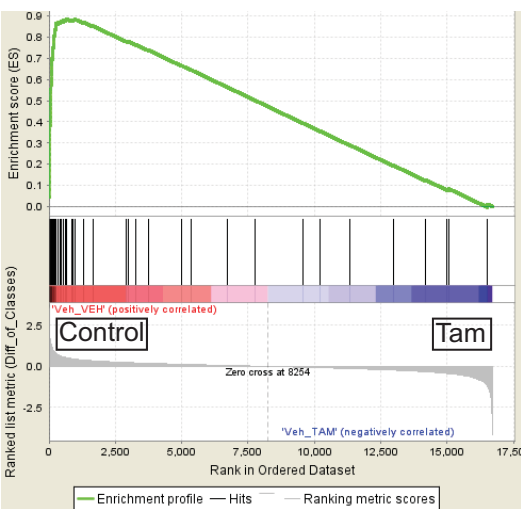


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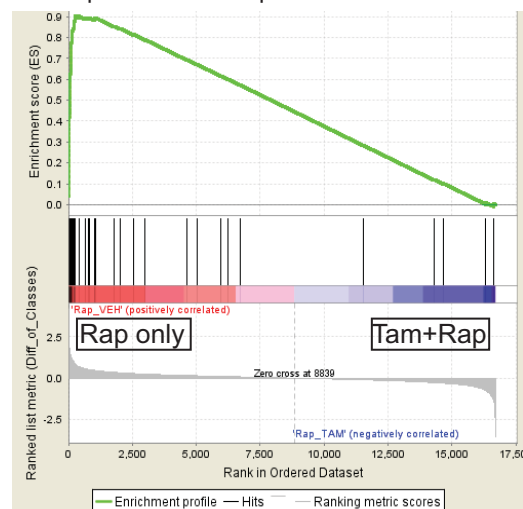
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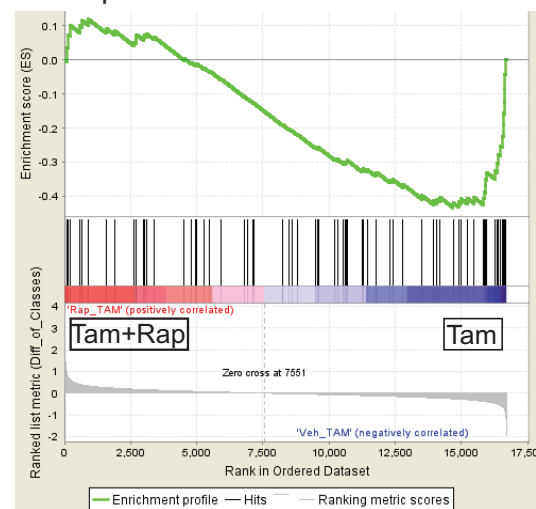
## A Control vs. Tam: Parietal Cells



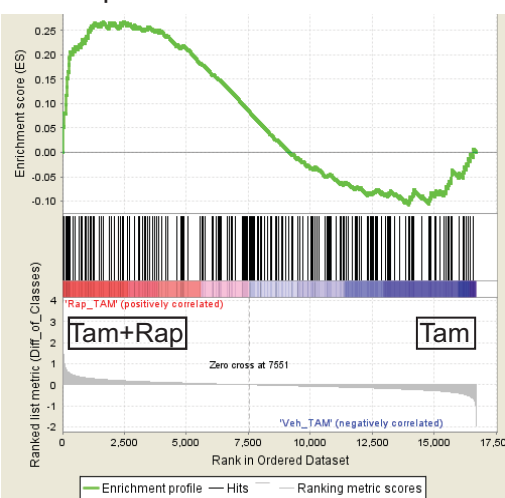
## B Rap Control vs. Rap+Tam: Parietal Cells



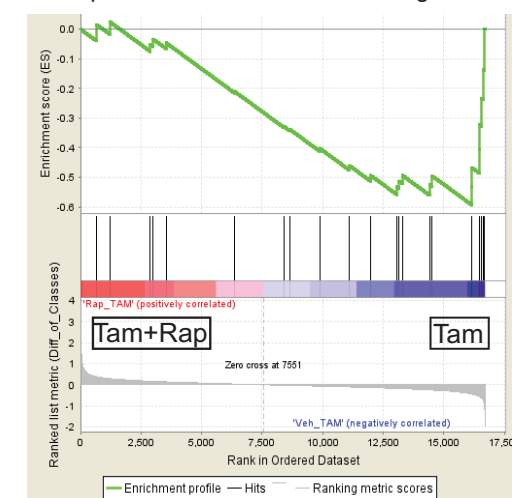
## C Rap+Tam vs. Tam: Parietal Cells



## D Rap+Tam vs. Tam: Chief Cells



## E Rap+Tam vs. Tam: known SPEM genes



Lamp1 DAPI

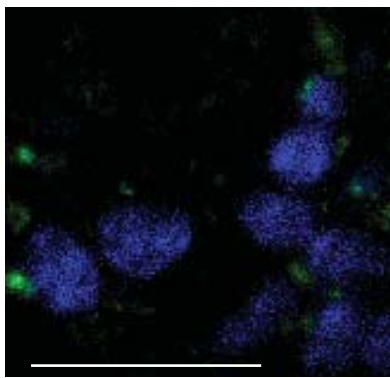
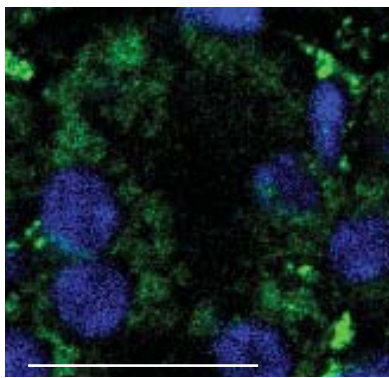
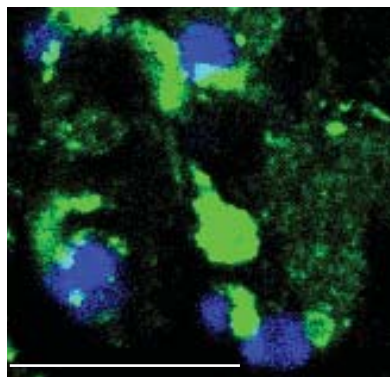
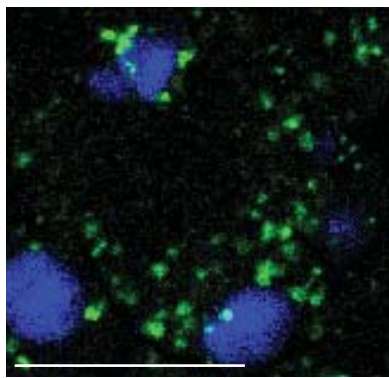
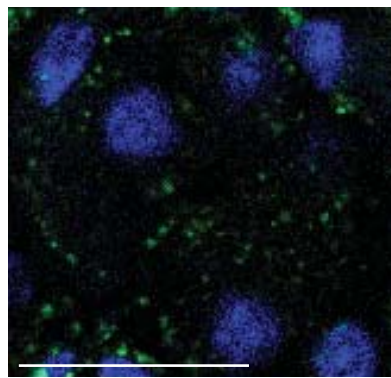
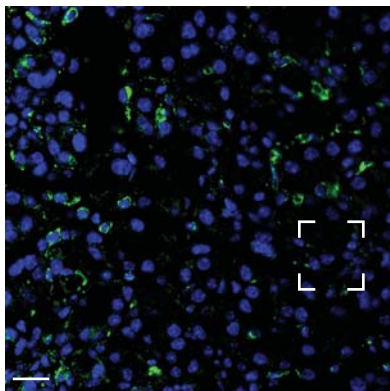
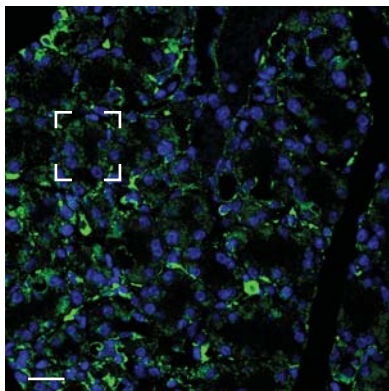
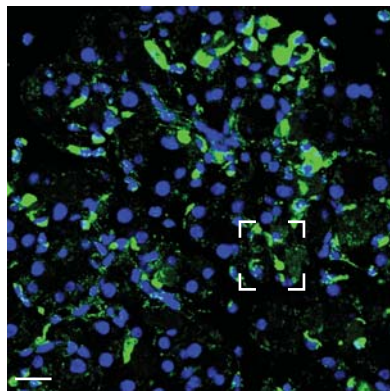
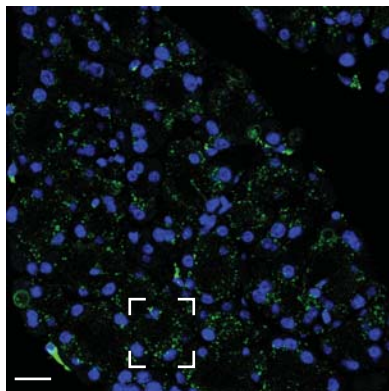
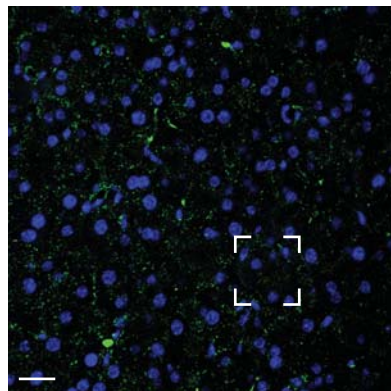
**Vehicle**

**8hr Cer**

**1D Cer**

**3D Cer**

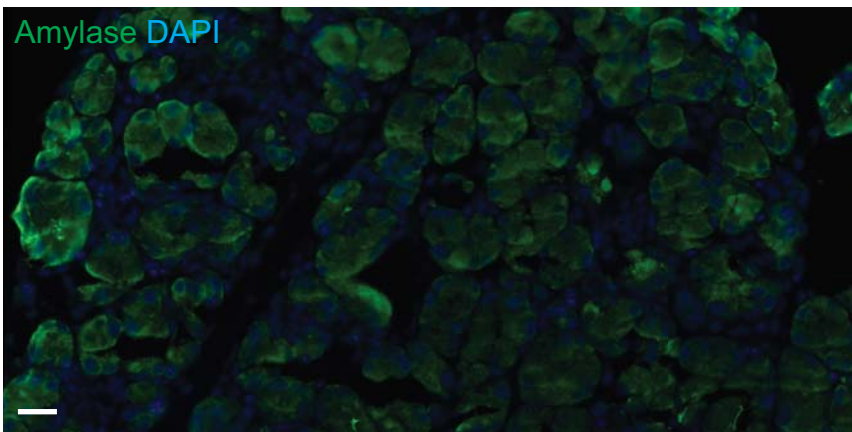
**5D Cer**



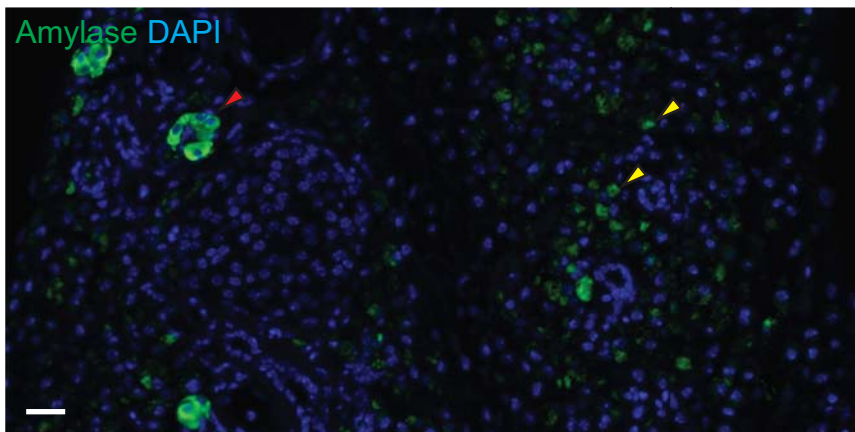
2 Week Cerulein

*Gnptab*<sup>+/-</sup>*Gnptab*<sup>-/-</sup>**A**

Amylase DAPI



Amylase DAPI

**B**

CK8/18

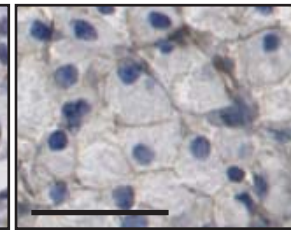
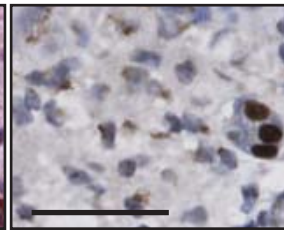
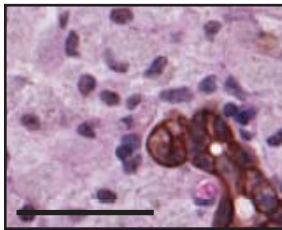
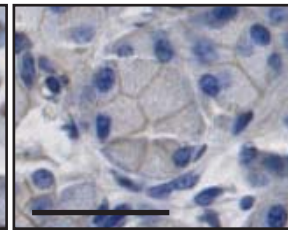
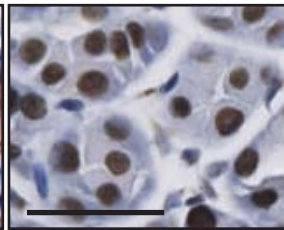
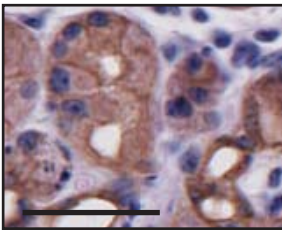
Gata4

Ecad

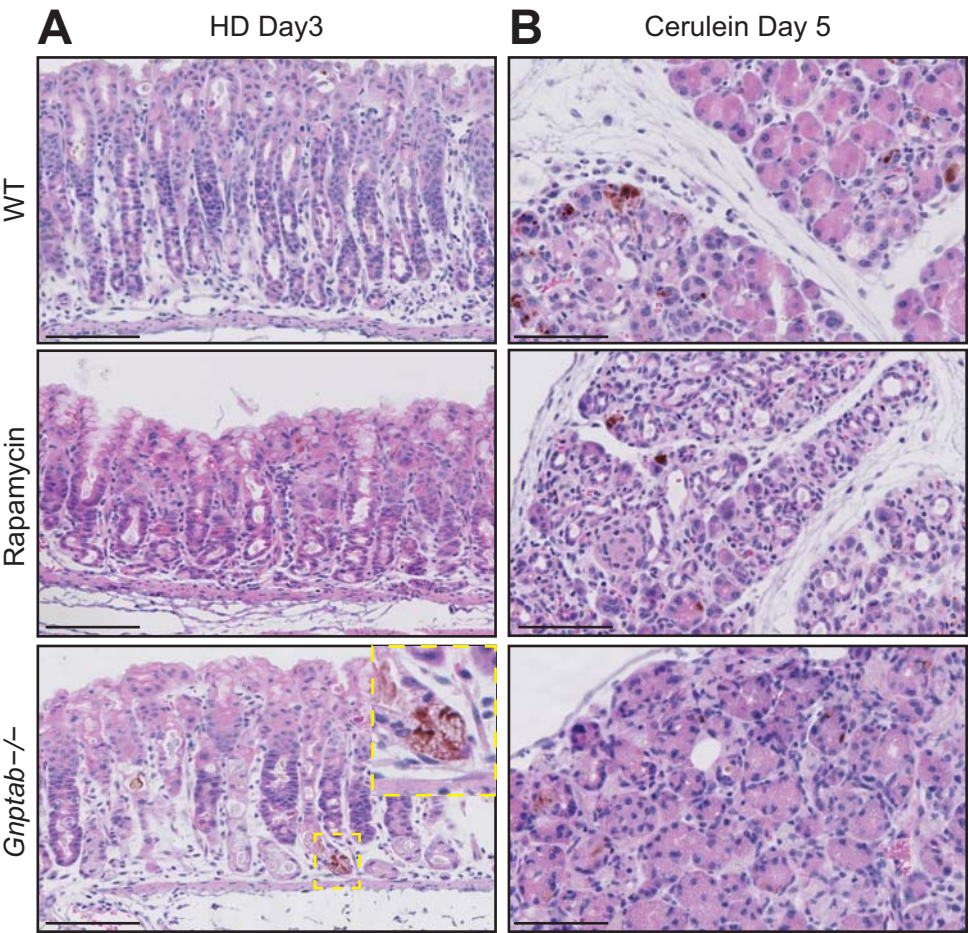
CK8/18

Gata4

Ecad



Cleaved Caspase 3



# Appendix Table S1: Patient Demographics

<b>Total Sample Number</b>	772
Normal Mucosa	100
SPEM	162
IM	163
Dysplasia	23
Cancer	324
Age Range	25-84
Average Age	64
<b>Gender</b>	
Male	448
Female	324

# Appendix Table S2: Antibodies

Antibody Table			
Antibodies	Company	Application	Dilution
BrdU	DHSB (G3G4)	IF,IHC	1:500
GIF	Gift, David Alpers, WashU	IF	1:250
Ezrin	Santa Cruz (sc-58758)	IF	1:1000
pS6 240/244	Cell Signaling (D68F8)	IF,IHC,WB	1:500
pS6 235/236	Cell Signaling (57.2.2E)	IF,WB	1:100
Pgc	Abcam (ab 31464)	IF	1:500
Cpa1	R&D Systems (AF2765)	IF	1:250
Amylase	Sigma-Aldrich (A8273)	IF	1:250
Sox9	Millipore (ABE571)	IHC	1:1000
GSII	Molecular Probes (L32451)	IF	1:250
Lamp1	DHSB (1D4B)	IF	1:500
Cathepsin D	Santa Cruz (sc- 6486)	IF	1:1000
$\beta$ tubulin	Abcam (ab21057)	WB	1:1000
Ki67	Abcam (ab15580)	IHC	1:500
CK8/18	Abcam (ab194130)	IHC	1:1000
Gata4	Santa Cruz (sc-9053)	IHC	1:500
E-Cadherin	BD Biosciences (610182)	IHC	1:250

# Appendix Table S3: qRT-PCR Primers

Primers Name	Sequence 5' to 3'
Atp4b F	CAGGAGAAGAAGTCATGCAGC
Atp4b R	GAAACCTGCGTAGTACAGGCT
Clu F	CCAGCCTTTCTTTGAGATGA
Clu R	CTCCTGGCACTTTTCACACT
Aurka F	TCTAGAATATGCGCCCCTTG
Aurka R	CCGTTTGAGCCAAGCAGTA
Aurkb F	GAAGAAGAGCCGTTTCATCG
Aurkb R	TCCGACTCTTCTGCAGTTCC
Ccna2 F	CTTGTAGGCACGGCTGCTAT
Ccna2 R	AGCCAAGTCAAAGCAAGGA
Ccnb2 F	CAAATCCGAGAAATGGAGA
Ccnb2 R	GCCACCTGAGAAGGATGGTA
Cdk1 F	CTGGGCAGTTCATGGATTCT
Cdk1 R	TCGGTATTCCAAACGCTCTG
Ccnd1 F	TTGACTGCCGAGAAGTTGTG
Ccnd1 R	CTGGCATTTTGGAGAGGAAG
TBP F	CAAACCCAGAATTGTTCTCCTT
TBP R	ATGTGGTCTTCCTGAATCCCT



**Appendix Figure S1 - GSEA of microarray data shows that Rapamycin does not affect injury-induced changes in parietal and chief cell gene expression but causes aberrant expression of a cohort of genes typically induced in SPEM.**

**A, B** GSEA and Genechip analyses were performed as for Fig.4, except panels **A** and **B** depict comparisons of a parietal cell specific gene set performed by flow cytometric purification of parietal cells (see Methods) with panel A showing how parietal cell gene expression is greatly enriched in vehicle control vs. HD-Tam and panel B showing that adding rapamycin with or without HD-Tam does not affect this pattern.

**C** Direct comparison of rapamycin+HD-Tam vs. HD-Tam shows that loss of parietal cell gene expression after HD-Tam treatment is not affected by rapamycin; if anything, rapamycin causes even more parietal cell injury as there is some enrichment of parietal cell gene expression in HD-Tam alone.

**D** Previously published chief cell-specific gene set also shows no relative enrichment in HD-Tam vs. HD-Tam+rapamycin, indicating chief cell palignosis is not affected by rapamycin.

**E** On the other hand, a previously published SPEM gene set shows enrichment in a specific sub-cluster of genes in HD-Tam vs. HD-Tam+rapamycin, indicating rapamycin blocks induction of a certain subset of SPEM genes. IM, intestinal metaplasia; pSPEM, proliferative SPEM; qSPEM, quiescent SPEM.

**Appendix Figure S2 - LAMP1 time course during cerulein injury shows a pattern of increased then decreased activation similar to that of stomach.**

Upon injury LAMP1 vesicles are induced in acinar cells starting around 8 hours and peak around 24 hours. By 3 to 5 days, the vesicles in exocrine cells begin to decrease back towards levels seen at homeostasis. Boxes in top panels are magnified to highlight acinar cells in bottom panels. Scale bars: 20  $\mu\text{m}$

**Appendix Figure S3 - *Gnptab*<sup>-/-</sup> acinar cells after 2 week cerulein treatment remain cryptically acinar.**

**A** Comparison of amylase staining between *Gnptab*<sup>-/-</sup> and *Gnptab*<sup>-/+</sup> following 2 weeks of cerulein treatment. In *Gnptab*<sup>-/-</sup> tissue, only scattered acinar cells remain highly positive for amylase (red arrowhead), with the vast majority only retaining weak positivity (yellow arrowheads). Scale bar: IF, 20 µm; IHC, 50 µm.

**B** Survey of metaplasia (CK8/18), mature acinar (GATA4), and epithelial markers (E-cadherin) on *Gnptab*<sup>-/-</sup> tissue. *Gnptab*<sup>-/-</sup> acinar tissue does not stain for the metaplasia marker CK8/18 or the mature acinar nuclear marker Gata4. The poorly differentiated acinar cells are positive for E-cadherin. Scale bar: IF, 20 µm; IHC, 50 µm.

**Appendix Figure S4 - Apoptotic cells death during HD tamoxifen or cerulein-induced injury.**

**A** At HD tamoxifen day 3 with or with rapamycin treatment, the stomach epithelium lacks apoptotic cells, indicating the main atrophy stage – in which parietal cells, but not chief cells, die by apoptosis – occurred earlier. In *Gnptab*<sup>-/-</sup> tissue, apoptotic cells can be found located at the base of some units consistent with the increased dropout of basal cells described in the results. Scale bar, 100 µm.

**B** During Cerulein at day 5, scattered apoptotic cells are seen in all experimental conditions, indicating the atrophy in this more asynchronous injury model is still occurring during this time window. No qualitative increase in cleave caspase positive cells were seen in rapamycin or *Gnptab*<sup>-/-</sup> tissue. Scale bar, 100 µm.