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Expression of Intrinsic Factor in Rat and Murine Gastric Mucosal Cell Lineages Is Modified by Inflammation

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Intrinsic factor is produced primarily by chief cells in rat and mouse, but 4 to 11% of isolated rat parietal cells also contain intrinsic factor. To test whether local conditions could alter the distribution of intrinsic factor expression, two rodent models of chronic lymphocytic gastric inflammation were examined. Immunocytochemistry was performed using antiserum against human intrinsic factor and H/K ATPase (a parietal cell marker), counting the percent of intrinsic factor-positive parietal cells. HLA-B27 transgenic rats develop chronic gastritis at age 3 months. Congenic controls expressed intrinsic factor in 8.9 ± 3.8% (mean ± SD) of parietal cells; in inflamed areas of transgenic rats 21 ± 5.2% ($P < 0.0001$) of parietal cells were positive. In adjacent areas without inflammatory infiltrate 16 ± 3.6% of parietal cells contained intrinsic factor. C57BL/6 mice inoculated with *Helicobacter felis* develop gastritis by 4 weeks. After 4 and 8 weeks of infection, intrinsic factor-positive parietal cells increased from 7.8 ± 2.8% in the congenic controls to 17.6 ± 4.1% in the inflamed gastric body ($P < 0.0001$). Isolated rat parietal cells incubated with interleukin-1β demonstrated a twofold increase in intrinsic factor-positive parietal cells. These studies are consistent with the concept that intrinsic factor expression is both predetermined in chief cells and can be expressed in parietal cells in response to local inflammatory factors. The differences between inflamed and adjacent noninflamed areas in the rat model suggest a tissue gradient of soluble inducer(s), possibly cytokines. *(Am J Pathol 2000, 157:1197–1205)*

Gastric glands in the zymogenic region of the stomach contain three major cell types: mucous surface cells, parietal cells, and zymogenic (chief) cells.[1] Intrinsic factor (IF) is a major secreted protein of the parietal cells in humans,[2] but in the mouse and rat IF is found in the zymogenic cells.[3,4] In human[5] and in rat gastric mucosa, IF is occasionally found inside cells of different lineage, especially in the rat in which 4 to 11% of isolated parietal cells express the protein.[6] These IF-expressing parietal cells were distributed in the lower neck and basal regions of the gastric glands, consistent either with predetermination of expression within cell lineages, with parietal cell maturation, with induction of IF production by local tissue factors, or with a combination of these mechanisms. Local factors may account for the phenomenon of mosaicism noted in small intestinal epithelium.[7,8] A number of cytokines, especially interleukin (IL)-1β and tumor necrosis factor (TNF)-α, can induce protein production in somatic cells.[9,10] Moreover, IL-1 receptors are found on the surface of parietal cells.[11] Therefore, models of chronic inflammation of the zymogenic mucosa were selected to test whether increased elaboration of cytokines could enlarge the population of parietal cells that produce IF.

HLA-B27, a serologically defined class 1 major histocompatibility complex allele, is associated with several human inflammatory disorders. An attempt was made to produce an animal model in transgenic mice, but despite physiologically normal function of B27 in hybrid mice, no features of human disease appeared.[12] Because rats are susceptible to experimental arthritis that cannot be produced in mice, transgenic technology was developed in Fisher 344 and Lewis rats, and animals expressing HLA-B27 and human β_2-microglobulin genes developed spontaneous multiorgan inflammatory disease.[13] Two of the seven transgenic lines developed inflammation, including gastrointestinal disease and arthritis, increasing in severity from 5 to 15 weeks of age. F344 transgenic rats raised in a specific pathogen-free environment develop histological evidence of colitis and gastroduodenal

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inflammation by 10 to 12 weeks of age. No disease occurs in the absence of bacterial stimulation[14] and disease correlates with cecal luminal anaerobic bacterial concentrations.[15] The incidence of disease varied from 30 to 100% in litters, and was affected by the genetic strain and density of animals/cage. The gastric body and antrum were involved with widely scattered mononuclear foci in the lamina propria and submucosa. The infiltrate occurred in some, but not all, crypt units, and was associated with a marked reduction in the number of parietal cells in some glands.[13] Subsequently the model was reproduced in transgenic mice (mostly males), where it was associated with the presence of free heavy chains on a subpopulation of B27-expressing lymphocytes.[16] In this model inflammation did not develop in germ-free animals, although no pathogen was detected in the gastrointestinal lumen.

Helicobacter pylori infection causes clinical gastritis and peptic ulcers and is associated with the development of gastric cancer. *Helicobacter felis* is a spiral bacteria isolated from feline stomach that colonizes gastric mucosa in mice, rats, and dogs.[17] *H. felis*-associated gastritis in mice reproduces many of the features of human disease, including a marked polymorphonuclear and mononuclear cell infiltrate.[18] Production of *H. felis* infection in C57BL/6 mice was achieved by inoculating mice orally, and observing a similar infiltrate with a marked reduction in parietal cells noted by 6 months of infection.[19] The organism colonizes the gastric mucous layer and causes gastritis in the antrum and body of the stomach by 4 weeks, with inflammation increasing further by 8 weeks after inoculation.[20]

These animal models were used to test the hypothesis that chronic inflammation could increase ectopic IF production in other gastric cell lineages, particularly the parietal cell that expresses IF in human mucosa. Despite the decrease in parietal cell populations that occurred during development of inflammation, both models demonstrated more than a twofold increase in the percent of parietal cells that expressed IF, but only when an inflammatory infiltrate was present in the tissue. Other gastric mucosal lineages did not express IF. These results are consistent with a cytokine-induced expression of IF in parietal cells, and suggest that IF expression in cells is not entirely predetermined, at least in certain subpopulations that might be potential precursors for zymogen cells.

Materials and Methods

Animals

A colony of transgenic HLA-B27 rats and nontransgenic littermates were derived in a sterile environment at the University of North Carolina School of Medicine, populated with specific pathogen-free bacteria (documented *Helicobacter sp.* free), and maintained in that environment.[15] The colony, derived from specific pathogen-free inbred Lewis/CrlBR (LEW) rats, was originally obtained from Dr. Joel D. Taurog (Southwestern Medical School, Dallas, TX). Female C57BL/6 mice, purchased from Taconic Laboratories (Germantown, NY), were inoculated intragastrically three times on alternate days at 5 weeks of age with 1×10^9 cfu of *H. felis* (ATCC 49179).

Tissues

Transgenic and control rats were killed at 1, 2, or 3 months of age. *H. felis* inoculated mice were maintained for up to 4 weeks after infection.[18] After rats or mice were euthanized with CO_2 inhalation, the glandular rat stomachs were fixed in Bouin's solution for 2 hours at room temperature, and transferred to 70% ethanol overnight at 4°C before embedding in paraffin. The body and antrum of the murine stomachs were fixed in 10% buffered formalin for a few hours, stored in 80% ethanol, and then embedded in paraffin. Sections were cut 4-μm thick and stained for hematoxylin and eosin (H&E), or used for immunocytochemistry. Inflammatory infiltrate was estimated as absent, moderate, or severe (0, +, or ++) by one observer (J-SS) in a blinded manner. These samples were obtained from the same animals reported previously.[20]

Immunocytochemistry

Immunostaining was performed using the standard avidin-biotin-peroxidase complex method as reported previously,[6] and counterstained with hematoxylin. Endogenous peroxidase was quenched by pretreatment with 1% H_2O_2 in methanol for 20 minutes. The primary antiserum used was rabbit polyclonal anti-human IF (1:200), raised against recombinant human IF produced in baculovirus-infected Sf9 cells.[5] In some experiments recombinant purified human IF made in *Pichia pastoris* was added to the antiserum before adding to the section.[21] Rabbit antibody against the β-subunit of rat H/K ATPase (amino acids 2 to 23) was obtained from Dr. Jeffrey I. Gordon (Washington University School of Medicine, St. Louis, MO). Second antibody was goat anti-rabbit IgG obtained from Vector Laboratories (Burlingame, CA). Parietal cells were identified by their large size, triangular shape, and different staining pattern compared with chief cells. Quantitation of parietal cells staining positively for IF was performed manually. All parietal cells in sections of rat and mouse stomachs were counted in eight $\times$200 magnified fields per section, prepared from four rats and three mice per group/time point. The mean $\pm$ SD values were compared by Student's *t*-test of paired samples.

Parietal Cell Incubation

Highly enriched preparations of parietal cells were isolated from rat gastric mucosa as described previously,[6] and cultured for 24 to 48 hours.[11] Enriched preparations of parietal cells were washed 3 times in serum-free culture medium, and cells were cultured for 48 hours in a 1:1 mixture of Ham's F-12 medium/Dulbecco's modified Eagle's medium with HEPES plus L-glutamine without bicarbonate, and supplemented with insulin (5 μg/ml), trans-

Table 1. Percent of Parietal Cells Expressing Intrinsic Factor (IF) in HLA-B27 Transgenic Rats

Animal (*n*)	Age (months)	Inflammation		Parietal cells/magnified field (mean no. ± SD)	IF-positive parietal cells (mean% ± SD)
		Body	Antrum		
Controls (4)	3	−	−	110 ± 27	8.9 ± 3.8
Transgenic (4)	1	−	−	122 ± 32	9.6 ± 5.6, $P = 0.6$
Transgenic (4)	2	−	+	100 ± 23	9.2 ± 4.4, $P = 0.7$
Transgenic (4)	3	+	+		
Non-inflamed areas				116 ± 38	16 ± 3.6, $P < 0.0001$*
Inflamed areas				77 ± 19	21 ± 5.2, $P < 0.0001$*

**P* by paired two-sample *t* test for means (with equal variance) of 3 month inflamed *versus* noninflamed areas. The gender of animals (male/female) was 0/4 for controls, 4/0 for 1-month-old transgenics, and 2/2 for 2- and 3-month-old transgenics.

ferrin (5 μg/ml), sodium selenite (5 ng/ml), hydrocortisone (4 mg/ml), epidermal growth factor (25 ng/ml), gentamicin (10 mg/100 ml), and bovine serum albumin (2 mg/ml).[11] Thereafter, recombinant human IL-1β (2.5 pg/ml) or recombinant human interferon-γ (1.5 ng/ml) were added to fresh culture media without added growth factors for 4 hours at 37°C. The medium was aspirated, centrifuged, and stored at −20°C. Adherent cells were removed by trypsinization, washed in phosphate-buffered saline (PBS), centrifuged, and fixed in Bouin's solution overnight before transfer to graded ethanol concentrations from 70 to 100%. The cells were embedded in paraffin and 5-μm sections of the cell pellet were prepared on slides, which were probed with antiserum against IF as described above. The cells on each slide were counted completely, each high-power field contained 108 to 384 parietal cells (total of 1773 to 4384 in each slide were counted), and the IF-positive cells re-

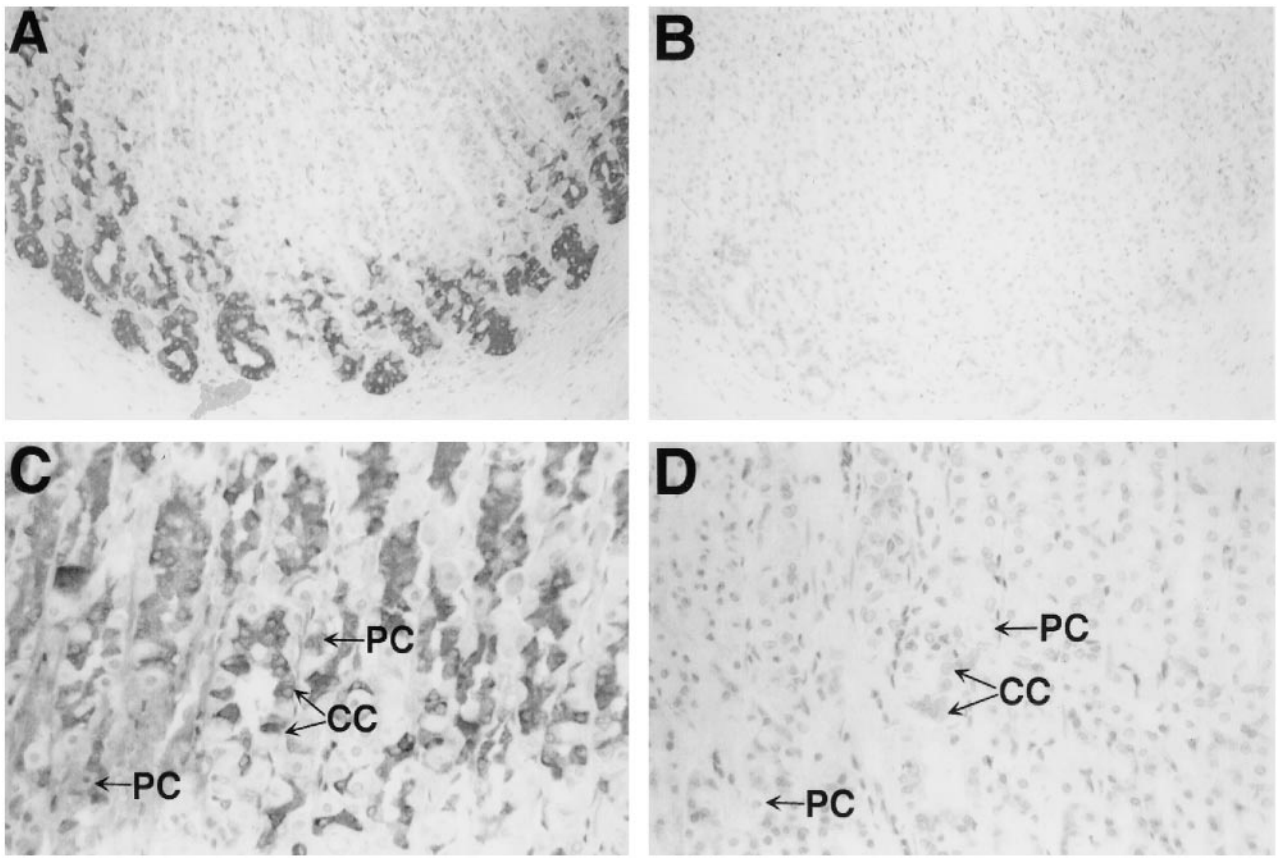
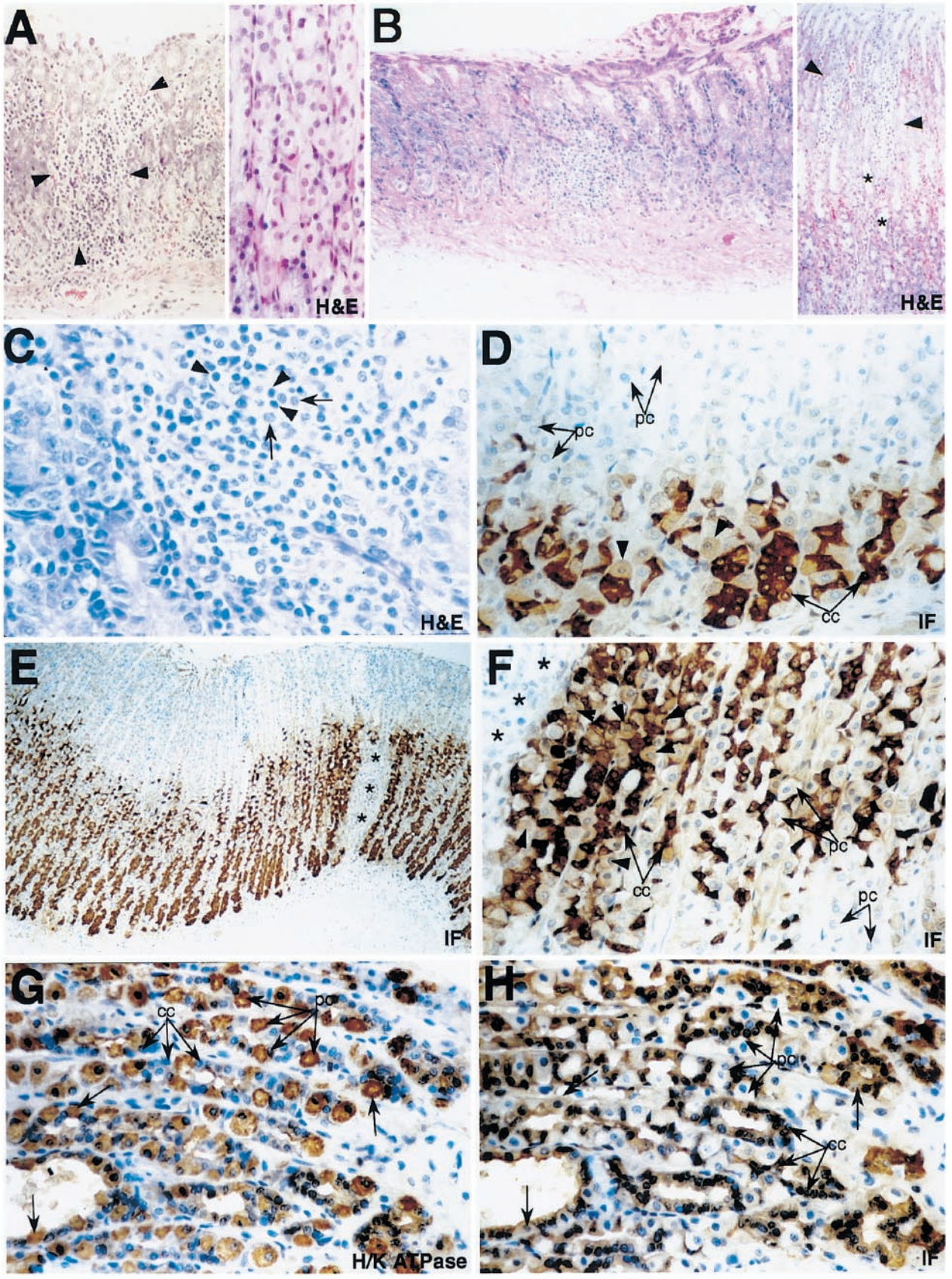


Figure 1. Immunocytochemical specificity for IF antiserum. Samples from control 3-month-old rats were processed and analyzed as described in Methods. **A:** Gastric body, showing IF-positive cells, mostly chief cells in the lower 2/3 of the glands (anti-IF 1:200; original magnification, ×250). **B:** Gastric body with control serum, showing no reactivity compared with **A** (normal rabbit serum 1:200; original magnification, ×250). **C:** Gastric body, showing IF-positive cells concentrated in chief cells at the base of the glands, with lesser reaction in parietal cells (anti-IF 1:200; original magnification, ×500). **D:** Gastric body using anti-human IF incubated with recombinant IF 12.8 μg/μL overnight at 4°C. Two hundred μl of the 1:200 dilution of antibody contained 1.7 μg of IF. Note that compared with **C** reactivity was completely inhibited (original magnification, ×500).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corded. The results were compared using a two-tailed Student's *t*-test.

Results

HLA-B27 Model

Transgenic animals were studied at 1, 2, or 3 months of age. Congenic control animals were examined only at 3 months of age. In the gastric body of the control rats, 8.9% of the parietal cells were positive for IF (Table 1 and Figure 1). Figure 1 demonstrates the specificity of the antiserum used against IF. Neither normal rabbit serum (Figure 1B) nor anti-IF antiserum incubated with recombinant IF (Figure 1D) showed any reactivity in either chief cells or parietal cells.

The percent of positive cells in transgenic HLA-B27 rats at 1 and 2 months of age (9.6 and 9.2, respectively) was no different from that found in the gastric body of control rats (Table 1). There was no inflammation found in the body of these animals, although mild inflammation had developed in the antrum by 2 months of age. No parietal cells are found in the antrum of adult rats, however, and stains for IF were also negative. After 2 months the infiltrate in the gastric body was not uniform, involving some gastric glands, but not others (Figure 2A). By 3 months submucosal abscesses were found occasionally in the antrum, and in the body more extensive inflammation with dilation of the gastric pits (Figure 2B). This inflammation was mononuclear (Figure 2C). In control rats the IF-positive parietal cells were mostly located in the lower part of the crypt (Figure 2D).

The findings in the 3-month-old transgenic rats were quite different. Chronic (lymphocytic) inflammation and mucosal hyperplasia was found in both the body and antrum of the stomach (Figure 2, A and B). The absolute number of parietal cells was decreased.[17] Control rats had 110 ± 27 (mean ± SD) parietal cells per magnified field ($n = 32$), whereas inflamed areas in transgenic rats showed 77 ± 19 parietal cells ($n = 32$). In the inflamed glands, 21% of parietal cells were IF-positive. Most of the positive cells were found in the lower neck and basal regions of the glands, and none appeared to be dying or apoptotic cells. In adjacent glands that were not inflamed there were still 16% of parietal cells that were positive for IF (Figure 2, E and F, and Table 1). These values were significantly greater than that for the control rats. In addition, the inflamed glands and those adjacent to them were also different from each other ($P < 0.0001$).

The identity of IF-positive cells with morphology-like parietal cells was confirmed using antiserum against H/K ATPase, a parietal cell marker. Figure 2G shows all parietal cells positive in a 3-month-infected transgenic animal. Figure 2H shows an adjacent section stained with antiserum against IF, demonstrating some cells positive for both markers (isolated arrows), and some parietal cells positive for H/K ATPase but negative for IF.

H. felis *Model*

After either 4 or 8 weeks of infection, the mucosa and the submucosa both showed inflammatory infiltration, although the degree and distribution of inflammation was somewhat variable. After 4 weeks the parietal cell density in some gastric glands was decreased, and scattered inflammatory cells were found in the mucosa of the gastric body (Figure 3, B compared with the control in A). The number of parietal cells seen in H&E sections was diminished by 8 weeks (see Figure 3C *versus* Figure 1,A and B).[20] Control mice (n = six animals, 70 fields) showed 70 ± 29 parietal cells/magnified field compared with the value in infected mice ($n = 6$, 62 fields) of 50 ± 41, but no mucosal hyperplasia was noted as in the HLA-B27 rat model. Moreover, submucosal inflammation was present, and atrophic parietal cells were noted by their smaller size and diminished eosinophilic stain. These cells were seen mostly in the middle part of the gastric gland (Figure 3, C and E). Further analysis of these atrophic cells was made using antiserum against H/K ATPase. In the normal control mice, all parietal cells stained strongly positive (Figure 3D). In the 8-week-infected mice, on the other hand, the stain for H/K ATPase is much diminished compared with control tissues, and some cells that appear by morphology to be atrophic parietal cells are negative (Figure 3E).

The percent of IF-positive cells doubled in the presence of inflammation (Table 2), and did not change from 4 to 8 weeks ($P = 0.49$). However, the degree of mucosal inflammation did not alter qualitatively either (compare Figure 3, B and C). Again, the increase in IF-positive cells was located primarily in the lower neck and basal regions of the gastric glands and these cells seemed normal morphologically (Figure 3, F–H).

Isolated Rat Parietal Cells

The percent of IF-positive parietal cells incubated with the cytokine interleukin-1β increased from 3.14 ± 1.41%

Figure 2. Gastric histopathology and immunocytochemistry in HLA-B27 transgenic rats. **A:** Gastric tissue from a 2-month-old transgenic rat. Note antral inflammation in the **left panel** (**arrowheads**) (H&E; original magnification, ×250). The mucosa of the gastric body (**right**) showed no inflammation (H&E; original magnification, ×500). **B:** Stomach from 3-month-old transgenic rat. The **left panel** shows antrum with focal inflammatory infiltration at the base of the glands (H&E; original magnification, ×125). The **right panel** shows gastric body with inflammatory infiltrate (**arrowheads**) with marked dilatation of pits and glands (**asterisk**; original magnification, ×250). **C:** Gastric body from 3-month-old transgenic rat. The inflammatory infiltrate is primarily lymphocytic (**arrowheads**) and monocytic (**arrow**) (H&E; original magnification, ×500). **D:** Immunocytochemistry (IF) of gastric body from 3-month-old control rat. Note that IF-positive cells are primarily confined to the lower parts of the crypt, and are less numerous than in **E** (anti-IF 1:200; original magnification, ×500). **E** and **F:** Immunocytochemistry (IF) of gastric body from 3-month-old transgenic rat. Note that IF-positive cells are more numerous (**arrowheads**) immediately next to inflammatory areas (**asterisk**) and less so in adjacent noninflamed areas, but more than in tissue from control animals (**D**) (anti-IF 1:200; original magnifications, ×250, ×500). **G:** Immunocytochemistry (H/K ATPase) of gastric body of 3-month-old transgenic rat, showing that all parietal cells (and no chief cells) were reactive (anti-H/K ATPase 1:200; original magnification, ×500). **H:** Immunocytochemistry (IF) of the section adjacent to **G**, showing that some parietal cells are positive for both IF and H/K ATPase (see isolated **arrows** in **G** and **H**) (anti-IF 1:200; original magnification, ×500). cc, chief cells; pc, parietal cells.

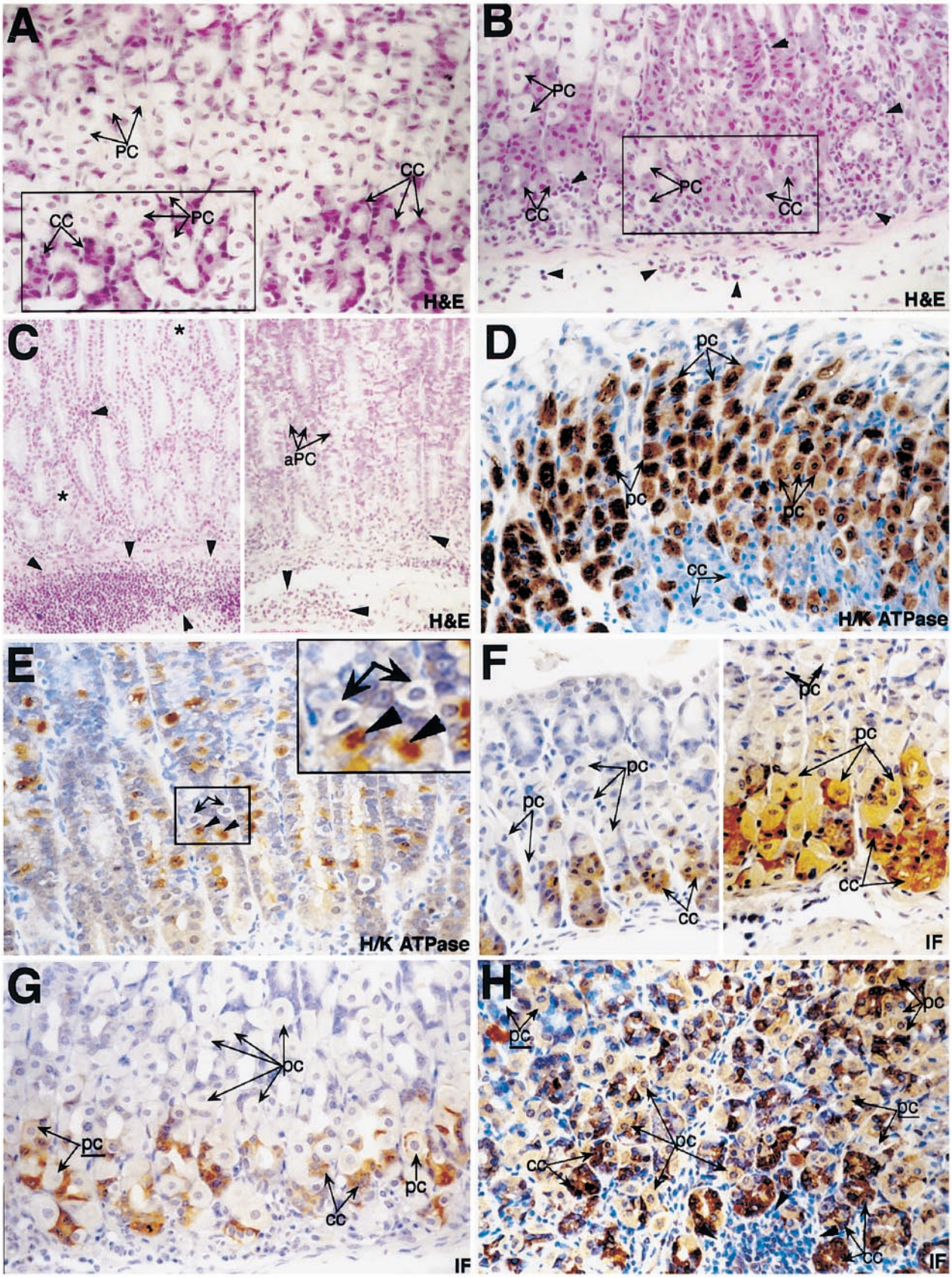
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Table 2. Percent of Parietal Cells Expressing Intrinsic Factor (IF) in *H. felis*-Infected Mice

Animal (*n*)	Time (weeks)	Inflammation		IF-positive parietal cells (mean % ± SD)
		Mucosa	Submucosa	
Control (6)	4/8	−	−	7.8 ± 2.8
H. felis (3)	4	+/++	+	17 ± 4.9, $P < 0.0001$*
H. felis (3)	8	+/++	++	17.2 ± 3.2, $P < 0.0001$*
H. felis (6)	4/8			17.6 ± 4.1, $P < 0.0001$*

All animals were females. *P value by paired two-sample t test for means of infected *versus* control animals. The P value comparing 4-week and 8-week infected animals was 0.49. Thus, these data were combined to provide an average value for all the infected animals (last line of table).

to 6.35 ± 4.05% (mean ± SD, $P < 0.005$, $n = 17$). On the other hand, incubation with interferon-γ produced a small decline in IF-reactive cells, from 1.83 ± 1.19% to 0.96 ± 0.85% ($n = 10$, $P < 0.1$). No difference in IF appearance in the medium was detected between control and cytokine-incubated cells.

Discussion

The findings in the control animals of both models confirms our earlier observations that IF was expressed in parietal cells of the gastric mucosa in rodents.[6] The percent of IF-positive cells in the control groups was higher than found in outbred Sprague-Dawley rats (1.5 to 4%), but consistent with the percent of IF-positive parietal cells in isolated parietal cell preparations (4 to 11%).[6] Previous studies of IF expression in mice using the same antiserum were unable to detect IF in parietal cells, although a different strain of mice was used, and the tissues were fixed for extended periods of time (usually days) before being analyzed.[4] It had been appreciated that IF is very sensitive to loss of antigenicity during fixation for electron microscopic findings,[22] but it was not so clear that the same problem existed for light microscopic studies. Perhaps the small size of the murine tissue requires shorter fixation times. We routinely use only a few hours for fixation of gastric tissue before immunolocalization studies and find that time quite sufficient for adequate tissue preservation.

The finding of ectopic production of IF, especially located in the lower neck and basal regions of the gastric gland, suggests that the expression of chief cell products in parietal cells is either hard-wired (predetermined by lineage or by functional maturation), or is influenced by environmental factors. The increase in IF-positive parietal cells in two models of chronic inflammation of the gastric body suggests that local environmental factors may be important. The rat model demonstrates gastric mucosal hyperplasia, whereas in the mouse model patches of atrophic mucosa are seen without intervening hyperplasia. Both models cause a marked decrease in the total number of parietal cells, and some of the remaining parietal cells in the middle of the murine gastric glands were atrophic. It seems unlikely that IF expression is solely a measure reflecting cell damage, as none of the IF-positive cells in or near the base of the gastric glands appeared abnormal morphologically. In addition, *H. felis* infection of C57BL6 mice show a marked diminution in chief cell number with a decrease in IF immunostaining.[23]

It is possible that the proliferative zone containing relatively undifferentiated cells is expanded whether mucosal hyperplasia or atrophy is present. For example, in the presence of inflammation the parietal cell precursors capable of IF expression (eg, preneck precursor lineage in the mouse,[1] might be preferentially preserved, creating a falsely elevated percent of IF-positive cells. However, in relatively normal gastric glands adjacent to the inflamed ones (in the rat model) the percent of IF-positive cells was also higher, although the number of parietal cells seemed normal. Thus, it seems unlikely that preservation of an IF-expressing lineage accounts for the observed changes.

The most likely explanation for these findings induced by inflammation is that they are related to recruitment of parietal cells newly expressing IF. The IF-positivity was present only when the gastric body is inflamed and the percent of positive cells was higher in inflamed areas than in noninflamed glands, at least in the rat model that allows such comparisons. Moreover, the difference between inflamed and noninflamed areas suggests a gradient effect, consistent with the presence of a diffusible inducer, perhaps secreted by (or liberated from) infiltrating inflammatory cells. The inflammation might be related either to a primary effect on the mucosa or a secondary one mediated by microbial presence and stimulation.[15]

Figure 3. Gastric histopathology and immunocytochemistry in *H. felis*-infected mice. **A:** Gastric body from uninfected control mouse age 4 weeks. Note the normal gastric glands (**box**), parietal cells, and chief cells (H&E; original magnification, ×500). **B:** Gastric body from 4-week-infected mouse, showing some decreased density of parietal cells in the gastric glands (**box**), and scattered inflammatory infiltrate throughout the mucosa and submucosa (**arrowheads**) (H&E; original magnification, ×500). **C:** Gastric body from 8-week-infected mouse. The **left panel** shows mucosal and submucosal infiltration (**arrowheads**) and dilated pits and glands (**asterisk**). In the **right panel** numerous atrophic parietal cells (aPC) are seen. These are identified by their retained pyramidal shape and location along the gastric pit, but smaller size and diminished eosinophilic staining (H&E; original magnification, ×250). **D:** Immunocytochemistry (H/K ATPase) of gastric body of 8-week control mouse, showing that all parietal cells, but no chief cells, were reactive (anti-H/K ATPase 1:300; original magnification, ×500). **E:** Immunocytochemistry (H/K ATPase) of a section adjacent to **C** from an 8-week-infected mouse. Numerous atrophic parietal cells are seen that are immunoreactive (**arrowheads**), but less strongly when compared to normal parietal cells in **D**. Some H/K ATPase-negative atrophic parietal cells are seen (**arrows**) (anti-H/K ATPase 1:300; original magnification, ×500). **F:** Immunocytochemistry (IF) of gastric body of 4-week control (**left**) and 4-week-infected (**right**) mice. In control mice nearly all IF-positive cells are chief cells, but after infection more parietal cells are positive (anti-IF 1:200; original magnification, ×500). **G:** Immunocytochemistry (IF) of gastric body of an 8-week control animal, showing only a few IF-positive parietal cells and many negative ones (anti-IF 1:200; original magnification, ×500). **H:** Immunocytochemistry (IF) of gastric body of an 8-week-infected mouse, showing increased IF-positive parietal cells, with surrounding inflammation (anti-IF 1:200; original magnification, ×500). pc, parietal cells; cc, chief cells.

The cytokines produced by inflammatory cells that have been often associated with increased protein expression are IL-1, TNF-α, and interferon-γ. The mRNAs encoding these cytokines (among others) are abundantly expressed in the gastric mucosa of patients with chronic gastritis,[24] and expression is increased in the inflamed colons of HLA-B27 transgenic rats.[15] Gastric parietal cells have receptors for IL-1 at least, and this cytokine has been demonstrated to have antisecretory activity.[11,25] IL-10 and TNF-α production[26] and IL-1β, IL-6, IL-8, and IL-12 as well,[27] are increased in antral mucosal biopsies from patients with chronic gastritis, and the cytokine secretion varies with the degree of inflammation.[26] IL-8 and TNF-α production were increased in patients with *H. pylori* infection in one study,[28] but not in another.[27] The studies with isolated parietal cells showed that at least one cytokine that contributes to a Th1 response (IL-1β) reproduced *in vitro* the twofold increase in IF-positivity seen *in vivo.* Atrophy of parietal and zymogenic cells is an eventual outcome of chronic inflammation of the gastric body, but dysplasia precedes the atrophy in most cases. The altered IF expression might be an early marker of such dysplastic changes.

It is possible that the observed increase in IF immunoreactivity is related to a decrease in IF secretion, as IF and H^+ secretion occur by the same canalicular pathway.[22] For this explanation to be valid, it would be necessary for some parietal cells to be producing undetectable IF under basal conditions. Alternatively, the cytokines released during inflammation could up-regulate expression of IF in cells which constitutively express undetectable amounts, recruit new cells to produce IF, expand a population of parietal cells that normally produce IF, or have combined effects. The results with isolated parietal cells favor up-regulation of IF expression.

This study did not evaluate the quantitative secretion of IF from chief cells, although there was no obvious change in their immunoreactivity (Figures 2 and 3). IL-1β, on the other hand, does not affect basal or stimulated pepsinogen secretion from chief cells.[29] Whatever the mechanism whereby cytokines may produce the effect noted on parietal cells, it is possible that increased IF-positivity represents a surrogate marker for the local effect of one or more cytokines. If so, this would be very instructive in following the tissue effects of cytokine stimulation and in evaluating this response as a marker for eventual mucosal atrophy.

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