*Helicobacter pylori*-Induced Macrophage Apoptosis Requires Activation of Ornithine Decarboxylase by c-Myc*

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Running Title: c-Myc in H. pylori-induced Macrophage Apoptosis

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*Helicobacter pylori* infection causes chronic inflammation of the gastric mucosa that results from an ineffective immune response. We have demonstrated that one underlying mechanism is induction of macrophage apoptosis mediated by polyamines. The transcription factor c-Myc has been linked to induction of ornithine decarboxylase (ODC), the rate limiting enzyme in polyamine synthesis. We determined whether *H. pylori* stimulates transcriptional activation of ODC in macrophages, if this occurs via c-Myc, and if these events regulate activation of apoptosis. *H. pylori* induced a significant increase in ODC promoter activity that peaked at 6 h after stimulation and was closely paralleled by similar increases in ODC mRNA, protein, and enzyme activity. By 2 h after stimulation, c-Myc mRNA and protein expression was induced, protein translocated to the nucleus, and there was specific binding of a consensus probe for c-Myc to nuclear extracts. Both an antennapedia-linked inhibitor of c-Myc binding (Int-H1-S6A, F8A) and transfection of a c-Myc dominant-negative construct significantly attenuated *H. pylori*-induced ODC promoter activity, mRNA, enzyme activity, and apoptosis in parallel. Transfection of ODC small interfering RNA inhibited ODC activity and apoptosis to the same degree as inhibition of c-Myc binding. These studies indicate that c-Myc is an important mediator of macrophage activation and may contribute to the mucosal inflammatory response to pathogens such as *H. pylori* by its effect on ODC.

*Helicobacter pylori* is a Gram-negative, microaerophilic bacterium that selectively colonizes the human stomach. It infects ~30-40% of the population in the United States (1) and has a higher prevalence in underdeveloped regions. *H. pylori* causes chronic gastritis, peptic ulcers, gastric adenocarcinoma, and lymphoma. Intriguingly, there is a vigorous gastric mucosal immune response, but this fails to eradicate the organism. *H. pylori* infection induces a chronic lymphocytic response and an innate immune response in neutrophils, monocytes, and macrophages (2-8). We have reported several strategies by which the bacterium can avoid host innate immunity by altering macrophage responses to the organism. In addition to interfering with antimicrobial NO production (7), *H. pylori* induces apoptosis of macrophages (5, 9). Although *H. pylori* is a noninvasive pathogen, it can disrupt epithelial integrity and its antigens are present in the lamina propria (3). *H. pylori* can induce innate immune response genes and cause apoptosis in macrophages even when separated by filter supports or when water extracts are used (5, 6).

We have demonstrated that *H. pylori* induces both arginase II and ornithine decarboxylase (ODC) in macrophages (5). Arginase converts L-arginine to L-ornithine, which is metabolized by ODC to produce the polyamine putrescine that is converted to the polyamines spermidine and spermine. When spermine is metabolized by spermine oxidase (SMO; polyamine oxidase 1) it generates H₂O₂ that causes apoptosis (9). ODC is the rate-limiting enzyme for polyamine synthesis. ODC activity can be regulated at multiple levels...
including promoter activation (10). Overexpression of the transcription factor c-Myc has been shown to activate the ODC promoter by forming a heterodimer with Max and binding to c-Myc consensus binding sequences in the promoter (11). Bacterial LPS has been shown to induce expression of c-Myc (12) and of ODC (13), but the role of c-Myc in the host response to pathogens has not been defined. We now report that *H. pylori* induces ODC and causes apoptosis by activation of the ODC promoter, and that this process is dependent on c-Myc expression and binding. These studies are the first to show that host innate immune response to a bacterial pathogen is compromised by the induction of c-Myc.

**EXPERIMENTAL PROCEDURES**

**Reagents**—All reagents for cell culture, RNA extraction, and RT-PCR were from Invitrogen. Restriction and DNA modifying enzymes were from NE Biolabs. c-Myc binding inhibitor (Int-H1-S6A, F8A) was purchased from BIOMOL (Plymouth Meeting, PA). All other chemicals were purchased from Sigma.

**Bacteria, Cells and Culture Conditions**—*H. pylori* SS1 was grown and used as described (4, 9). In some experiments *H. pylori* lysate (HPL) prepared with a French press was used (4, 9), and in others live bacteria co-cultured with macrophages above a 0.4 µm transwell filter (Nunc, Naperville, IL) was used (5-7, 9, 14). A multiplicity of infection of 100 was used in all studies. The murine macrophage cell line RAW 264.7 was maintained in complete DMEM (4, 9).

**ODC-Luc construct**—A PCR fragment (from –264 bp to +2152 bp) was generated by PCR using the ODC-CAT plasmid (10) as template (provided by J. L. Cleveland, St. Jude Children’s Research Hospital, Memphis, TN). This PCR product contains the ODC promoter, exon 1 (which includes the c-Myc binding region) and part of exon 2. Primers were: sense 5‘-GCCCAGTGGAGGATATCTGA-3’; antisense 5‘-ATCGCAGATGACTCCTGGT-3’; product size is 226 bp. PCR conditions were the same as described for ODC (9).

**Transient Transfection and Luciferase Assays**—RAW 264.7 cells were transiently transfected with ODC-Luc, cells were stimulated with *H. pylori*, and luciferase activity determined as described (15). Transfection efficiency was calculated by measuring the β-Galactosidase activity in transfected cells (15).

**RT-PCR and Real Time PCR**—ODC mRNA expression was measured by real time PCR and RT-PCR as described (9), using the following primers: sense 5‘-GCCCAGTGGAGGATATCTGA-3’; antisense 5‘-ATCGCAGATGACTCCTGGT-3’; product size is 226 bp. PCR conditions were the same as described for ODC (9).

**ODC-Luc activity** was determined by a radiometric analysis in which the amount of 14CO2 liberated from L-[14C]ornithine was measured as described (5).

**Immunoblots for ODC and c-Myc**—For ODC, RAW 264.7 cells were treated with HPL for 0–12 h. Cells were lysed and Western blotting performed as described (14). For c-Myc, cells were treated with HPL for 0–4 h in the absence and presence of actinomycin D (2 µg/ml). Nuclear and cytoplasmic extracts were prepared using an extraction kit from Pierce. Equal amounts of nuclear and cytoplasmic proteins were loaded and immunoblotted with mouse monoclonal anti-c-Myc antibody (1:2000; Biosource).

**Electrophoretic Mobility Shift Assay (EMSA)**—Nuclear extracts were prepared as above. 40 bp complimentary oligonucleotides (5’-TGCTTTAAGTCTATGATCACGTGCACATC-3’) with the c-Myc consensus-binding site as shown (underlined) were synthesized. 50 ng of double-stranded oligonucleotides were labeled with [γ32P]ATP using T4 polynucleotide kinase (Promega). Binding reactions were carried out with 20,000 cpm labeled oligonucleotides and 2 µg of nuclear protein. For competition experiments, 200-fold excess of cold oligonucleotides with either the c-Myc binding sequence or the AP-2 binding sequence was used. The entire reaction was
loaded on a 6% polyacrylamide gel and run at room temperature at 60 mA for 1 h. Gels were dried and visualized using a PhosphorImager (14).

**Transient Transfection of Dominant-Negative c-Myc Plasmid in Macrophages**–RAW 264.7 cells were transfected with 1 µg dominant-negative c-Myc plasmid [pCMVMadMyc; provided by R. Bernards, The Netherlands Cancer Institute, Amsterdam (16)] or control plasmid (pCMV). For promoter activity, the c-Myc dominant negative or control plasmid was cotransfected with pODC-Luc.

**Transient Transfection of ODC siRNA in Macrophages**–RAW 264.7 cells were transfected with ODC siRNA duplex or scrambled siRNA exactly as described (14).

**Measurement of Apoptosis**–Apoptosis was measured by annexin V-FITC staining and flow cytometry as described (9). Spectral overlap was electronically compensated using single color control cells stained with PI or FITC. Analysis of the multivariate data was performed with CELLQuest™ software (BD Biosciences). The upper right (annexin V+/PI+) quadrant representing late apoptotic cells was used based on our previous findings that this was the most consistent indicator of apoptosis in *H. pylori*-stimulated macrophages (9). In some experiments apoptosis was also assessed by ELISA of cytoplasmic histone-associated DNA fragments (5).

**Statistical Analysis**–Quantitative data are shown as the mean ± SE. Comparisons between groups were made by using analysis of variance with the Student-Newman-Keuls multiple comparisons test.

### RESULTS

*H. pylori* stimulates parallel induction of ODC promoter activity, mRNA, protein, and enzyme activity–Because we have reported that *H. pylori* can induce ODC expression and activity in macrophages (5, 9), we now sought to establish the mechanism by studying the time course and degree of initial induction. We compared each of the potential levels of regulation in response to *H. pylori*. As shown in Fig. 1A, *H. pylori* addition to RAW 264.7 macrophages resulted in a time-dependent, 12-fold increase in ODC promoter activity that peaked at 6 h. There was a nearly identical degree and time course of induction of ODC mRNA expression by real time PCR (Fig. 1B) and enzyme activity (Fig. 1C). The real time data were confirmed by conventional RT-PCR (Fig. 1D) and Western blotting also showed a peak increase at 6 h. Taken together, these data indicate that the observed increase in ODC mRNA expression, protein expression, and functional ODC activity derives from *H. pylori*-induced ODC transcription.

*Induction of c-Myc expression, and translocation to the nucleus with *H. pylori* activation*–Increased c-Myc expression has been reported in *H. pylori*-stimulated gastric epithelial cells (17), but the role of c-Myc in macrophage response to this infection has not been determined. When macrophage c-Myc expression was assessed, we found an 8–10-fold increase in mRNA levels that peaked earlier than ODC, with maximal levels reached at 2–4 h as determined by real time PCR (Fig. 2A) and RT-PCR (Fig. 2B). In parallel, *H. pylori* stimulation resulted in a marked increase in total c-Myc protein levels at 2–4 h (Fig. 2C). When nuclear accumulation of c-Myc was assessed (Fig. 2D) there was a similar increase at 2–4 h after stimulation. There was no increase in cytosolic c-Myc with *H. pylori* exposure, and a decrease at 4 h. This raised the question as to whether the increase in c-Myc nuclear protein was due only to translocation from the cytosol, or required *de novo* c-Myc synthesis. We therefore treated *H. pylori*-stimulated macrophages with the transcriptional inhibitor actinomycin D, and found that the nuclear accumulation was abolished. Thus, the expression of c-Myc mRNA is necessary to cause nuclear accumulation of c-Myc protein.

Additionally, we used EMSA to demonstrate that there was significant binding to a c-Myc oligonucleotide probe by nuclear proteins extracted from *H. pylori*-stimulated macrophages (Fig. 2E). This provides further evidence that c-Myc is translocated to the nucleus and since c-Myc must form a heterodimer with its partner protein Max in order to bind to consensus c-Myc binding sites, it also indicates that in response to *H. pylori*, functional c-Myc heterodimers are formed that are capable of binding to such sites.

*Prevention of c-Myc binding to the ODC promoter inhibits ODC promoter activity, mRNA expression, enzyme activity, and apoptosis*–Since ODC is a known transcriptional target of c-Myc,
we sought to determine if c-Myc caused the induction of ODC by *H. pylori*. As shown in Fig. 3A, transfection with a c-Myc dominant-negative construct resulted in a marked $87.7 \pm 5.7\%$ inhibition of *H. pylori*-stimulated ODC promoter activity. Similarly, inhibition of c-Myc binding with Int-H1-S6A, F8A caused a $78.2 \pm 9.2\%$ inhibition of ODC promoter activity (Fig. 3B). Inhibition of ODC mRNA expression (Fig. 3C, D) paralleled these changes in the ODC promoter activity.

To determine the functional significance of inhibition of c-Myc interaction with the ODC promoter, we assessed the effect on ODC enzyme activity and determined how this related to changes in apoptosis (Fig. 4). The c-Myc dominant-negative reduced *H. pylori*-stimulated ODC activity by $72.4 \pm 10.6\%$ (Fig. 4A) which resulted in an $84.8 \pm 13.1\%$ inhibition of apoptosis relative to the empty vector and complete inhibition compared to unstimulated cells transfected with pCMVMadMyc (Fig. 4B, C). Similarly the c-Myc binding inhibitor blocked stimulated ODC activity by $77.3 \pm 11.7\%$ (Fig. 4D) and apoptosis by $84.4 \pm 7.6\%$ (Fig. 4E, F). We confirmed these data by DNA fragmentation ELISA, which revealed an $86.9 \pm 9.6\%$ inhibition of stimulated apoptosis with the c-Myc binding inhibitor ($p < 0.01$, $n = 3$ experiments in duplicate, not shown). We also determined whether specific inhibition of ODC would mimic the effect of c-Myc inhibition. We have previously demonstrated effective knockdown of ODC expression with transient transfection of ODC siRNA (14). We now determined that when ODC activity (Fig. 4G) is inhibited by this strategy to the same degree as achieved by the interference of c-Myc binding, there is an identical degree of inhibition of apoptosis ($84.5 \pm 2.2\%$; Fig. 4H, I) as was observed with either the c-Myc dominant-negative or binding inhibitor.

**DISCUSSION**

In the current report we have demonstrated that *H. pylori* induces substantial ODC promoter activation in macrophages that is closely paralleled by concomitant increases in ODC mRNA and protein, as well as functional enzyme activity. Thus, in this model of innate immune cell activation by bacterial exposure, ODC is transcriptionally regulated. ODC mRNA induction has been reported in T cell lines in response to IL-2 and phorbol esters (18) and ODC promoter activation and mRNA expression has been demonstrated in murine myeloid cells in response to IL-3 (11). There is also a report of *E. coli* lipopolysaccharide-stimulated expression of ODC mRNA in mouse peritoneal macrophages (13). The current study is the first to demonstrate that an important bacterial pathogen induces macrophage ODC via promoter activation and that *H. pylori* activates ODC via c-Myc.

In addition to activation of the ODC promoter (10), c-Myc has been shown to mediate apoptosis of myeloid cells caused by IL-3 withdrawal and this has been attributed to the induction of ODC (19). The major significance of our findings is that we have demonstrated that an underlying mechanism for the apoptosis of macrophages in response to *H. pylori* is mediated by c-Myc via its effects on ODC. This leads to the question as to how c-Myc is activated by *H. pylori*. Activation of MAP kinases by *H. pylori* has been demonstrated in gastric epithelial cells (20), and these signaling pathways have been implicated in c-Myc induction (21). We have conducted studies of MAP kinase pathways in macrophages and found that induction of c-Myc, ODC, and apoptosis is inhibited by PD98059, an MEK1/2 inhibitor, and that *H. pylori* stimulated rapid phosphorylation of extracellular signal-regulated kinase (ERK)1/2 in these cells; in contrast, inhibition of p38 MAP kinase or c-Jun N-terminal kinase had no effect.

A related question is whether specific bacterial factors derived from *H. pylori* play a role in the induction of macrophage apoptosis, and whether these factors work through the c-Myc/ODC pathway. Notably, we have reported that *H. pylori* LPS is not a significant activator of macrophages (4), but that urease, a major protein product of *H. pylori* required for colonization of the organism in *vivo*, is a major inducing factor for inducible NO synthase in macrophages (6). Along these lines, we have found that urease-deficient mutant strains of *H. pylori* have attenuated ability to induce c-Myc, ODC, and apoptosis, and recombinant urease activates each of these pathways. Further issue for consideration is what is the specificity of the c-Myc and ODC response to *H. pylori* in macrophages? For comparison, we have studied the Gram-negative enteric pathogen *Citrobacter*
rodentium, which causes colitis in mice (22), and the effect of the chemical inducer of apoptosis, staurosporine, and found that both agents cause apoptosis in macrophages without inducing ODC or c-Myc (data not shown). Additionally, inhibition of H. pylori-induced apoptosis with catalase or cyclosporine A did not prevent induction of ODC or c-Myc (data not shown), indicating that the process of apoptosis itself is not required to stimulate this pathway of polyamine generation.

The induction of ODC may not a generalized phenomenon, since we have reported that ODC was not increased in gastric epithelial cells exposed to H. pylori (15). However, in these cells there is significant basal expression of ODC, and the apoptosis is dependent on the induction of SMO(PO1), which generates oxidative stress from the H2O2 production (15). In contrast, in macrophages, our current data indicate that there is substantial induction of ODC and that this is required for apoptosis, along with the induction of SMO(PO1) that is also needed (9). In terms of in vivo relevance, there are reports of increased levels of c-Myc and ODC in human H. pylori gastritis tissues; these studies have focused on the association of these genes with intestinal metaplasia and gastric cancer (23-25) and used immunohistochemical detection. However, we have assessed c-Myc and ODC levels by real time PCR in mouse H. pylori gastritis tissues in which atrophy and metaplasia are not evident and found consistent induction of both genes with this more sensitive technique (data not shown). In our recent reports we have also shown that spermine generation by ODC in stimulated macrophages contributes to H. pylori pathogenesis by inhibiting NO-dependent bacterial killing (14) and providing substrate for SMO(PO1) and generation of H2O2 leading to apoptosis (9). Our current results directly implicate c-Myc as a major mediator in ODC-associated immune dysregulation by its transactivation of the ODC promoter and provides a target for therapeutic manipulation of the innate immune response to this infection.

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FOOTNOTES

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1The abbreviations used are: ODC, ornithine decarboxylase; SMO, spermine oxidase; PAO1, polyamine oxidase 1; si, small interfering; RT, reverse transcription; DMEM, Dulbecco’s modified Eagle’s medium

2 M. Asim, R. Chaturvedi, Y. Cheng, F.I.Bussière, H. Xu, R.A. Casero, Jr., and K.T. Wilson, manuscript in preparation.

3Y. Cheng, R. Chaturvedi, M. Asim, F.I.Bussière, H. Xu, R.A. Casero, Jr., and K.T. Wilson, manuscript in preparation.

FIGURE LEGENDS

FIG 1. Time course of induction of ODC in H. pylori-stimulated macrophages. RAW 264.7 cells were exposed to HPL for the times indicated. A, Promoter activity, determined by luciferase reporter assay using a –264 bp functional ODC promoter. B, mRNA levels determined by real time PCR. C, ODC activity, by radiochemical assay. D, RT-PCR for ODC. E, Western blot for ODC (53 kDa) and β-actin (42 kDa). *<p < 0.05, **<p < 0.01 versus time 0; in A-C, each experiment was performed a minimum of 3 times, each in duplicate. In D and E, the data are representative of 3 experiments.

FIG. 2. H. pylori-stimulates c-Myc expression and nuclear translocation in macrophages. RAW 264.7 cells were exposed to HPL as in Fig. 1. A-D, time course of expression of c-Myc as indicated. A, real time PCR; B, RT-PCR; C, Western blotting for c-Myc from total cell lysates (64 kDa). D, Western blotting for c-Myc in nuclear and cytoplasmic cell fractions in the absence and presence of 2 μg/ml of...
actinomycin D, as indicated. 

E, EMSA. Cells were stimulated for 2 h with HPL. Nuclear proteins were extracted, incubated with a $^{32}$P-labeled probe specific for the consensus binding sequence for c-Myc, electrophoresed, and phosphorimaged. In lanes 4 and 5, excess unlabeled (cold) probes for c-Myc and AP-2 were used; the cold c-Myc competed away the binding of the labeled probe, while the non-specific competitor, AP-2, had no effect. In A, **$p < 0.01$ versus unstimulated control (time 0); $n = 3$, in duplicate. Data in B, and C-E are representative of 3 and 2 separate experiments, respectively.

FIG. 3. Effect of Inhibition of c-Myc binding on ODC promoter activation and mRNA expression in H. pylori-stimulated macrophages. A and B, ODC promoter activity, determined by luciferase reporter assay; C and D, RT-PCR. In A and C, cells were transfected with either empty vector (pCMV), or plasmid expressing MadMyc, which functions as a dominant-negative by interfering with formation of the heterodimer MycMax required for binding to the ODC promoter. In B and D, cells were treated with the c-Myc inhibitor Int-H1-S6A, F8A (10 µM). In A and C, cells were stimulated with HPL; similar results occurred with live bacteria. In B and C, cells were exposed to live bacteria above transwell filters; similar results were obtained with HPL. **$p < 0.01$ versus control; §§$p < 0.01$ versus H. pylori alone, $n = 4$ experiments in duplicate.

FIG 4. Effect of Inhibition of c-Myc binding to the ODC promoter or knockdown of ODC on H. pylori-induced macrophage apoptosis. A, C, G: ODC enzyme activity in the absence and presence of c-Myc dominant-negative, c-Myc inhibitor, and ODC siRNA, respectively. B, E, H: Concomitant changes in apoptosis, determined by flow cytometry using the upper right quadrant as shown in the representative tracings in C, F, and I. **$p < 0.01$ versus control; §§$p < 0.01$ versus H. pylori alone, $n = 4$ experiments in duplicate. Scr: scrambled.
Figure 1
Figure 2

A. c-Myc mRNA Expression (Fold Increase) over time.

B. c-Myc and β-actin expression at different time points.

C. Total c-Myc expression at different time points.

D. c-Myc expression in nuclear and cytosolic fractions.

E. Effects of Nucl Prot, HP, Cold AP-2, and Cold c-Myc on protein expression.
Figure 3

ODC Promoter Activity (Fold Increase)

A

- pCMV
- pCMV MadMyc

Ctrl |
| HP |

0
1
2
3
4
5
6

B

- No Inhib
- c-Myc Inhib

Ctrl |
| HP |

0
1
2
3
4
5
6

C

- - + + HP
MadMyc

ODC

β-actin

D

- - + + HP
c-Myc Inhib

ODC

β-actin

**

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Figure 4
Helicobacter pylori-induced macrophage apoptosis requires activation of ornithine decarboxylase by c-Myc

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The RNA binding domains of the nuclear poly(A)-binding protein.

Uwe Kühn, Anne Nemeth, Sylke Meyer, and Elmar Wahle

Page 16918: The unit of dissociation constants reported in Table I was incorrectly given as micromolar (µm). The unit should have been nanomolar (nm).

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MUC1 membrane trafficking is modulated by multiple interactions.

Carol L. Kinlough, Paul A. Poland, James B. Bruns, Keri L. Harkleroad, and Rebecca P. Hughey

Page 53071, in the Introduction: The second sentence of the second paragraph should read as follows: “Schroeder et al. (12) found a tumor-specific complex between MUC1 and β-catenin in the cytoplasm and membrane of infiltrating ductal breast carcinoma and lymph node metastases; aberrant cytoplasmic and nuclear levels of activated β-catenin in breast tumors also correlates with a poor prognosis for the patient (13).”

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Helicobacter pylori-induced macrophage apoptosis requires activation of ornithine decarboxylase by c-Myc.

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Dr. Adina Scholz was inadvertently omitted from the author list. Her affiliation is Department of Medicine, Division of Gastroenterology, University of Maryland School of Medicine, Baltimore, Maryland 21201. The correct author list is shown above.

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