

Supporting Information

(Supplementary Figures and Legends)

Supplementary Figure Legends

Figure S1: Effect of Famotidine and GRL-0617 in PLpro transfected cells.

- (a) Interaction between catalytically inactive PLpro and ISG15 in interferon- α treated A549 cells.
- (b) Levels of indicated proteins in lysates from interferon- α treated A549 cells expressing GFP PLpro^{CoV2}. Cells were treated with Interferon- α for 36h. Famotidine or GRL-0617 was added in the medium 12h prior to cell lysis.
- (c) Effect of PLpro on luciferase (interferon- β) expression. A549 cells expressing indicated luciferase constructs were transfected with indicated GFP-PLpro and treated with poly (I:C) to induce interferon- β expression. Fold changes of luciferase expression are presented. Data are presented as mean \pm S.D. * $p < 0.05$.
- (d) Effect of PLpro on luciferase (NF- κ B) expression. A549 cells expressing indicated luciferase constructs were transfected with indicated GFP-PLpro and treated with TNF- α (20ng/ml,1h) to induce NF- κ B expression. Fold changes of luciferase expression are presented. Data are presented as mean \pm S.D. * $p < 0.05$, ** $p < 0.01$.
- (e) GFP-PLpro^{CoV2} transfected cells were treated with TNF- α (10ng/ml, 2h) or treated with interferon- α (200 U/ml, 36 h) in presence or absence of Famotidine or GRL-0617 followed by RNA isolation, cDNA preparation and real time PCR using primers against IL6, IL8 or ISG15. Interferon- α treatment was used to activate ISG15 mRNA expression while TNF- α treatment was used to test the expression of IL6 and IL8 genes. Data represents 6 biological replicates taken from 3 experiments, data are presented as mean \pm S.D. * $p < 0.1$, ** $p < 0.01$.

Figure S2: Proteome of Famotidine treated cells upon SARS-CoV2 infection

Caco2 cells infected with SARS-CoV2 after pretreatment with histamine (12h,100 μ M) and Famotidine (50 μ M,12h) were lysed in SDS lysis buffer, followed by proteomic analysis of lysates from cells treated with and without of famotidine. Data was analyzed by Perseus. Volcano plot indicates proteins which are enriched and de-enriched in Famotidine treated cells. Number of biological replicates used in analysis=3.

Figure S3: Pathway analysis of proteome from Famotidine treated cells

- (a) Proteins which were significantly reduced in the proteome of Famotidine treated cells ($p < 0.01$) (from experiment in Fig S3) were subjected to network analysis using the online Metascape software.
- (b) GO analysis of proteins which were significantly reduced in famotidine treated cells.
- (c) GO analysis of proteins which are significantly upregulated in proteome of famotidine treated cells.

Figure S4: Expression of histamine receptors and TLRs

- (a) cDNA from A549 cells was used as template to amplify histamine receptors (H1R, H2R, H3R, H4R) in a PCR for 30 cycles followed by running the reaction product in a 1% agarose gel.
- (b) mRNA expression of TLRs were assayed by RT-PCR from cDNA prepared from A549 cells treated with 20 μ g/ml poly(I:C) for 12h. Error bars indicate s.d, $p^{**} < 0.01$, $p^* < 0.05$
- (c) Expression of TLRs was assayed by RT-PCR using RNA isolated from CoV2 infected Caco2 cells 24h after infection. Error bars indicate s.d, $p^{**} < 0.01$, $p^* < 0.05$.
- (d) Cell viability was assessed by MTT assay after treatment of A549 cells with increasing amounts of poly (I:C) in presence or absence of histamine/Famotidine pretreatment (left panel). Poly(I:C) treatment was given for 12h. For pretreatment histamine (100 μ M) and Famotidine(50 μ M) was used for 12h.
- (e) TLR3 siRNA treated cells were treated with poly(I:C) for 12h with or without pretreatment with 100 μ M histamine and 50 μ M Famotidine. TLR3 levels were assayed by immunostaining with TLR3 antibody. Scalebars: 10 μ m.

Figure S5: Effect of Famotidine and GRL-0617 on SARS-CoV2 infected cells

SARS-CoV2 infected Caco2 cells were treated with 50 μ M of Famotidine or GRL-0617 added at the time of infection. Lysates were immunoblotted with indicated antibodies.

Figure S1

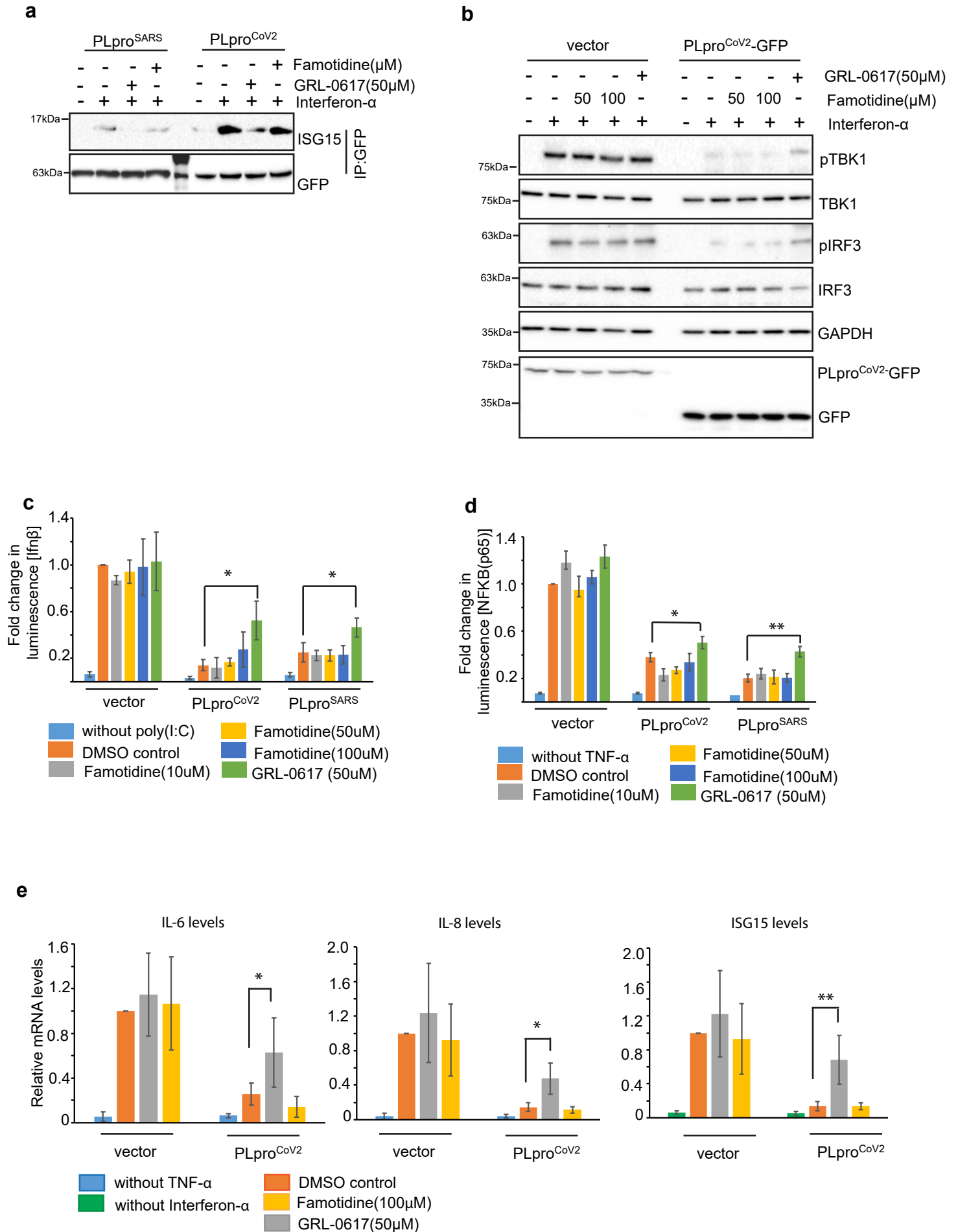
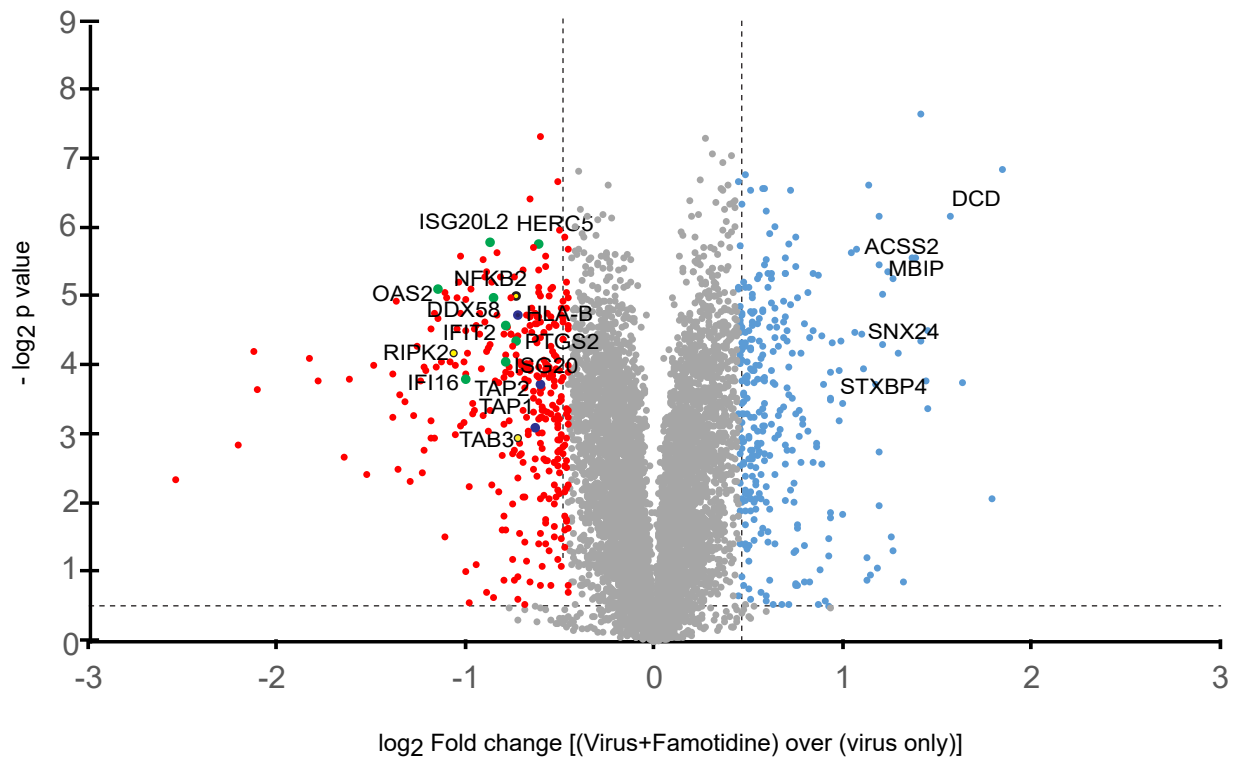


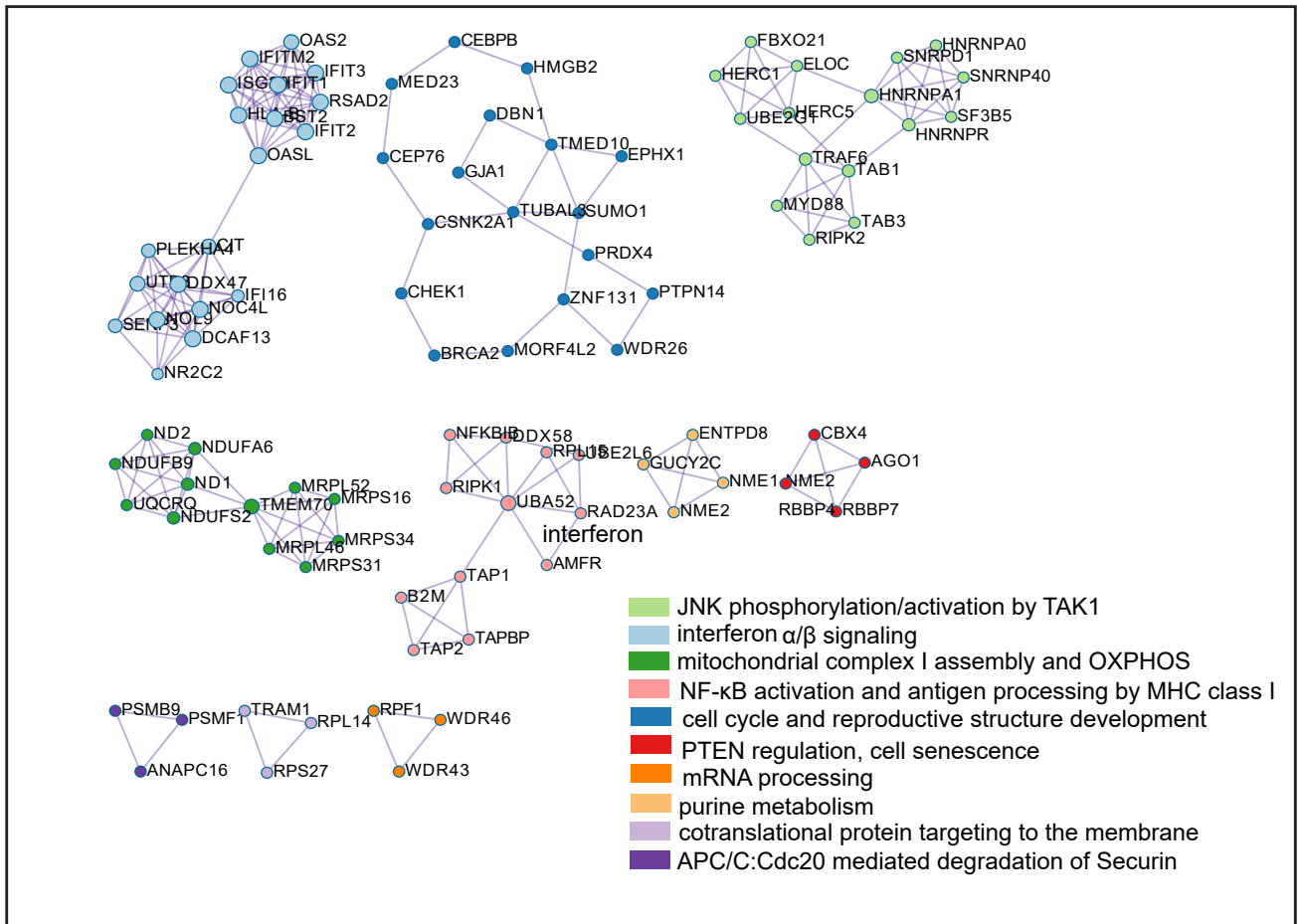
Figure S2



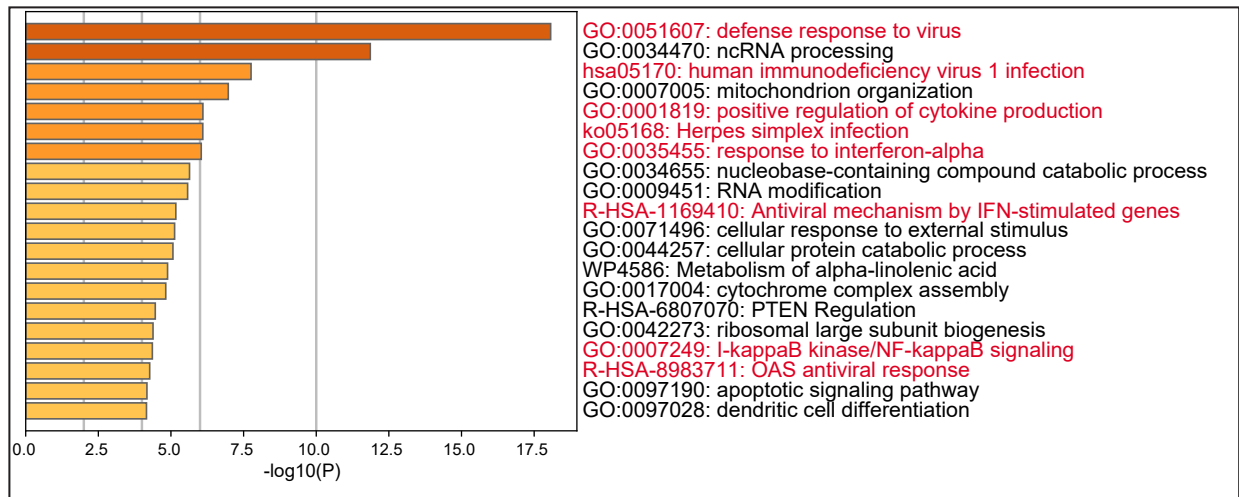
- Proteins de-enriched upon Famotidine treatment
- Proteins enriched upon Famotidine treatment
- Proteins related to interferon response
- Proteins related to antigen processing and presentation
- Proteins related to NF-κB pathway

Figure S3

(a)



(b)



(c)

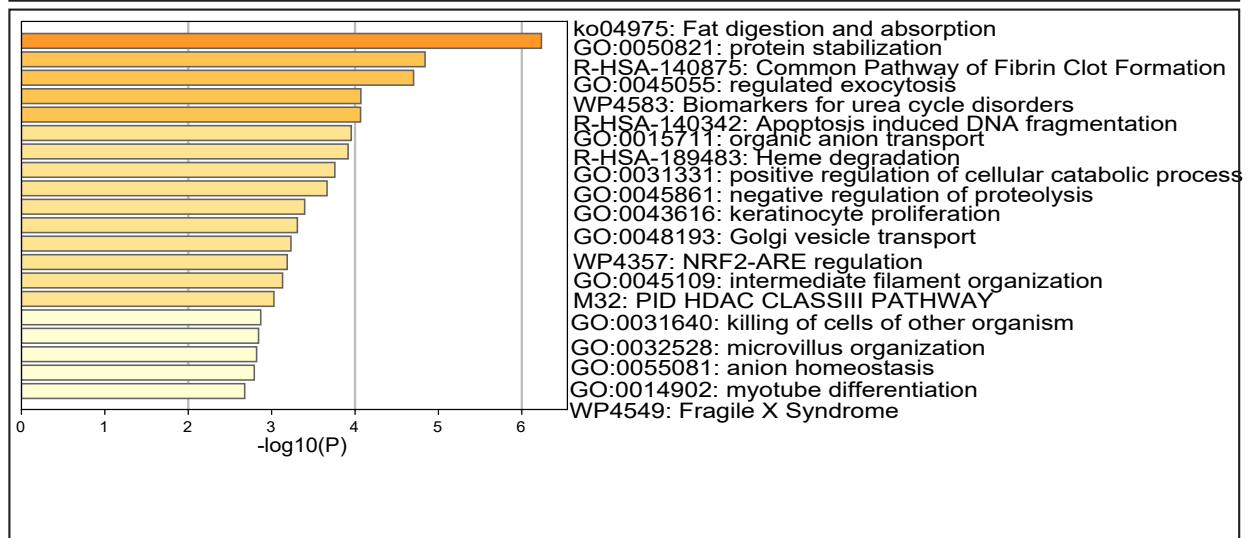


Figure S4

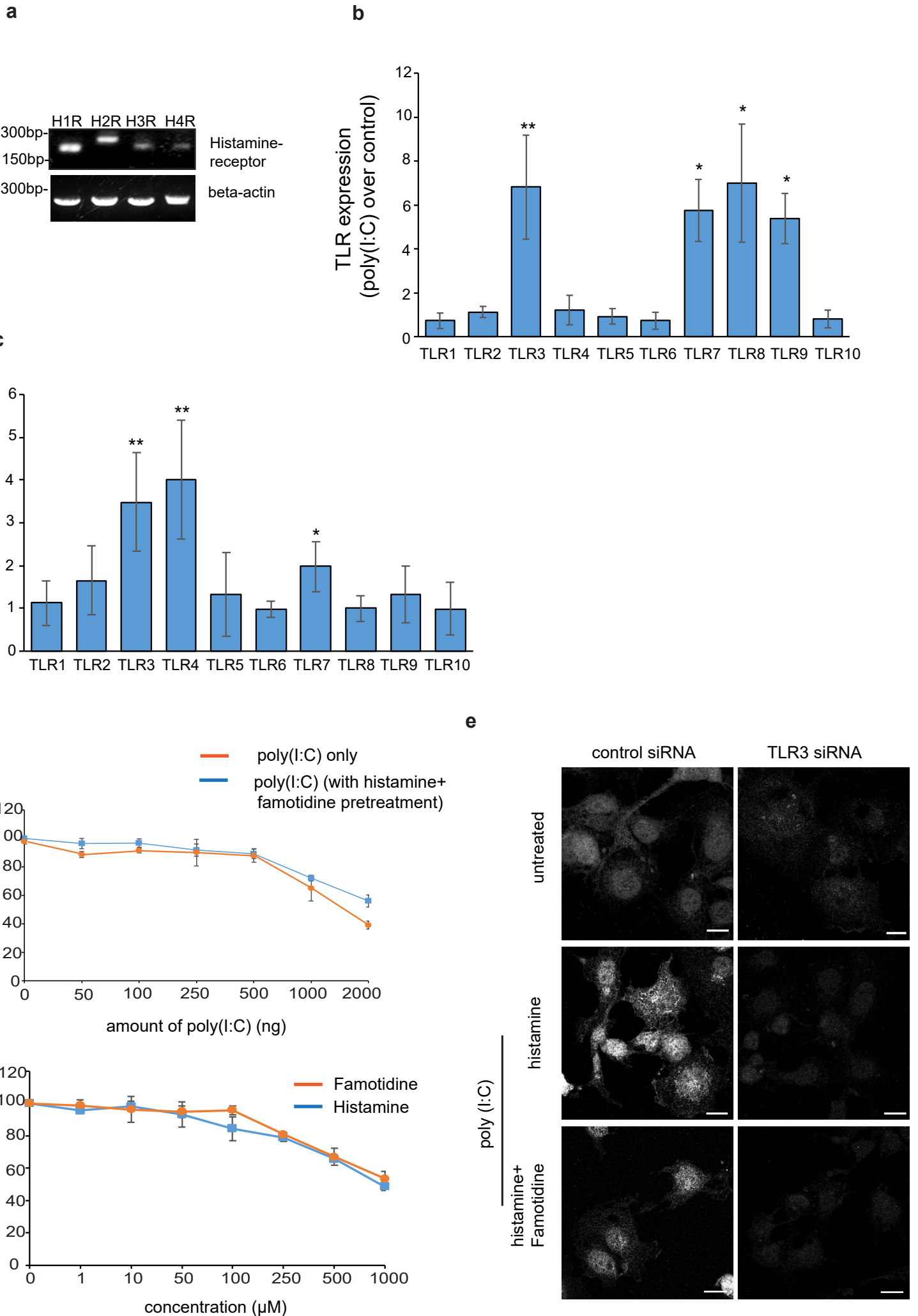


Figure S5

