031 |
| CG | -0.066 | 0.032 | -0.045 | 0.614* | -0.258 | 0.294 |
| IM | 0.156 | -0.222 | -0.238 | -0.084 | -0.106 | -0.127 |
| Dys | 0.255 | -0.012 | 0.339 | -0.111 | -0.232 | 0.155 |
| GC | -0.127 | -0.008 | -0.146 | 0.069 | 0.146 | 0.057 |
| Helicobacter pylori− | 0.104 | -0.156 | -0.001 | -0.233* | 0.112 | 0.024 |
| NGM | 0.039 | -0.142 | -0.140 | 0.356 | 0.129 | 0.116 |
| IM | 0.106 | 0.221 | -0.129 | 0.079 | -0.111 | 0.078 |
| Dys | -0.320 | 0.041 | -0.114 | -0.212 | -0.218 | -0.283 |
| GC | 0.213 | -0.196 | -0.210 | -0.459* | 0.241 | 0.075 |

* p < 0.05
** p < 0.01
PUMA, which may be decreased in late stages of gastric carcinogenesis in the presence of *H. pylori* infection. However, there are a few limitations in the present study. For example, the study was based only on correlations, and they were descriptive and not mechanistic. In addition, the sample size was relatively small, the study only focused on the immunohistochemical staining of protein expression, and the measures were partially subjective. Therefore, more clinical and experimental studies are required to test our hypothesis.

In conclusion, overall expression of MDM2 and Bax is progressively increased from NGM to GC. PUMA expression is increased in CG but subsequently decreased after the development of IM. *H. pylori* infection is associated with increased mutant p53 and Bax expression but decreased PUMA expression in IM, and increased MDM2 expression in Dys. These results suggest that different p53-MDM2 feedback loop related proteins are distinctly expressed in the various stages of gastric carcinogenesis; their roles in gastric carcinogenesis in the presence of *H. pylori* infection need to be further investigated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

We would like to thank Drs Shi-Wen Luo and Ai-Ping Bai, and Medjaden Bioscience Limited for their proofreading of the manuscript. This work was supported by the National natural science foundation of China (Grant Number: 30660067).

Author contributions: NH Lu, X Shu and Y Xie designed the study; Z Yang, X Shu, L Chen and J Chen performed the study; Z Yang analysed the data; Z Yang and NH Lu drafted the manuscript.

References


Expression of p53-MDM2 feedback loop related proteins in gastric pathologies


