Supplemental Methods:

Mice treatments and injections-

Treatment	Dose (body weight)	Vehicle	Injection Scheme	Source
Tamoxifen	5mg/20g	10% ethanol + 90% sunflower seed oil	i.p. one day, sacrificed as indicated	Sigma
U-0126	50mg/kg	10% DMSO (Sigma) + 90% sunflower seed oil	i.p. one hour before and every two hours after tamoxifen	Sigma
WP1066	2mg/20g	20% DMSO + 80% sunflower seed oil.	i.p. one hour before and every 12 hours after tamoxifen	EMD Millipore
Hyaluronan (HA)	30mg/kg	0.9% sterile saline	i.p. twice a week since weaning, for 5 weeks	Sigma
PEP-1 (5 week)	40mg/kg	Sterile water	i.p. twice a week since weaning, for 5 weeks	New England Peptide, Gardner, MA
PEP-1 (3 days)	40mg/kg	Sterile water	i.p. once a day for 3 days, starting one day before tamoxifen injection	New England Peptide, Gardner, MA

H. pylori growth conditions and murine infection- The wild-type rodent-adapted *cag*$^{+}$ *H. pylori* strain PMSS1 was cultured on trypticase soy agar with 5% sheep blood agar plates (BD Biosciences) for in vitro passage, as previously described(1). It was then cultured in Brucella broth (BB, BD Biosciences) supplemented with 10% fetal bovine serum (FBS, Atlanta Biologicals) for 16 to 18 hours at 37°C with 5% CO_2. Male C57BL/6 mice were purchased from Jackson Laboratories and housed in the Vanderbilt University Animal Care Facilities in a room with a 12-hour light-dark cycle at 21°C to 22°C. Mice were orogastrically challenged with either Brucella broth (BB), as an uninfected (UI) control, or with the mouse-adapted wild-type *cag*$^{+}$ H. pylori strain PMSS1. Mice were euthanized at 4 and 8 weeks post-challenge and gastric tissue was harvested for immunohistochemistry.

Immunofluorescence and Immunohistochemistry – Immunohistochemistry was performed using ABC reagent and DAB substrate kits (Vector Labs) as per the manufacturer's instructions. For BrdU/Ki67 quantifications, positive cells were counted in >50 gastric units per mouse and >3 mice per experiment. Total number of positive cells was divided by the total number of gastric units for each mouse. Stomachs were prepared, and stained, and imaged using methods modified from Ramsey et al (2). Primary antibodies used for immunostaining are listed below:

Serial No.	Antibody	Dilution	Source
1	Goat α-BrdU	1:20,000	Jeffrey Gordon, Washington University
2	Rabbit α-pERK1/2	1:100	Cell Signaling Technology, Danvers, MA
3	Rabbit α-Ki67	1:100	Abcam, Cambridge, MA
4	Rat α-CD44	1:50	BD Biosciences, San Jose, CA
5	Mouse α-E-cadherin	1:200	BD Biosciences, San Jose, CA
6	Rabbit α-Atp4a	1:10,000	Dr. Michael Caplan, Yale University

Hyaluronan-binding protein staining was performed as described (3). Secondary antibodies, lectins and BrdU labeling were as described (2).

Western Blotting – Primary antibodies used are listed below:

Serial No.	Antibody	Dilution	Source
1	Rabbit α-Cyclin D1	1:1,000	Cell Signaling Technology, Danvers, MA
2	Rabbit α-pERK1/2	1:1000	Cell Signaling Technology, Danvers, MA
3	Rabbit α-p-p38MAPK	1:1000	Cell Signaling Technology, Danvers, MA
4	Rabbit α-SAPK/JNK	1:1000	Cell Signaling Technology, Danvers, MA
5	Rabbit α-pAKT	1:1000	Cell Signaling Technology, Danvers, MA
6	Rabbit α-PLCγ	1:1000	Cell Signaling Technology, Danvers, MA
7	Rabbit α-Egr1	1:1000	Cell Signaling Technology, Danvers, MA
8	Rabbit α-pSTAT3	1:1000	Cell Signaling Technology, Danvers, MA
9	Rabbit α-STAT3	1:2000	Cell Signaling Technology, Danvers, MA
10	Rat α-CD44	1:500	BD Biosciences, San Jose, CA
11	Goat α-HAS1	1:1000	Santacruz Biotechnology Inc., CA
12	Goat α-HAS2	1:1000	Santacruz Biotechnology Inc., CA

Secondary antibodies were horseradish peroxidase (HRP)-conjugated donkey anti-rabbit IgG (1:2,000, Santa Cruz Biotenchnology, Inc.), goat anti-rat IgG (1:1000, Santa Cruz Biotechnology, Inc.) and donkey anti-goat IgG (1:1000, Santa Cruz Biotechnology, Inc.).

Flourescence Activated Cell Sorting - Gastric corpora were collected, washed in PBS, dissected into ~1mm^2 pieces, suspended in 1mL HBSS, and mechanically disaggregated with two 20 second pulses in a Medimachine (BD). Tissue was incubated for 1h with vigorous shaking at 37° C in 10mL HBSS supplemented with 1mM DTT and 5mM EDTA. The cell suspension was filtered (50μm filter, Partek) and the filtrate incubated at 37° C, 5% CO_2 until staining. The remaining mucosa/tissue left on the filter was rinsed in 10mL RPMI, then incubated at 37° C with vigorous shaking in 10mL RPMI containing 5% BSA and 1.5mg/mL Dispase II (Stem Cell Technologies) for 1.5 h. This cell suspension was filtered, and the second filtrate pooled with the first, washed, and surfaced labeled for flow cytometry. Cells were stained with Alexa Fluor™ 647-conjugated with either anti-mouse Epcam (Cell signaling) or Alexa Fluor™ 647-conjugated anti-mouse E-cadherin (for some experiments), and APC-Cy™7-conjugated anti-mouse CD44. Labeled cells were analyzed with a FACScan (BD) flow cytometer. The use of high wavelength fluorophores avoided considerable autofluorescence of living gastric epithelial cells.

Supplemental Figure Legends

Supp. Fig. 1: The $CD44^+$ cells expanding from the isthmus upon tamoxifen induced parietal cell atrophy were epithelial. In vehicle treated mice, there was little overlap between CD44 (red) and the epithelial marker, E-cadherin (green) (***A***, note only one isthmal cell with partial CD44- partial E-cadherin label in magnified box at right), but this population expanded gradually over 3 days after tamoxifen treatment (***B, C***). Mesenchymal $CD44^+$ cells are labeled with a white bracket, and $CD44^+$ immune cells are marked by white arrowheads. Insets show magnified images of the cells showing overlap between CD44 and E-cadherin (yellow).

Supp. Fig. 2: Loss of functional CD44 caused abbreviated pit/foveolar regions. While wildtype mice showed long pit regions (***A***) with ~11 pit cells per unit (**Fig. 1D**), *Cd44*$^{-/-}$ mice showed shorter pits with almost 2-fold reduced number of normal foveolar cells per unit (***B,* Fig. 1D**). Mice treated with PEP-1, showed a similar foveolar phenotype as *Cd44*$^{-/-}$ (***C,* Fig. 1D**), whereas, those treated with the CD44 ligand HA showed longer pit regions (***D***) with an average of ~13 foveolar cells per unit (**Fig. 1D**) and almost twice the rate of proliferation of WT mice (***E***). None of the conditions changed the parietal census significantly (***F***). In all figures: *P<0.05, **P<0.01, ***P<0.001.

Supp. Fig. 3: $CD44^+$ epithelial cells expand 5-7 fold upon parietal cell atrophy a quantified by FACS. A representative FACS graph from an experiment shows that CD44+ epithelial cells increase ~5-7 fold upon treatment with tamoxifen for 12h and day 3 compared to vehicle controls.

Supp. Fig. 4: Hyaluronic acid (HA), a ligand of CD44, was increased upon atrophic injury with tamoxifen. HA (stained using Hyaluronan-binding protein; in green) and CD44 (red) were increased in expression towards the base of the gastric unit during tamoxifen induced metaplasia (***A***, arrowheads). HAS1 and HAS2, enzymes that synthesizes HA, were also increased by 12h of tamoxifen treatment (***B***).

Supp. Fig. 5: *Cd44*$^{-/-}$ mice have compensatory mechanisms for increasing proliferation following tamoxifen induced atrophy. When treated with tamoxifen, *Cd44*$^{-/-}$ mice were able to increase proliferation to almost normal levels (***A***; one-tailed, paired Student's t test), despite the defect in basal levels of proliferation. Although there was a decrease in pSTAT3 in the *Cd44*$^{-/-}$ mice (***B***), similar to PEP-1 treatment (***Fig. 6E***), Cyclin D1 levels did not change in the *Cd44*$^{-/-}$ mice (***B***), suggesting that there might be a CD44-STAT3 independent compensatory mechanism in these mice that regulates proliferation in the face of atrophy.

Supp. Fig. 6: CD44 and pERK label the same population of cells as they start expanding from the isthmus during tamoxifen induced metaplasia. Immunohistochemical staining of serial sections of mouse stomachs treated for 12h with tamoxifen show that CD44 (yellow arrowhead) and pERK (green arrowheads) label a similar, overlapping population of isthmal cells during atrophy.

Supp. Fig. 7: ERK signaling is activated after parietal cell atrophy in both, humans and mice. Immunohistochemical staining for pERK showed numerous positive nuclei of metaplastic cells in mice infected with the PMSS1 strain of *H. pylori* (***A***; green arrowheads), whereas uninfected controls did not stain positive for pERK (***A***). pERK staining was also observed in gastric tissues of human patients undergoing intestinal metaplasia (***B, C***; green arrowheads) in regions of transition between normal gastric tissue and glands developing early intestinal metaplasia with appearance of goblet cells (yellow arrowhead).

1. Nagy TA, Frey MR, Yan F, Israel DA, Polk DB, Peek RM, Jr. Helicobacter pylori regulates cellular migration and apoptosis by activation of phosphatidylinositol 3-kinase signaling. The Journal of infectious diseases. 2009;199(5):641-51.
2. Ramsey VG, Doherty JM, Chen CC, Stappenbeck TS, Konieczny SF, Mills JC. The maturation of mucus-secreting gastric epithelial progenitors into digestive-enzyme secreting zymogenic cells requires Mist1. Development. 2007;134(1):211-22.
3. Zheng L, Riehl TE, Stenson WF. Regulation of colonic epithelial repair in mice by Toll-like receptors and hyaluronic acid. Gastroenterology. 2009;137(6):2041-51.