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Gastric Transcription Profile of *Helicobacter pylori* Infection in the Rhesus Macaque

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Infection with *Helicobacter pylori* is usually asymptomatic but sometimes progresses to peptic ulcer disease or gastric adenocarcinoma. The development of disease involves both host and bacterial factors. In order to better understand host factors in pathogenesis, we studied the gastric transcription profile of *H. pylori* infection in the rhesus macaque by using DNA microarrays. Significant changes were found in the expression of genes important for innate immunity, chemokines and cytokines, cell growth and differentiation, apoptosis, structural proteins, and signal transduction and transcription factors. This broad transcription profile demonstrated expected up-regulation of cell structural elements and the host inflammatory and immune response, as well as the novel finding of down-regulation of heat shock proteins. These results provide a unique view of acute *H. pylori* infection in a relevant animal model system and will direct future studies regarding the host response to *H. pylori* infection.

Helicobacter pylori is a gram-negative spiral bacterium that chronically infects the gastric mucosa of approximately 60% of the world's population. All infected individuals develop histologic gastritis, but most have no clinical disease. However, 10 to 15% of those infected develop peptic ulcer disease or gastric adenocarcinoma (68, 93), which is the second most common cause of cancer mortality worldwide (43). The development of disease associated with *H. pylori* infection is a multifactorial process that is not well understood (69) but involves both host and bacterial factors. Infection with strains of *H. pylori* that contain the *cag* (cytotoxin-associated gene) pathogenicity island (PAI) has been associated with a greater degree of inflammation and with the development of peptic ulcer disease and gastric cancer in developed countries, but not in many developing countries, where nearly all *H. pylori* strains have the Cag PAI (16). The response to chronic *H. pylori* infection is also influenced by host genetic factors (30) and probably by environmental factors, such as diet and others (52).

Analysis of host gene expression in response to *H. pylori* infection is one way to better understand the role of host factors in pathogenesis. Most investigators have exploited gastric cancer cell lines cocultured with *H. pylori* and subsequent analysis by DNA microarray (5, 17, 21, 40, 48, 54, 57, 65, 81, 98). Although cell culture experiments offer the advantage of a defined cell type, there are some important disadvantages to this strategy. Cell culture experiments are generally limited to 24 to 48 h of infection, while natural infection is typically lifelong. Perhaps more importantly, experiments using cell culture lack the rich microenvironment and cell diversity, including cellular and humoral constituents of the host immune response, that are encountered in the gastric mucosa. Furthermore, cancer cell lines frequently differ in gene expression from normal tissue (13, 51). While some findings from these cell culture experiments have been validated in infected human tissues by reverse transcription-PCR (21), there is little known of global host gene expression in infected humans. Human studies are limited because, in the absence of human challenge, which is generally considered unacceptable, control over the particular *H. pylori* strain, duration of infection, and other variables is impossible.

Animal models provide a means to study the acute host response to *H. pylori* infection by comparison of gene expression before and after experimental infection (66). Perhaps the most relevant model to human infection is the rhesus macaque, which in captive populations is naturally infected with strains of *H. pylori* that are indistinguishable from strains that infect humans (26, 29, 85). Infection is associated with rapid induction of histologic gastritis that mimics what is seen in infected humans (28, 85). Furthermore, some animals go on to develop atrophic gastritis, the histologic precursor to gastric adenocarcinoma (29). Thus, the rhesus macaque model provides a unique opportunity to study acute infection; the time during which the host and bacteria establish an equilibrium and the outcome of the relationship has yet to be determined.

Although nonhuman primate-based DNA microarrays are not currently available, there is sufficient DNA sequence similarity between humans and nonhuman primates that human genome microarrays can be used to analyze samples from rhesus macaques and other nonhuman primates (12, 47, 104). For example, analysis of normal human and rhesus macaque jejunum showed that comparable numbers of expressed genes were identified by microarray, with about 90% overlap (36). Therefore, the purpose of this study was to examine host gene expression during acute *H. pylori* infection with use of the rhesus macaque model and DNA microarrays of the human genome.

MATERIALS AND METHODS

Animals. Three male rhesus macaques (*Macaca mulatta*) were housed at the California National Primate Research Center (CNPRC), which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal

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Care. All experiments were approved by the Research Advisory Committee of the CNPRC and the Institutional Animal Care and Use Committee of the University of California, Davis, and were conducted by trained staff of the CNPRC. All monkeys were hand raised in the nursery from the day of birth by methods described previously (85). At approximately 6 months of age they were documented to be specific pathogen free for *H. pylori* by serology, histology, and culture of gastric biopsy specimens. To eliminate "*Helicobacter heilmannii*" infection, which causes minimal inflammation and does not lead to *H. pylori* seroconversion (85), monkeys were treated by gavage with omeprazole (0.3 mg/kg of body weight), clarithromycin (11 mg/kg), bismuth subsalicylate (20 mg/kg), and amoxicillin (14 mg/kg) twice daily for 14 days.

Bacterial strains. *H. pylori* J166 is a human-derived strain that has previously been shown to effectively colonize rhesus macaques (27, 86). Six low-passage-number *H. pylori* J166 isolates, each derived from experimentally infected monkeys, were used for inoculation. A mixture of six J166 strains was chosen because inoculation with single-colony isolates colonizes less efficiently in both primates (J. V. Solnick, unpublished observations) and mice (K. A. Eaton, Abstr. 104th Gen. Meet. Am. Soc. Microbiol., abstr. D-213, 2004). All strains were determined to contain the Cag PAI by PCR with use of primers and conditions that have been described previously (90). The six strains were analyzed in vitro for induction of interleukin 8 (IL-8) and CagA phosphorylation in AGS cell culture by methods previously described (3, 79). Of the six strains, three induced IL-8 (mean = 1,594 pg/ml; standard deviation = 396 pg/ml) and showed CagA tyrosine phosphorylation and three did not (mean = 482 pg/ml; standard deviation = 81 pg/ml).

Bacterial inoculation. *H. pylori* J166 aliquots were subcultured once on brucella agar with 5% newborn calf serum (Gibco Invitrogen, Grand Island, N.Y.) supplemented with TVPA (trimethoprim, 5 mg/liter; vancomycin, 10 mg/liter; polymyxin B, 2.5 IU/liter; amphotericin B, 4 mg/liter; all from Sigma, St. Louis, Mo.) and incubated at 37°C with 5% CO_2. The subculture was then used to inoculate brucella broth (Difco Laboratories, Detroit, Mich.) with 5% newborn calf serum and TVPA. The liquid culture was incubated at 37°C with 5% CO_2 until the optical density at 600 nm was approximately 0.2 to 0.4 (about 15 h). The bacteria were pelleted and resuspended at a concentration of 10^5 CFU/2 ml of brucella broth. Prior to inoculation, the culture was examined by Gram stain, wet mount, and rapid urease assay with urea-indole medium. Quantitation of the inoculum was confirmed by plating serial dilutions. Monkeys under ketamine anesthesia (10 mg/kg intramuscularly) were inoculated with a 2-ml bacterial inoculum followed by a 5-ml phosphate-buffered saline flush of the orogastric tube.

Endoscopy and quantitative culture. Endoscopy was performed under ketamine anesthesia (10 mg/kg intramuscularly) after an overnight fast. Samples were obtained before and 2, 8, and 24 weeks after inoculation with *H. pylori*. Three biopsy specimens of the gastric antrum were processed for quantitative culture by serial dilution as previously described (86). *H. pylori* infection was confirmed in the conventional manner by colony morphology (pinhead-sized translucent colonies), microscopy (gram-negative curved organisms), and biochemistry (oxidase, catalase, and urease positive).

RNA isolation. Ten gastric biopsy specimens, five each from the antrum and corpus, were taken at each time point. The antral and corporal biopsy specimens for each animal were pooled and processed together to provide enough RNA for microarray analysis. Biopsy specimens were ground with a glass pestle in Trizol reagent (Sigma), and RNA was isolated according to protocols provided by the manufacturer. All RNA samples were treated with DNase I (Roche Applied Science, Mannheim, Germany), purified with an RNeasy kit (Qiagen, Valencia, Calif.) according to the RNA cleanup protocol, and resuspended in molecular-biology-grade water (BioWhittaker, Rockland, Maine). The yield of RNA was between 17.7 and 37.3 μg for 10 gastric biopsy specimens. Samples were stored at −80°C prior to analysis.

Microarray methods. Labeling and hybridization to Affymetrix HumanFL (HuFL) chips were done according to the recommendations of the manufacturer (Affymetrix, Santa Clara, Calif.). Briefly, biotin-labeled RNA was prepared by first reverse transcribing the RNA into double-stranded cDNA (Superscript II; Invitrogen Life Technologies, Carlsbad, Calif.) with an oligo$(dT)_{24}$ primer containing a T7 RNA polymerase promoter. Then an in vitro transcription reaction was carried out (Enzo High Yield RNA Transcript Labeling kit; Enzo Biochem, Farmingdale, N.Y.) during which biotin-labeled ribonucleotides were incorporated into the cRNA. Following fragmentation by heating to 94°C for 35 min, 10 μg of labeled cRNA was hybridized first to a Test Array (Affymetrix) to verify cRNA quality and then to HuFL chips for 16 h at 45°C. Arrays were washed and stained with streptavidin-phycoerythrin with use of an automated fluidics station. The chips were then scanned with an Agilent GeneArray scanner.

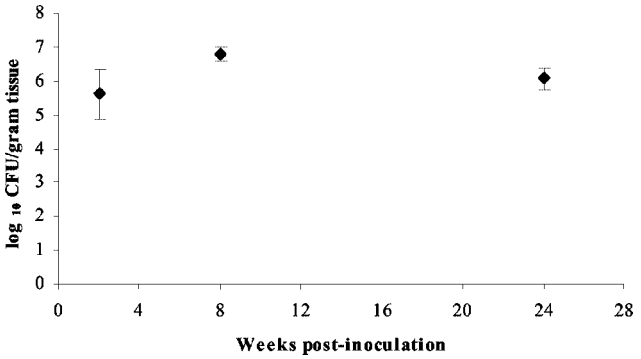

FIG. 1. Mean quantitative *H. pylori* cultures from three biopsy specimens of the gastric antrum taken from three monkeys 2, 8, and 24 weeks p.i. with 10^5 CFU of *H. pylori* J166, with error bars showing standard deviations. All animals were culture negative for *H. pylori* prior to inoculation (0 weeks).

Data analysis. Three independent analyses were performed. All data were first collated and scaled (scaling factor between 10 and 30) in Microarray Suite 5.0 (MAS 5.0; Affymetrix). Initial analysis was performed by inspection with use of Microsoft Excel and cross comparisons imported from MAS 5.0. For this analysis each animal's preinoculation time point (baseline) was compared to its own postinoculation (p.i.) time point as well as the p.i. time point of the other two animals, yielding nine total comparisons per time point. Genes were considered significantly changed if at least seven of nine comparisons indicated increased or decreased expression and had a P value of ≤ 0.05. P values for this analysis were determined in MAS 5.0 and were based on the comparisons at the probe level ($n = 20$ probes/probe set). We next used dChip (version 1.2) for comparison of baseline to each p.i. time point with use of fluorescence intensity values (.CEL files) from MAS 5.0 (www.dchip.org) (53). Finally, BRB ArrayTools (version 3.1), developed by Richard Simon and Amy Lam of the Biometric Research Branch of the National Cancer Institute, was used for microarray analysis (http://linus.nci.nih.gov/BRB-ArrayTools.html). Baseline and p.i. data were compared with the class comparison tool, which uses a t test to compare the log signal intensity between two classes (i.e., baseline and one p.i. time point). The t test uses a pooled variance (pooled across all genes) to estimate the variability of the log signal for each gene (97). However, it uses a separate estimate of variability for each gene rather than assuming the same variability for all genes. Genes with at least 2.0-fold change averaged over three animals and a P value of ≤ 0.05 were considered changed over preinfection values. Genes were annotated using DRAGON View (http://pevsnerlab.kennedykrieger.org/dragon.htm) (14) and individual gene queries of the National Center for Biotechnology Information-PubMed (http://www.ncbi.nlm.nih.gov).

RESULTS AND DISCUSSION

Quantitative culture. Three juvenile rhesus macaques specific pathogen free for *Helicobacter* species were inoculated with a mixture that contained 10^5 CFU of six rhesus-passaged *H. pylori* J166 isolates. Quantitative cultures of three biopsy specimens from the gastric antrum at 2, 8, and 24 weeks p.i. showed that all animals were chronically infected with 10^5 to 10^7 CFU/g of gastric tissue (Fig. 1). This degree of colonization resembles that seen in natural human infection (4).

Host gene expression. Microarray analysis was performed on samples of the gastric antrum and corpus for each time point with use of the Affymetrix HuFL DNA GeneChip, which contains oligonucleotides representing over 7,000 cDNAs. Three independent methods of analysis were employed as described above. Although the fold change varied somewhat depending upon the method used, a core group of genes with consistently altered expression was identified with each analysis. Here we

TABLE 1. Changes in expression 2 weeks p.i.[a]

Category	Description	Accession no.	Fold change	*P* value
Innate immune-inflammatory response	**Antithrombin III**	**M21642**	**−5.35**	**0.046**
	MMP-3	X05232	−3.70	0.002
	Serine protease inhibitor, Kazal type 1	**M20530**	**−3.23**	**0.003**
	Alpha-1-antitrypsin	X05826	−3.21	0.035
	Squamous cell carcinoma antigen 2	U19557	−2.86	0.012
	Leukocyte immunoglobulin-like receptor	U82275	−2.49	0.040
	Peroxisomal farnesylated protein	X75535	−2.26	0.040
	Human epididymis-specific 3 alpha	X76383	−2.16	0.038
	Cysteine-rich secretory protein 3 (CRISP 3)	X95240	−2.07	0.011
	Sialidase 1 (lysosomal sialidase)	X78687	2.12	0.046
	MMP-15	Z48482	2.51	0.027
	Eosinophil cationic-related protein	**X55989**	**2.63**	**0.015**
	Cathepsin O	X77383	2.85	0.041
	Fc fragment of immunoglobulin G binding protein	D84239	2.86	0.026
	Polymeric immunoglobulin receptor	X73079	2.87	0.008
	Prostaglandin E receptor EP3 subtype	**D86096**	**3.04**	**0.001**
	CD44 glycoprotein	**L05424**	**3.17**	**0.030**
	ICAM-5	U72671	3.28	0.035
	Pregnancy specific beta-1-glycoprotein 5	M25384	3.88	0.018
	Neutrophil cytosolic factor 4	X77094	4.41	0.003
	Glutaredoxin (thioltransferase)	X76648	4.62	0.022
	Tibrinogen	HG2730-HT2828	4.78	0.026
	Neutrophil gelatinase-associated lipocalin	**X99133**	**4.80**	**0.013**
	Neutrophil gelatinase-associated lipocalin	**S75256**	**5.10**	**0.011**
	Defensin, beta 2	**Z71389**	**11.88**	**0.003**
	Protease inhibitor 3 (elafin)	**L10343**	**41.53**	**0.002**
Chemokine-cytokine	Small inducible cytokine B11 (CXCL11)	U59286	−2.98	0.044
	CCR6	U68031	−2.34	0.048
	IL-2-inducible T-cell kinase	L10717	2.76	0.049
	Leptin receptor	U66497	2.88	0.048
	CCR2	**U95626**	**3.07**	**0.048**
	Leukemia inhibitory factor receptor	X61615	3.51	0.020
Heat shock	**DnaJ (Hsp40) B4**	**U40992**	**−2.19**	**0.031**
	Heat shock 70-kDa protein 1B	**M59830**	**−2.26**	**0.029**
	Heat shock 70-kDa protein 1A	**M11717**	**−2.46**	**0.026**
Cell growth and differentiation	**Fibroblast activation protein, alpha**	**U09278**	**−8.62**	**0.000**
	Ret proto-oncogene	M57464	−3.42	0.033
	Platelet-derived growth factor receptor-like protein	**D37965**	**−3.05**	**0.040**
	Retinoblastoma binding protein 1	S57153	2.63	0.028
	Ras-related protein Rab-3B	M28214	3.15	0.003
	Latent TGF-β binding protein 2	**Z37976**	**3.62**	**0.005**
	Receptor protein-tyrosine kinase erB-4	L07868	3.86	0.009
	Synaptotagmin I	**M55047**	**5.34**	**0.026**
Apoptosis	TNF receptor-associated factor 3	U15637	2.17	0.030
	Prothymosin, alpha	**M14483**	**2.27**	**0.017**
	Death-associated protein	X76105	2.97	0.037
Structural	Tropomodulin	M77016	−3.61	0.040
	Actin-related protein 1B	X82207	−2.06	0.020
	Collagen, type XIX, alpha 1	D38163	2.38	0.030
	Cytokeratin 20	X73501	2.88	0.010
	Myosin IF	X98411	2.92	0.050
	Elastin	**S57887**	**3.56**	**0.039**
	Dynamin 1-like	AF000430	4.36	0.020
	F-actin capping protein, alpha 2	**U03851**	**6.05**	**0.040**
Signal transduction	Protein tyrosine phosphatase type 2	M25393	−4.72	0.036
	G protein-coupled receptor 21	**U66580**	**−2.79**	**0.024**
	G protein-coupled receptor 22	U66581	−2.13	0.038
	TYRO3 protein tyrosine kinase	U02566	−2.10	0.012
	Guanylate cyclase 2C	**M73489**	**2.14**	**0.036**
	MAPK kinase 1 (MAP2K1)	L05624	2.19	0.045
	MAPK10	U07620	3.03	0.001
	Guanine nucleotide binding protein, alpha 13	**L22075**	**3.14**	**0.008**
	Phospholipase C, gamma 1	M34667	3.21	0.045
	Calcium, calmodulin-dependent protein kinase II gamma	U50360	3.57	0.012
	Protein tyrosine phosphatase, receptor type, J	D37781	4.39	0.031

Continued on following page

TABLE 1—*Continued*

Category	Description	Accession no.	Fold change	*P* value
Transcription factor	**Zinc finger protein 77**	**X65230**	**−3.61**	**0.008**
	Hepatocyte nuclear factor 1-beta	X71348	−2.01	0.047
	Glucocorticoid receptor DNA binding factor 1	M73077	2.23	0.036
	Homeobox D3	Y09980	2.55	0.039
	Signal transducer and activator of transcription (STAT1)	M97935	2.97	0.019
	Homeotic protein Hpx-2	**X74861**	**3.36**	**0.002**

[a] Data for genes with altered expression at more than one time point are shown in boldface.

present the results from BRB ArrayTools primarily because of its ease of use and strong statistical methods.

Approximately one-third of the genes represented had a positive signal intensity on the microarray, which is similar to previous studies with Affymetrix human arrays with nonhuman primate samples (18). Comparison of each p.i. transcription profile to the baseline profile identified 148 genes (84 up, 64 down) at 2 weeks p.i., 129 genes (66 up, 63 down) at 8 weeks p.i., and 206 genes (105 up, 101 down) at 24 weeks p.i. that were significantly changed. A subset of the genes whose expression changed significantly were grouped into functional categories, which included the innate immune-inflammatory response, chemokines and cytokines, cell growth and differentiation, apoptosis, structural proteins, signal transduction, and transcription factors (Tables 1 to 3). A full data set that includes all genes with significantly altered expression is available at http://solnicklab.compmed.ucdavis.edu/.

Innate immune-inflammatory response. (i) Antimicrobial proteins and peptides. At each time point p.i., there was up-regulation of antimicrobial proteins or peptides (Tables 1 to 3), including human beta-defensin 2 (hBD-2), protease inhibitor 3 (elafin), neutrophil gelatinase-associated lipocalin (NGAL), and surfactant. The best studied of these molecules are the defensins, which are a family of antimicrobial peptides that are expressed in neutrophils and on mucosal surfaces, where they are thought to play an important role in innate host defense (11). Recent evidence from cell culture experiments and gastric biopsies of chronically infected humans supports our finding that hBD-2 is induced by *H. pylori* and can inhibit its growth at concentrations as low as 10^{-5} μmol/μl (6, 41, 92, 95). Protease inhibitor 3 (elafin) is a defensin-like protein with a clear antimicrobial role in innate immune defense in the lung (78). Similarly, NGAL has direct antimicrobial effects as well as the ability to scavenge bacterial products (56) and is expressed in normal gastric mucosa by parietal cells (33). During *H. pylori* infection NGAL may also be expressed from neutrophils or even Paneth cells, which may be present in the setting of intestinal metaplasia after chronic infection (56). Finally, surfactant protein A2 delta expression may also contribute antimicrobial effects similar to those of surfactant protein D, which binds bacteria, causing aggregation and phagocytosis, and is up-regulated during *H. pylori* infection (64). Taken together, these results extend previous findings of *H. pylori*-induced expression of hBD-2 to an experimental model system and suggest that this is part of a family of antimicrobial peptides whose expression in the stomach is increased by *H. pylori* infection.

(ii) Mucin. The gastric mucous layer also provides a protective barrier against infection. Mucins 1 and 6, which are key components of the mucous layer, showed increased expression at 24 weeks p.i. (Table 3). Mucin 1 can limit cell-cell adhesion and *H. pylori* binding to the gastric epithelium and may have the additional function of signal transduction to alert the cell to changing extracellular conditions (35). Increased expression of mucin 1 fits with decreased expression of transcription factor 8 (ZEB1) (Table 3), which is known to repress mucin 1 in epithelial cells (39). *H. pylori* infection has been associated with an increase in the expression of mucin 6 and expansion of mucin 6 expression from mucous glands to surface mucous cells (15, 59). It is not known what effect up-regulation of mucins 1 and 6 have on the *H. pylori* adhesion in vivo. Mucin 5AC was not significantly changed in this study. This may at first seem surprising, since mucin 5AC has recently been identified as the primary source for Lewis^b binding of *H. pylori* BabA adhesin (94), and its expression in humans is induced by *H. pylori* infection (15). However, passage of *H. pylori* J166 through rhesus macaques results in deletion of *babA* and duplication of *babB* (84). This gene conversion event results in loss of adhesion to Lewis^b, and it may explain the failure of *H. pylori* J166 to induce expression of mucin 5AC in rhesus macaques. Alternatively, since the mucin 5AC DNA sequence is not known for rhesus macaques, a lack of up-regulation could be due to sequence differences.

(iii) Extracellular matrix remodeling. Expression of collagen VIII and IX was increased following *H. pylori* infection (Tables 1 to 3). Altered expression was found for several protease inhibitors, such as antithrombin III, serine protease inhibitor (Kazal type I), alpha-1-antitrypsin, and matrix metalloproteinase 3 (MMP-3) (all decreased) and MMP-15 (increased) (Tables 1 to 3). These results differ somewhat from recent studies using cultured gastric epithelial cells that demonstrated increased expression of proteases and protease inhibitors, such as MMP-1, -2, -3, -7, and -9 and ADAM (a disintegrin and metalloproteinase)-10 and -17 in gastric epithelial cells (9, 10, 24, 38, 48, 63, 99). Our results may emphasize differences between gene expression in cultured cells and an experimental animal model associated with *H. pylori* infection. Overall there is a growing appreciation that remodeling of the extracellular matrix is a key event in *H. pylori* infection. Up-regulation of some of these proteins may contribute to the carcinogenic potential of *H. pylori*, as up-regulation of MMP-7 has been associated with both gastric adenocarcinoma and premalignant lesions in the stomach and other tissues of the gastrointestinal tract (24).

(iv) Cell adhesion molecules. Changes in cell adhesion molecules were also present at all time points p.i. CD44 and intercellular adhesion molecule 5 (ICAM-5) were increased in expression 2 weeks p.i. ICAM-5 has previously been associated with expression in neuronal tissue (55). CD44 and ICAM-1

TABLE 2. Changes in expression 8 weeks p.i.[a]

Category	Description	Accession no.	Fold change	*P* value
Innate immune-inflammatory response	**Chitinase 1**	**U29615**	**−6.25**	**0.007**
	Fatty acid binding protein 1, liver	**M10050**	**−6.10**	**0.007**
	Placental protein 14, glycodelin	**HG721-HT4827**	**−4.88**	**0.018**
	Hemochromatosis	U60319	−4.72	0.010
	CD1B antigen, b polypeptide	M28826	−3.26	0.006
	Leukocyte immunoglobulin-like receptor	U82275	−3.22	0.009
	Antithrombin III	**X00237**	**−3.04**	**0.031**
	Transferrin receptor	X01060	−2.95	0.037
	Killer cell lectin-like receptor	X54867	−2.50	0.038
	Adhesion glycoprotein	U56102	2.11	0.002
	Eosinophil peroxidase	X14346	2.40	0.008
	Prostaglandin E receptor EP3 subtype	**D86096**	**2.51**	**0.028**
	Pancreatitis-associated protein (HIP/PAP)	D30715	2.70	0.035
	Eosinophil cationic-related protein	**X55989**	**2.93**	**0.023**
	Interferon, alpha-inducible protein 27 (IFI27)	X67325	2.97	0.029
	Histidine-rich glycoprotein	M13149	3.02	0.008
	Tenascin XB	U24488	3.39	0.013
	Calcitonin-related polypeptide, beta	X02404	3.74	0.046
	Thrombospondin 1	X14787	4.56	0.015
Chemokine-cytokine	Cytokine receptor common beta chain	M59941	2.02	0.019
Heat shock	**DnaJ (Hsp40) B4**	**U40992**	**−3.12**	**0.025**
	Heat shock 70-kDa protein 1B	**M59830**	**−3.07**	**0.005**
	DnaJ (Hsp40) A1	L08069	−2.05	0.040
Cell growth and differentiation	Hepatocyte growth factor	X16323	−4.63	0.046
	Fibroblast activation protein, alpha	**U09278**	**−4.52**	**0.043**
	Fibroblast growth factor 5	M37825	−3.85	0.033
	c-myc proto-oncogene	L00058	−3.64	0.011
	c-myc binding protein	D50692	−2.29	0.036
	Basic fibroblast growth factor receptor 1	X66945	2.47	0.009
	Cyclin-dependent kinase inhibitor 1C	U22398	2.91	0.000
	Teratocarcinoma-derived growth factor 1	X14253	4.30	0.019
	Fibroblast growth factor 8	U47011	5.60	0.008
Apoptosis	**Glucagon**	**J04040**	**−3.82**	**0.049**
	Fas ligand	D38122	−3.17	0.021
	TNF receptor superfamily, member 25	U83598	2.39	0.045
Structural	Matrilin 3	AJ001047	−4.12	0.038
	Villin 1	X12901	−3.98	0.005
	Desmocollin 3	**X83929**	**−3.66**	**0.024**
	Coronin, actin binding protein, 2A	U57057	−2.56	0.007
	Myosin, nonmuscle	**M69180**	**−2.30**	**0.040**
	Utrophin	X69086	2.11	0.008
	Elastin	**X52896**	**2.31**	**0.048**
	Collagen, type VIII, alpha 2	M60832	2.67	0.026
Signal transduction	T-cell lymphoma invasion and metastasis 1	U16296	−3.92	0.012
	Protein tyrosine phosphatase, type 11	D13540	−3.69	0.032
	RAB3 GTPase-activating protein	D31886	−2.67	0.048
	Wiskott-Aldrich syndrome	U12707	−2.31	0.026
	Guanine nucleotide binding protein, alpha 13	**L22075**	**2.42**	**0.028**
	Guanylate cyclase 2C	**M73489**	**2.51**	**0.030**
	G protein-coupled receptor 18	L42324	2.79	0.049
	Protein tyrosine phosphatase, nonreceptor type 9	**M83738**	**5.59**	**0.002**
	Protein tyrosine phosphatase, receptor type, M	X58288	6.19	0.001
Transcription factor	**Zinc finger protein 77**	**X65230**	**−2.01**	**0.022**
	Runt-related transcription factor 3	Z35278	2.81	0.024
	Transcription factor 4	M74720	3.92	0.044
	DNA binding protein for surfactant protein B	L10403	4.05	0.003
	Zinc finger protein ZFP-36	**X51760**	**5.52**	**0.003**

[a] Data for genes with altered expression at more than one time point are in boldface.

were up-regulated in *H. pylori*-infected AGS cell cultures (32), and CD44 expression was found in gastric epithelial cells of *H. pylori*-infected patients (31). CD44 expression was decreased at 24 weeks postinfection as were the integrins α3 and αL (CD11A). These changes generally reflect alterations in cell-cell interactions and cell migration. CD44, a hyaluronin receptor, provides a docking station for MMP-9 (100). MMP-9 and MMP-2 cleave latent transforming growth factor β (TGF-β)

TABLE 3. Changes in expression 24 weeks p.i.[a]

Category	Description	Accession no.	Fold change	*P* value
Innate immune-inflammatory response	CEA-related cell adhesion molecule 5	M29540	−8.77	0.004
	Fatty acid binding protein 1, liver	**M10050**	**−5.15**	**0.013**
	Placental protein 14, glycodelin	**HG721-HT4827**	**−4.55**	**0.039**
	CD44 glycoprotein	**M83328**	**−4.26**	**0.046**
	Histatin 3	L05514	−3.89	0.036
	Integrin, alpha 3	M59911	−3.76	0.028
	Tissue plasminogen activator	K03021	−3.75	0.042
	Hyaluronidase PH-20	S67798	−3.70	0.035
	Serine protease inhibitor, Kazal type 1	**M20530**	**−3.45**	**0.007**
	Integrin, alpha L (CD11A)	Y00796	−3.18	0.013
	Chitinase 1	**U29615**	**−2.85**	**0.028**
	Lymphocyte antigen 9	L42621	−2.84	0.032
	Annexin II	D28364	−2.26	0.048
	Peroxisome receptor 1	U35407	2.28	0.009
	Heparin cofactor	M58600	2.30	0.008
	Mucin 1	X83412	2.37	0.022
	Mucin 6	L07517	2.44	0.010
	Surfactant protein Sp-A2 delta	S69683	2.90	0.006
	Sucrase-isomaltase	X63597	3.14	0.011
	Carboxypeptidase B2	M75106	3.19	0.034
	Peroxisomal biogenesis factor 12	U91521	3.29	0.038
	Ceruloplasmin	M13699	3.44	0.008
	Galectin 8	L78132	3.82	0.048
	2′–5′-Oligoadenylate synthetase 2	M87284	4.21	0.002
	Defensin, beta 2	**Z71389**	**4.39**	**0.045**
	Protease inhibitor 3 (elafin)	**L10343**	**10.97**	**0.007**
Chemokine-cytokine	Small inducible cytokine B10 (CXCL10)	X02530	−2.26	0.038
	CCR2	**AF014958**	**−2.16**	**0.028**
	IL-2 receptor, beta	M26062	2.94	0.049
	CCR2	**U95626**	**3.05**	**0.012**
	IL-10 receptor, alpha	U00672	4.76	0.008
	Chemokine-like receptor 1	U79526	5.40	0.021
Heat shock	Heat shock 70-kDa protein 2	L26336	−3.41	0.044
	Heat shock 70-kDa protein 1B	**M59830**	**−2.68**	**0.013**
	Heat shock 70-kDa protein 1A	**M11717**	**−2.65**	**0.015**
Cell growth and differentiation	**Fibroblast activation protein, alpha**	**U09278**	**−5.24**	**0.002**
	Cyclin-dependent kinase inhibitor	L25876	−4.74	0.026
	RAB5B, member RAS oncogene family	X54871	−2.35	0.036
	Platelet-derived growth factor alpha polypeptide	**M19989**	**−2.07**	**0.024**
	Peptidyl-prolyl isomerase G (cyclophilin G)	U40763	2.15	0.015
	M-phase phosphoprotein 9	X98258	2.23	0.038
	Proto-oncogene tyrosine-protein kinase ABL1	U07563	2.41	0.029
	Lethal giant larva homolog 1	D50550	2.45	0.031
	Mast/stem cell growth factor receptor	X06182	2.66	0.041
	Glypican 3	Z37987	3.11	0.007
	Latent TGF-β binding protein 2	**Z37976**	**3.62**	**0.005**
	BRCA1-associated RING domain 1	U76638	3.81	0.049
	Synaptotagmin I	**M55047**	**5.14**	**0.040**
Apoptosis	TNF-α	X02910	−3.83	0.049
	Glucagon	**J04040**	**−3.56**	**0.038**
	FK506 binding protein 8 (Bcl-2 interacting)	L37033	−2.79	0.006
	Prothymosin, alpha	**M14483**	**−2.27**	**0.019**
	Milk fat globule-EGF 8 protein	U58516	2.38	0.003
	Bcl-2 homolog	S82185	2.57	0.038
	TNF receptor superfamily, member 6	X89101	3.36	0.001
Structural	**Myosin, nonmuscle**	**M69180**	**−4.24**	**0.022**
	Desmocollin 3	**X83929**	**−2.68**	**0.044**
	2′,3′-Cyclic nucleotide 3′ phosphodiesterase	M19650	−2.36	0.031
	Procollagen C-endopeptidase enhancer	L33799	−2.15	0.027
	Elastin	**X52896**	**2.68**	**0.023**
	F-actin capping protein, alpha 2	**U03851**	**9.00**	**0.022**
Signal transduction	Tyrosine kinase, nonreceptor, 1	U43408	−4.44	0.010
	Protein tyrosine kinase	U07794	−4.17	0.020
	G protein-coupled receptor 21	**U66580**	**−3.09**	**0.032**
	Tyrosine kinase 2	X54637	−2.69	0.014

Continued on following page

TABLE 3—*Continued*

Category	Description	Accession no.	Fold change	*P* value
	Serine/threonine kinase 4	U18297	−2.49	0.011
	Protein tyrosine phosphatase, nonreceptor type 9	**M83738**	**2.42**	**0.014**
	Protein tyrosine phosphatase, nonreceptor type substrate 1	Y10375	2.76	0.020
	Bone morphogenetic protein 5	S81957	3.01	0.037
	PCTAIRE protein kinase 3	X66362	3.41	0.010
	Protein kinase C, beta 1	X07109	3.50	0.025
	MAP–microtubule affinity-regulating kinase 3	M80359	3.94	0.012
	Cadherin 3, type 1, P cadherin	X63629	4.23	0.018
	Cadherin 12, type 2	L33477	4.49	0.010
	MAPK kinase kinase 10 (MAP3K10)	X90846	5.89	0.004
Transcription factor	Transcription factor 8	D15050	−4.67	0.010
	ZFP-36 for a zinc finger protein	**X51760**	**3.00**	**0.042**
	Homeotic protein Hpx-2	**X74861**	**3.33**	**0.049**

[a] Data for genes with altered expression at more than one time point are shown in boldface.

to form active TGF-β. Both CD44 and a TGF-binding protein were up-regulated 2 weeks p.i., and MMP-9 is increased in expression in *H. pylori*-infected human patients (10). These changes reflect alterations in cell-cell interactions and cell migration that support and extend previous findings from cell culture and clinical samples (31, 32). Together they suggest participation by and interaction among tissue remodeling enzymes, cell surface receptors, and growth factors.

Also observed was the increased expression of galectin 8 (24 weeks p.i., Table 3), which regulated inflammatory cell adhesion (67, 103) and is a member of a family of highly conserved β-galactoside binding lectins that mediate cell-cell and cell-matrix interactions. Galectins 3 and 4 also had increased expression in our study but did not meet the significance criteria. Up-regulation of galectins 1 and 3 has been observed in AGS cells (54) but has not been studied in vivo. Galectins 1 and 3 are important mediators of the inflammatory cascade via neutrophil recruitment and induction of the respiratory burst (1). Galectin expression is typically altered in neoplastic tissue, including gastric adenocarcinoma (61). Although early changes in galectin expression could represent preneoplastic changes in gastric epithelial cells as has been suggested previously (54), the functional role of the galectins and the acute timing in these animals suggest that they are part of the innate immune response to infection. It is also possible that binding between galectins and *H. pylori* could occur. β-Galactoside carbohydrates are common components of bacterial membranes, and interactions between host galectins and other microorganisms such as *Leishmania* spp. and *Neisseria gonorrhoeae* have been described previously (45, 74), as have associations between *H. pylori* and host glycoproteins (44).

(v) Hsp. The expression of several heat shock proteins (Hsp) was decreased at all time points p.i. (Tables 1 to 3). Although best described as protein chaperones during cellular stress (42), recent evidence suggests that Hsp are also important for activation of the innate immune response (8). Release of the inducible Hsp, such as Hsp70, from necrotic cells provides a danger signal to antigen-presenting cells, which induces cellular activation and cytokine production (88, 91). In addition, peptides bound to Hsp70 serve as a source of antigen and Hsp70 itself is a maturation signal for dendritic cells (60, 88). Up-regulation of Hsp is the general response to all types of cellular stress, including infection (50). We propose that down-regulation of host Hsp70 by *H. pylori* is a mechanism to limit the host inflammatory response and facilitate chronic infection. This immunomodulation can be viewed in the larger context of emerging evidence that *H. pylori* has multiple strategies to promote chronic infection and avoid host immunity, such as synthesis of a lipopolysaccharide with low biological activity (62), down-regulation of IL-2 signaling (34), and the presence of flagellar proteins that do not activate toll-like receptor 5 (37). These results suggest that the role of Hsp70 expression in *H. pylori* infection, which to date has been little studied (49, 89), may be a fruitful area of investigation to better understand bacterial persistence in the face of an active humoral and cellular immune response.

Cytokines-chemokines. One of the hallmarks of infection with Cag PAI-positive strains of *H. pylori* is the up-regulation of IL-8 expression by gastric epithelial cells (23). It was therefore surprising that we and others (72, 96) did not find IL-8 expression increased according to the data analysis criteria that were established. One possible explanation for this observation is sequence differences between rhesus macaques and humans for IL-8. Since the monkeys were inoculated with a mixture of strains of *H. pylori* J166, only some of which induced IL-8 in cell culture, there was a possibility that only non-IL-8-inducing strains colonized the monkeys or that colonizing strains subsequently lost the ability to induce IL-8. This latter observation has been reported previously in a mouse model of *H. pylori* (75). However, assays of IL-8 induction from multiple bacterial colonies at each time point p.i. showed that IL-8-inducing strains were recovered from each monkey at all time points p.i. (data not shown). Analysis of the fluorescence intensity values for the IL-8 expression indicated increased expression at 24 weeks with a fold change that was just below the twofold cutoff (Fig. 2). In addition to IL-8, other proinflammatory chemokines such as IL-1β, epithelial neutrophil-activating peptide 78, growth-related oncogene α, and monocyte chemotactic protein 1 are also up-regulated by *H. pylori* infection (22, 82), which serves to recruit neutrophils and monocytes and promote the T-cell response to infection. While no changes in these chemokines were noted, increased expression of chemokine receptor 2, the receptor for monocyte chemotactic protein 1, was present at 2 and 24 weeks p.i.

Evidence of an anti-inflammatory response was also found p.i., such as decreased expression of T-cell chemotactic factors

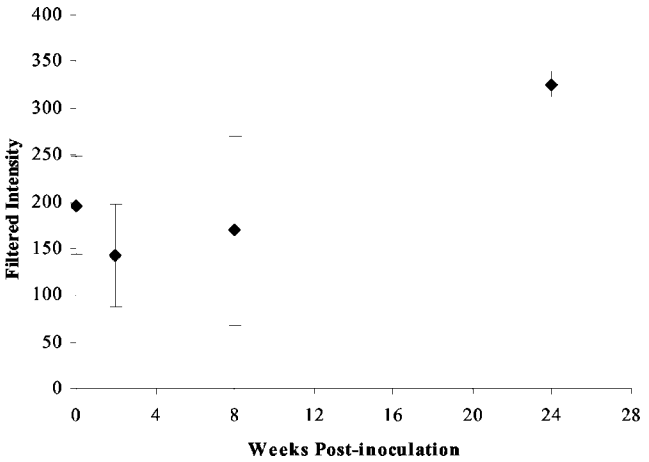

FIG. 2. Plot of mean filtered intensity for IL-8 (accession no. M28130) on Affymetrix HuFL chip. Intensity values were filtered in BRB ArrayTools (Materials and Methods). Each point represents the mean filtered intensity for three monkeys, with error bars showing standard deviations. At 24 weeks p.i. mean filtered intensity was above the preinoculation value ($P = 0.026$), but it failed to meet the twofold change cutoff.

(CXCL11 and CXCL10) (19) at 2 and 24 weeks p.i. Similarly, expression of glycodelin (placental protein 14) was decreased at 8 and 24 weeks p.i. This extensively glycosylated protein primarily has a role in pregnancy, where it appears to inhibit T-cell proliferation (77), and it may have similar immunomodulatory effects in *H. pylori* infection. These findings are consistent with recent observations that *H. pylori* can interfere with the normal host immune response and can alter the degree of inflammation in the epithelium, thus permitting chronic infection. For example, a recent study has shown that VacA, the *H. pylori* vacuolating cytotoxin, directly interferes with T-cell receptor and IL-2 signaling (34). Increased expression of IL-2-inducible T-cell kinase (2 weeks p.i.) and the IL-2 receptor (24 weeks p.i.) may be compensatory changes in response to VacA-induced down-regulation of the IL-2 signaling pathway. These results emphasize that the response to *H. pylori* infection must be viewed in a systems manner, with attention to both inflammatory and anti-inflammatory circuits, which likely represent a mechanism of immune evasion.

Structural elements. Structural changes to gastric epithelial cells are a key feature of *H. pylori* infection. Attachment to the host epithelial cell allows Cag PAI-positive *H. pylori* to translocate CagA into the host epithelial cell by a type IV secretion system, which leads to signaling events that cause cell elongation (80). Changes in actin, elastin, and cytoskeletal gene expression were apparent at all three time points p.i. (Tables 1 to 3). Tropomodulin was decreased in expression 2 weeks p.i., while F-actin capping protein was increased in expression at 2 and 24 weeks p.i., indicating changes in the actin structure. Other actin-associated genes were changed at 2 weeks, such as myosin IF (increased) and actin-related protein 1B (decreased), both of which are involved in intracellular transport and indicate alterations in this mechanism in the gastric mucosa. Decreased expression of coronin 2A, which interacts with the actin cytoskeleton in epithelial cells (25), was noted 8 weeks p.i. Recently VacA of *H. pylori* was shown to interrupt phagosome maturation in macrophages by retaining coronin 1 in the phagosome, preventing phagosome-lysosome fusion (101). It is not known whether VacA could interact with coronin 2A in epithelial cells. Finally, at 8 and 24 weeks p.i. there was a decrease in desmocollin 3 expression, indicating a change in desmosomal junction structure. At 24 weeks p.i., just below the twofold change cutoff, decreases in tight junction protein 1 (zona occludens 1) and gap junction protein beta 1 expression were noted (data not shown). These changes are intriguing in light of recent evidence that CagA directly interacts with zona occludens 1 of the apical-junctional complex of epithelial cells (2).

Cell growth and differentiation. In the face of gastritis, there is an expectation to find promotion of cell growth to replace dying cells. However, the gene expression pattern suggests that cell growth was suppressed at all time points p.i. Numerous growth factors associated with wound healing were decreased in expression, such as fibroblast activation protein α (all time points), fibroblast growth factor (8 weeks p.i.), hepatocyte growth factor (24 weeks p.i.), and platelet-derived growth factor α (24 weeks p.i.). Glypican 3 was increased in expression 24 weeks p.i. Glypican 3 is a heparin sulfate proteoglycan that suppresses cell growth (87), and it is markedly decreased in gastric cancer (102). Suppression of cell growth may favor *H. pylori* infection by limiting repair and allowing nutrient leakage through damaged epithelium.

Apoptosis. Both pro- and antiapoptotic gene expression were present p.i., which is consistent with previous findings in vivo (70, 73). Both the Fas-tumor necrosis factor (TNF) receptor-mediated pathway and the mitochondrially based pathway involving cytochrome *c* have been implicated (46, 58). Evidence for the Fas-TNF apoptotic pathway was present at each time point. At 8 and 24 weeks p.i., members of the TNF receptor superfamily showed increased expression. These receptors interact with the death domain-containing protein TRADD to induce apoptosis (7). Daxx, which mediates the apoptotic signal from Fas to JNK, was increased in expression 2 weeks p.i. Conversely, while the TNF receptor was up-regulated, TNF-α expression was decreased (24 weeks p.i.), as was that of Fas ligand (8 weeks p.i.). The mitochondrially based apoptotic pathway may not be active early in infection (2 weeks p.i.) due to the increased expression of prothymosin α, which acts as a negative regulator of caspase 9, inhibiting formation of the apoptosome (76). Subsequently, prothymosin α was decreased in expression (24 weeks p.i.), indicating a change in apoptosis at this time. In conflict with the apparent proapoptotic state at 24 weeks p.i. was increased expression of two Bcl-2-interacting proteins. These results again emphasize the complexity and reciprocity of host gene expression in response to *H. pylori* infection.

Signal transduction pathways and transcription factors. There were changes noted in transcription factor and signal transduction pathway components present at all time points p.i. Most of these genes are not well defined and have not been associated specifically with *H. pylori* infection. Of the pathways and factors that have been associated with *H. pylori* infection, the extracellular signal-regulated kinase–mitogen-activated protein kinase (MAPK) pathway was best represented (71, 83). At both 2 and 24 weeks p.i., elements of the MAPK pathway were increased in expression (Tables 1 and 3). Additional

changes in the expression of tyrosine kinases and phosphatases were present at each time point; however, there were no consistencies in the direction of change. No specific changes in the NF-κB pathway were noted, although this pathway is known to be active in *H. pylori* infection (71).

Conclusions. High-throughput gene expression technology, together with the rhesus macaque model, provides unprecedented opportunities to examine the *H. pylori* host-pathogen interaction in a model system that is relevant to human infection. The results from this initial effort partially confirm and in some cases extend previous results drawn largely from cell culture experiments or observational studies of infected human tissue. Our results only partially agree with a recent study that focused on the expression of inflammatory genes in human patients infected with *H. pylori*, which could stem from true biological differences or from technical differences. The complexity of the results should not be discouraging. It probably reflects in part technical limitations, such as the use of human rather than rhesus DNA sequences, and the failure to analyze expression of individual cell types, a problem that can be solved in future studies through the use of laser capture microdissection. However, we would argue that the complexity also reflects a biological system that is not simply proinflammatory or anti-inflammatory, proapoptotic or antiapoptotic, but is rather a complex host response composed of circuits and compensatory responses. Like any screening analysis, the strength of these data lies in the uncovering of potential novel mechanisms of pathobiology that may provide clues for future studies using more conventional methods of hypothesis-driven biological research (20). For example, the unexpected, but consistent, finding that *H. pylori* down-regulates Hsp provides an impetus to study their role in immunomodulation by using knockout and transgenic mice infected with *H. pylori*. We are currently beginning these and other studies that derive from this data set, as well as systematic studies to analyze the effects of well-defined knockout strains of *H. pylori* on host gene expression.

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